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Pharmacological intervention for irritability, aggression, and self-injury in autism spectrum disorder (ASD) (Review)

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[Intervention Review]

Pharmacological intervention for irritability, aggression, and self-injury in autism spectrum disorder (ASD)

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ABSTRACT

Background

Pharmacological interventions are frequently used for people with autism spectrum disorder (ASD) to manage behaviours of concern, including irritability, aggression, and self-injury. Some pharmacological interventions might help treat some behaviours of concern, but can also have adverse effects (AEs).

Objectives

To assess the effectiveness and AEs of pharmacological interventions for managing the behaviours of irritability, aggression, and self-injury in ASD.

Search methods

We searched CENTRAL, MEDLINE, Embase, 11 other databases and two trials registers up to June 2022. We also searched reference lists of relevant studies, and contacted study authors, experts and pharmaceutical companies.

Selection criteria

We included randomised controlled trials of participants of any age with a clinical diagnosis of ASD, that compared any pharmacological intervention to an alternative drug, standard care, placebo, or wait-list control.

Data collection and analysis

We used standard Cochrane methods. Primary outcomes were behaviours of concern in ASD, (irritability, aggression and self-injury); and AEs. Secondary outcomes were quality of life, and tolerability and acceptability. Two review authors independently assessed each study for risk of bias, and used GRADE to judge the certainty of the evidence for each outcome.

Main results

We included 131 studies involving 7014 participants in this review. We identified 26 studies as awaiting classification and 25 as ongoing. Most studies involved children (53 studies involved only children under 13 years), children and adolescents (37 studies), adolescents only (2 studies) children and adults (16 studies), or adults only (23 studies). All included studies compared a pharmacological intervention to a placebo or to another pharmacological intervention.

Atypical antipsychotics versus placebo

At short-term follow−up (up to 6 months), atypical antipsychotics probably reduce irritability compared to placebo (standardised mean difference (SMD) −0.90, 95% confidence interval (CI) −1.25 to −0.55, 12 studies, 973 participants; moderate-certainty evidence), which may indicate a large effect. However, there was no clear evidence of a difference in aggression between groups (SMD −0.44, 95% CI −0.89 to 0.01; 1 study, 77 participants; very low-certainty evidence). Atypical antipsychotics may also reduce self-injury (SMD −1.43, 95% CI −2.24 to −0.61; 1 study, 30 participants; low-certainty evidence), possibly indicating a large effect.

There may be higher rates of neurological AEs (dizziness, fatigue, sedation, somnolence, and tremor) in the intervention group (low-certainty evidence), but there was no clear evidence of an effect on other neurological AEs. Increased appetite may be higher in the intervention group (low-certainty evidence), but we found no clear evidence of an effect on other metabolic AEs. There was no clear evidence of differences between groups in musculoskeletal or psychological AEs.

Neurohormones versus placebo

At short-term follow-up, neurohormones may have minimal to no clear effect on irritability when compared to placebo (SMD −0.18, 95% CI −0.37 to −0.00; 8 studies; 466 participants; very low-certainty evidence), although the evidence is very uncertain. No data were reported for aggression or self -injury.

Neurohormones may reduce the risk of headaches slightly in the intervention group, although the evidence is very uncertain. There was no clear evidence of an effect of neurohormones on any other neurological AEs, nor on any psychological, metabolic, or musculoskeletal AEs (low- and very low-certainty evidence).

Attention-deficit hyperactivity disorder (ADHD)-related medications versus placebo

At short-term follow-up, ADHD-related medications may reduce irritability slightly (SMD −0.20, 95% CI −0.40 to −0.01; 10 studies, 400 participants; low-certainty evidence), which may indicate a small effect. However, there was no clear evidence that ADHD-related medications have an effect on self-injury (SMD −0.62, 95% CI −1.63 to 0.39; 1 study, 16 participants; very low-certainty evidence). No data were reported for aggression.

Rates of neurological AEs (drowsiness, emotional AEs, fatigue, headache, insomnia, and irritability), metabolic AEs (decreased appetite) and psychological AEs (depression) may be higher in the intervention group, although the evidence is very uncertain (very low-certainty evidence). There was no evidence of a difference between groups for any other metabolic, neurological, or psychological AEs (very low-certainty evidence). No data were reported for musculoskeletal AEs.

Antidepressants versus placebo

At short-term follow-up, there was no clear evidence that antidepressants have an effect on irritability (SMD −0.06, 95% CI −0.30 to 0.18; 3 studies, 267 participants; low-certainty evidence). No data for aggression or self-injury were reported or could be included in the analysis.

Rates of metabolic AEs (decreased energy) may be higher in participants receiving antidepressants (very low-certainty evidence), although no other metabolic AEs showed clear evidence of a difference. Rates of neurological AEs (decreased attention) and psychological AEs (impulsive behaviour and stereotypy) may also be higher in the intervention group (very low-certainty evidence) although the evidence is very uncertain. There was no clear evidence of any difference in the other metabolic, neurological, or psychological AEs (very low-certainty evidence), nor between groups in musculoskeletal AEs (very low-certainty evidence).

Risk of bias

We rated most of the studies across the four comparisons at unclear overall risk of bias due to having multiple domains rated as unclear, very few rated as low across all domains, and most having at least one domain rated as high risk of bias.

Authors' conclusions

Evidence suggests that atypical antipsychotics probably reduce irritability, ADHD-related medications may reduce irritability slightly, and neurohormones may have little to no effect on irritability in the short term in people with ASD. There was some evidence that atypical antipsychotics may reduce self-injury in the short term, although the evidence is uncertain. There was no clear evidence that antidepressants had an effect on irritability. There was also little to no difference in aggression between atypical antipsychotics and placebo, or self-injury between ADHD-related medications and placebo. However, there was some evidence that atypical antipsychotics may result in a large reduction in self-injury, although the evidence is uncertain. No data were reported (or could be used) for self-injury or aggression for neurohormones versus placebo. Studies reported a wide range of potential AEs. Atypical antipsychotics and ADHD-related medications in particular were associated with an increased risk of metabolic and neurological AEs, although the evidence is uncertain for atypical antipsychotics and very uncertain for ADHD-related medications. The other drug classes had minimal or no associated AEs.

PLAIN LANGUAGE SUMMARY

Which medications reduce irritability, aggression or self-harm in people with autism spectrum disorder (ASD)?

Key messages

• Only 3 classes of medications showed any reduction in irritability, aggression or self-harm when compared to placebo (a dummy medication). Atypical (second-generation) antipsychotic medications probably reduce irritability and aggression, but appear to have little to no effect on self-injury. Attention deficit hyperactivity disorder (ADHD)-related medications may reduce irritability, although the evidence is uncertain. Neurohormones (oxytocin and secretin) may also reduce irritability, but we are very uncertain about the evidence.

• Antidepressants appear to have no effect on irritability. Studies did not report on the effects of antidepressants, ADHD-related medications and neurohormones on aggression or self-injury.

• Studies reported a wide range of unwanted effects, but only atypical antipsychotics, ADHD-related medications, and neurohormones showed evidence of a higher risk of any unwanted effects compared to placebo.

What is autism spectrum disorder (ASD)?

Autism is a disorder that affects a child's physical, mental and behavioural development. It is a lifelong disability that starts in childhood but continues throughout adulthood. People with autism may find it difficult to communicate and interact with the world. However, autism affects each person differently and may be more or less severe in different people, so it is described as a 'spectrum' disorder. Some people with autism spectrum disorder (ASD) may be irritable, angry or aggressive, or hurt themselves physically (self-injury), which are 'behaviours of concern' that can be difficult to manage and distressing for the person.

How are behaviours of concern managed?

Behaviours of concern are frequently managed with various types of medications that have been developed to treat other conditions. This means that their effectiveness for behaviours of concern is largely unknown, and they may cause serious and varied unwanted effects that affect all parts of the body. For example:

• the heart and lungs;

• the stomach and digestive system;

• the immune system;

• movement, joints and bones; and

• mood and emotion.

What did we want to find out?

We wanted to know which types of medication were effective in reducing behaviours of concern in people with ASD and whether they caused unwanted effects.

What did we do?

We searched for studies that investigated any medication used to manage behaviours of concern. Studies compared the medication with placebo (a dummy medication) or another medication. People in the studies could be adults or children, but all had ASD with behaviours of concern. We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 131 studies with 7014 people. Most studies involved children, although some studies involved both children and adults, or adults only. Studies looked at a wide range of medications, including those usually used to treat schizophrenia or bipolar disorder, depression, attention deficit hyperactivity disorder (ADHD), convulsions, emotional problems, heart and lungs, dementia, Parkinson's, and anxiety.

Atypical (second-generation) antipsychotics are usually used to treat schizophrenia or bipolar disorder. They probably reduce irritability, but they may have little to no effect on aggression and self-injury. People receiving antipsychotics might be more likely to experience unwanted effects such as increased appetite, dizziness, sedation (slowed thought and movement), sleepiness, tiredness and tremor compared to those receiving no treatment or other medications. People receiving antipsychotics may be no more or less likely than those receiving placebo to experience other unwanted effects.

Neurohormones (such as oxytocin and secretin) may have a minimal to small effect on irritability but no studies reported data for the effects of neurohormones on self-harm or aggression. People receiving neurohormones may be no more or less likely than those receiving placebo to experience unwanted effects.

ADHD-related medications may reduce irritability but may have no effect on self-injury. No studies reported data for aggression. People receiving ADHD-related medications might be more likely to experience unwanted effects such as drowsiness, tiredness, headache, difficulties sleeping, and decreased appetite. But they may be no more or less likely than those receiving placebo to experience other unwanted effects.

Antidepressants may have little to no effect on irritability. No studies reported useful data for aggression and self-injury. People receiving antidepressants might be more likely to experience unwanted effects such as impulsive behaviour and making repetitive movements or sounds (stereotypy) compared to placebo. But they may be no more or less likely than those receiving placebo to experience other types of unwanted effects.

What are the limitations of the evidence?

Most of the studies lasted less than 3 months, and very few studies involved adults. Therefore, we are uncertain if the same effects would be seen over a longer period of time or in adults.

How up-to-date is the evidence?

The review authors searched for studies that had been published up to June 2022.

Summary of findings 1. Atypical antipsychotics compared to placebo for irritability, aggression, and self-injury in autism spectrum disorder (ASD)

Atypical antipsychotics compared to placebo for irritability, aggression, and self-injury in autism spectrum disorder (ASD)

Patient or population: participants (any age) with a clinical diagnosis of ASD who have displayed one or more unwanted or challenging behaviours at baseline assessment
Setting: hospital inpatient or outpatient centres, education or disability settings, mental health settings, or clinics and research centres associated with universities
Intervention: atypical antipsychotics
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with atypical antipsychotics				
Irritability Follow-up: short term (up to 6 months) Measured via Aberrant Behaviour Checklist (Irritability subscale (ABC-I), score range 0-45; Aman 1985) and the Ritvo Freeman RealLife Rating Scale (RFRLRS; Freeman 1986). Lower scores indicate lower severity	The mean score in the placebo group ranged from −8.40 to 25.5	SMD 0.90 lower (95% CI 1.25 lower to 0.55 lower)	-	973 (12 studies: risperidone 6 studies; aripiprazole 5 studies; lurasidone 1 study)	⊕⊕⊕⊖ Moderate[a]	An SMD of 0.90 may represent a large effect (small = 0.2; medium = 0.5; and large = 0.8; Cohen 1988)
Aggression Follow-up: short term (up to 6 months) Measured via: Nisonger Child Behaviour Rating Form (conduct problem subscale; Aman 1996) Score range 0-48: lower scores indicate lower severity	The mean score in the placebo group was −6.6	SMD 0.44 lower (95% CI 0.89 lower to 0.01 higher)	-	77 (1 study, risperidone)	⊕⊖⊖⊖ Very low[b]	There was no clear evidence of a difference however, results are uncertain.
Self-injury	The mean score in the placebo group was −4.90	SMD 1.43 lower	-	30	⊕⊕⊖⊖	An SMD of 1.43 may rep-

Follow-up: short term (up to 6 months) Measured via: Self-Injurious Behaviour Questionnaire (SIB-Q Self-injury subscale; Gualtieri 2002) Score range 0-20; lower scores indicate lower severity			(95% CI 2.24 lower to 0.61 lower)		(1 study, risperidone)	Low[c]	resent a large effect (small = 0.2; medium = 0.5; and large =0.8; Cohen 1988)
Adverse effects (AEs) Follow-up: short term (up to 6 months)	**Neurological**	There was evidence of a higher rate of AEs in the intervention group for **dizziness** (14% vs 3%, P = 0.04)	RR 4.19 (95% CI 1.10 higher to 16.00 higher; 2 studies, risperidone)	974 (11 studies)	⊕⊕⊖⊖ Low[d]	
		There was evidence of a higher rate of AEs in the intervention group for **fatigue** (15% vs 5%, P < 0.001)	RR 2.58 (95% CI 1.68 higher to 3.97 higher; aripiprazole 2 studies; risperidone 4 studies)			
		There was evidence of a higher rate of AEs in the intervention group for **sedation** (18% vs 3%, P = 0.02)	RR 2.98 (95% CI 1.15 higher to 7.73 higher; aripiprazole 1 study; lurasidone 1 study; risperidone 4 studies)			
		There was evidence of a higher rate of AEs in the intervention group for **somnolence** (26% vs 6%, P < 0.00001)	RR 4.84 (95% CI 3.18 higher to 7.36 higher; aripiprazole 3 studies; lurasidone 1 study; risperidone 5 studies)			
		There was evidence of a higher rate of AEs in the intervention group for **tremor** (10% vs 1%, P = 0.003)	RR 5.99 (95% CI 1.87 higher to 19.19 higher; aripiprazole 3 studies; risperidone 2 studies)			
		There was little to no evidence of a difference between groups for: **drowsiness** (P = 0.06); **extrapyramidal** disorder (P = 0.15); **hypersomnia** (P = 0.29); **lethargy** (P = 0.19); **restlessness** (P = 0.98); or **agitation** (P = 0.23)				
	Psychological	There was little to no evidence of a difference between groups for **anxiety** (P = 0.42) or **depression** (P = 0.21).		218 (4 studies)	⊕⊖⊖⊖ Very low[e]	
	Metabolic	There was evidence of a higher rate of AEs in the intervention group for **increased appetite**	RR 2.38 (95% CI 1.69 higher to 3.34 higher; aripipra-	702 (8 studies)	⊕⊕⊖⊖ Low[d]	

		zole 3 studies; risperidone 5 studies)		
	There was little to no evidence of a difference between groups for **decreased appetite** (P = 0.11), **weight gain** (P = 0.10) or **thirst** (P = 0.39).			
Musculoskeletal	There was little to no evidence of a difference between groups for **rigidity** (P = 0.13), **movement disorder** (P = 0.27) or **dyskinesia** (P = 0.28)	182 (2 studies)	⊕⊖⊖⊖ Low[f]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AE: adverse effect; **ASD:** autism spectrum disorder; **CI:** confidence interval; **RR:** risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded 1 level for study limitations (high risk of bias across multiple domains). Not downgraded for inconsistency, as high I^2 statistic (83%) can be attributed to 2 outlier studies.
[b]Downgraded 1 level for study limitations (high risk of bias across multiple domains), 1 level for imprecision (small sample size of 77 participants) and 1 level for imprecision (95% confidence intervals includes both benefit and harm).
[c]Downgraded 1 level for imprecision (small sample size of 30 participants), and 1 level for indirectness (available evidence relates to adults only).
[d]Downgraded 1 level for study limitations (high risk of bias across multiple domains) and 1 level for inconsistency (direction of effect varies across studies).
[e]Downgraded 1 level for study limitations (high risk of bias across multiple domains), 1 level for imprecision (small sample size of 79 participants), and 1 level for indirectness (available evidence relates to children only).
[f]Downgraded 1 level for study limitations (high risk of bias across multiple domains), and 1 level for indirectness (available evidence relates to children only) and 1 level for imprecision (small sample size of 182 participants).

Summary of findings 2. Neurohormones compared to placebo for irritability, aggression, and self-injury in autism spectrum disorder (ASD)

Neurohormones compared to placebo for irritability, aggression, and self-injury in autism spectrum disorder (ASD)

Patient or population: participants (any age) with a clinical diagnosis of ASD who have displayed one or more unwanted or challenging behaviours at baseline assessment
Setting: hospital inpatient or outpatient centres, education or disability settings, mental health settings, or clinics and research centres associated with universities
Intervention: neurohormones
Comparison: placebo

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with placebo	Risk with neurohormones				
Irritability Follow-up: short term (up to six months) Measured via Aberrant Behaviour Checklist (Irritability subscale) (ABC-I) (Aman 1985, Score range (0-45)). Lower scores indicate lower severity		See comment	SMD 0.18 lower (95% CI 0.37 lower to 0.00 lower)	-	466 (8 studies: secretin 3 studies; ACTH 1 study; oxytocin 3 studies; vasopressin 1 study)	⊕⊖⊖⊖ Very low[a]	An SMD of 0.18 may represent a small effect (small = 0.2; medium = 0.5; and large = 0.8; Cohen 1988)
Aggression		No data were reported for this outcome in this comparison					
Self Injury		No data were reported for this outcome in this comparison					
Adverse effects Follow-up: short term (up to six months)	**Neurological**	There was evidence of a lower rate of AEs for **headaches** in the neurohormone group		RR 0.58 (95% CI 0.38 to 0.89) (7 studies: oxytocin 6 studies; balovaptan 1 study)	863 participants (10 studies)	⊕⊖⊖⊖ Very low[b]	-
		The was little to no evidence of a difference between groups for **absence seizures** (P = 0.52), **aggression** (P = 0.68), **agitation** (P = 0.67), **decreased attention** (P = 0.68), **dizziness** (P = 0.69), **dysphoria** (P = 0.49); **excessive talking** (P = 0.52), **fatigue** (P = 0.76), **forgetfulness** (P = 0.52), **insomnia** (P = 0.08), **irritability** (P = 0.22), **leg shaking** (P = 0.52), **nervous sytem disorders** (P = 0.47), **oppositional** (P = 0.69), **restlessness** (P = 0.67), **seizure** (P = 0.52), **sedation** (P = 0.16), **somnolence** (P = 0.22), **tics** (P = 0.49)					-
	Psychological	The was little to no evidence of a difference between groups for **anxiety** (P = 0.23), **depression** (P = 0.83), **panic attacks** (P = 0.45), **psychiatric events** (P = 0.21), or **self-injury** (P = 1.00)			570 participants (6 studies)	⊕⊕⊖⊖ Low[c]	-
	Metabolic	The was little to no evidence of a difference between groups for any of the metabolic AEs including **decreased appetite** (P = 0.19), **increased appetite** (P = 0.07), **metabolism and nutrition disorders** (P = 0.57), thirst (P = 0.62), **weight change** (P = 0.50), **weight gain** (P = 0.67), and **weight loss** (P = 0.20)			515 participants (5 studies)	⊕⊕⊖⊖ Low[c]	-

Musculoskeletal	The was little to no evidence of a difference between groups for **muscle spasms** (P = 0.52), **musculoskeletal and connective tissues disorder** (P = 0.50) and **rhabdomyolysis** (P = 0.81)	355 participants (3 studies)	⊕⊖⊖⊖ Very low[d]	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AE: adverse effect; **ASD:** autism spectrum disorder; **CI:** confidence interval; **RR:** risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded 1 level for imprecision (95% CI includes both benefit and harm), 1 level for study limitations (all studies involved children) and 1 level for imprecision (95% confidence intervals includes both benefit and harm).
[b]Downgraded 1 level for study limitations (high risk of bias across multiple domains), 1 level due to inconsistency (direction of effect varies across studies) and 1 level for imprecision (95% confidence intervals includes both benefit and harm).
[c]Downgraded 1 level for study limitations (high risk of bias across multiple domains), and 1 level for imprecision (95% confidence intervals includes both benefit and harm).
[d]Downgraded 1 level for imprecision (95% CI includes both benefit and harm), 1 level for study limitations (high risk of bias across multiple domains) and 1 level for imprecision (95% confidence intervals includes both benefit and harm).

Summary of findings 3. Attention deficit hyperactivity disorder (ADHD)-related drugs compared to placebo for irritability, aggression, and self-injury in autism spectrum disorder (ASD)

ADHD-related medications compared to placebo for irritability, aggression, and self-injury in autism spectrum disorder (ASD)

Patient or population: participants (any age) with a clinical diagnosis of ASD who have displayed one or more unwanted or challenging behaviours at baseline assessment
Setting: hospital inpatient or outpatient centres, education or disability settings, mental health settings, or clinics and research centres associated with universities
Intervention: ADHD-related medications
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with ADHD-related drugs				
Irritability	See comment	SMD 0.20 lower (95% CI 0.40 lower to 0.01 lower)	-	400 (10 studies: methylphenidate	⊕⊕⊖⊖ Low[a]	An SMD of 0.20 may represent a small effect

All ADHD-related medications Follow-up: short term (up to six months) Measured via Aberrant Behaviour Checklist (Irritability subscale) (Score range (0-45)) (Aman 1985) and the Ritvo-Freeman Real Life Rating Scale (Freeman 1986 (score range 0-15). Lower scores indicate lower severity.				2 studies; clonidine 2 studies; guanfacine 2 studies; atomoxetine 4 studies)		size (small = 0.2; medium =0.5; large = 0.8, Cohen 1988).
Aggression	No data were reported for this outcome in this comparison					
Self-injury Follow-up: short term (up to six months) Measured via the Repetitive Behaviour Scale - Revised (self-injury subscale) (Bodfish 2000)	See comment	SMD 0.62 lower (95% CI 1.63 lower to 0.39 higher)	-	16 participants (1 study)	⊕⊖⊖⊖ Very low[b]	There was no clear evidence of a difference, but results are uncertain.
Adverse effects Follow-up: short term (up to six months)	**Neurological**	There was evidence of a higher rate of AEs in the intervention group for **drowsiness**	RR 3.42 (95% CI 1.54 higher to 7.59 higher); atomoxetine 2 studies; guanfacine 1 study; methylphenidate 1 study)	511 (9 studies)	⊕⊖⊖⊖ Very low[c]	-

	There was evidence of a higher rate of AEs in the intervention group for **emotional**	RR 6.32 (95% CI 2.47 higher to 16.18 higher); methylphenidate 1 study; guanfacine 1 study			
	There was evidence of a higher rate of AEs in the intervention group for **fatigue**	RR 3.73 (95% CI 1.98 higher to 7.03higher); atomoxetine 3 studies; guanfacine 1 study			
	There was evidence of a higher rate of AEs in the intervention group for **headache**	RR 1.63 (95% CI 1.09 higher to 2.44 higher); atomoxetine 4 studies; methylphenidate 2 studies; guanfacine 1 study; amphetamine 1 study			
	There was evidence of a higher rate of AEs in the intervention group for **insomnia**	RR 1.58 (95% CI 1.01 higher to 2.47 higher); methylphenidate 2 studies; atomoxetine 3 studies; guanfacine 1 study; amphetamine 1 study			
	There was evidence of a higher rate of AEs in the intervention group for **irritability**	RR 1.61 (95% CI 1.25 to 2.07 higher); atomoxetine 3 studies; guanfacine 1 study; methylphenidate 2 studies			
	There was little to no evidence of a difference between groups for **aggression** (P = 0.82), **agitation** (P = 0.85), **dizziness** (P = 0.22), **drowsiness** (P = 0.003), **hyperactivity** (P = 0.75), **increased motor activity** (P = 0.36), **motor tics** (P = 0.28), **nightmares** (P = 0.57), **repetitive behaviour** (P = 0.23), **restlessness** (P = 0.80), **sleep disturbance** (P = 0.76), **talking excessively** (P = 0.05), **waking** (P = 0.59), or **tremor** (P = 0.48).				
Psychological	There was evidence of a higher rate of **depression** in the intervention group	RR 2.45 higher (95% CI 1.12 higher to 5.36 higher); methylphenidate 2 studies; guanfacine 1 study	252 (5 studies)	⊕⊖⊖⊖ Very low[d]	-
	There was little to no evidence of a difference between groups for **anxiety** (P = 0.30); **mood change** (P = 0.07), "**silly behaviour**" (P = 0.51), **self-injury** (P = 0.19), or **social withdrawal** (P = 0.36).				
Metabolic	There was evidence of a higher rate of AEs in the intervention group for **decreased appetite**	RR 2.15 (95% CI 1.55 higher to 2.99 higher); atomoxetine 5 studies; guanfacine 1 study; amphetamine 1 study; methylphenidate 2 studies	511 (9 studies)	⊕⊖⊖⊖ Very low[c]	-
	There was little to no evidence of a difference between groups for increased appetite (P = 0.63) and increased energy (P = 0.31).				

Musculoskeletal	No data were reported for this outcome in this comparison.

AE: adverse effect; **ASD:** autism spectrum disorder; **CI:** confidence interval; **RR:** risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded 1 level due to study limitations (high risk of bias across multiple domains) and 1 level due to imprecision (95% confidence intervals includes both benefit and harm).
[b]Downgraded 1 level due to study limitations (high risk of bias across multiple domains) and 1 level for indirectness (available evidence relates to children only) and 1 level for imprecision (small sample size of n = 16 and 95% confidence intervals includes both benefit and harm).
[c]Downgraded 1 level due to study limitations (only involving children), 1 level due to inconsistency (direction of effect varies across studies) and 1 level due to imprecision (95% confidence intervals includes both benefit and harm).
[d]Downgraded 1 level due to study limitations (high risk of bias across multiple domains), 1 level due to inconsistency (direction of effect varies across studies) and 1 level due to imprecision (95% confidence intervals includes both benefit and harm).

Summary of findings 4. Antidepressants compared to placebo for irritability, aggression, and self-injury in autism spectrum disorder (ASD)

Antidepressants compared to placebo for irritability, aggression, and self-injury in autism spectrum disorder (ASD)

Patient or population: participants (any age) with a clinical diagnosis of ASD who have displayed one or more unwanted or challenging behaviours at baseline assessment
Setting: hospital inpatient or outpatient centres, education or disability settings, mental health settings, or clinics and research centres associated with universities
Intervention: antidepressants
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with antidepressants				
Irritability Follow-up: short term (up to six months) Measured via Aberrant Behaviour Checklist (Irritability subscale) (ABC-I) (Aman 1985), Score range (0-45)	The mean score in the placebo group ranged from 10.2 to 13.8	SMD 0.06 lower (95% CI 0.30 lower to 0.18 higher)	-	267 (3 studies)	⊕⊕⊖⊖ Low[a]	There was no evidence of a difference, but results are uncertain.

Lower scores indicate lower severity					
Aggression		No data were reported for this outcome in this comparison			
Self-injurious behaviour - no data could be used for this outcome because of skewness (see Table 1)					
Adverse effects Follow-up: short term (up to six months)	**Neurological**	There was evidence of a higher rate of **decreased attention** in the intervention group	RR 4.16 (95% CI 1.07 higher to 16.11 higher); citalopram 1 study; clomipramine 1 study; fluoxetine 5 studies; fluvoxamine 1 study; sertraline 1 study; tianeptine 1 study	815 (10 studies)	⊕⊕⊖⊖ Low[b]
		The was little to no evidence of a difference between groups for any of the other neurological adverse effects including **activation syndrome** (P = 0.64), agitation (P = 0.96), **aggression or hostility** (P = 0.83), **anger or irritability** (P = 0.35), **autonomic disturbance** (P = 0.83), **CNS disturbance** (P = 0.50), **diaphoresis** (sweating) (P = 0.49), **drowsiness** (P = 0.50), **headache** (P = 0.23), **hyperactivity** (P = 0.36), **insomnia** (P = 0.29), **sedation** (P = 0.16), **sleep disturbance** (P = 0.76), **mood lability** (P = 0.43), **restlessness** (P = 0.13), **twitching** (P = 0.17), **tremor** (P = 0.22), or **vertigo** (P = 0.65)			
	Psychological	The was evidence of a higher rate of AEs in the intervention group for **impulsive behaviour**	RR 2.92 (95% CI 1.11 higher to 7.68 higher); citalopram 1 study	243 (4 studies)	⊕⊖⊖⊖ Very low[c]
		The was evidence of a higher rate of AEs in the intervention group for **stereotypy**	RR 8.33 (95% CI 1.07 higher to 64.95 higher); citalopram 1 study		
		The was little to no evidence of a difference between groups for **anorexia** (P = 0.42), **verbal aggression** (P = 0.36), **suicidal ideation** (P = 0.65), **bad dreams** (P = 0.28), **unstable mood** (P = 0.66), **anxiety** (P = 0.16) and **depression** (P = 0.79)			
	Metabolic	There was evidence of a higher rate of **decreased energy** in the antidepressant group	RR 1.94 (95% CI 1.13 higher to 3.33 higher); citalopram 1 study	512 (7 studies)	⊕⊖⊖⊖ Very low[d]
		The was little to no evidence of a difference between groups for **appetite disturbance** (P = 0.40), **decreased appetite** (P = 0.39), **increased appetite** (P = 0.85), and **weight gain** (P = 0.80)			
	Musculoskeletal	The was little to no evidence of a difference between groups for **motor disturbance** (P = 0.30) or **neck pain** (P = 0.65)		202 (2 studies)	⊕⊖⊖⊖

					Very low[e]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

AE: adverse effect; **ASD:** autism spectrum disorder; **CI:** confidence interval; **CNS:** central nervous system; **RR:** risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded 1 level for imprecision (95% confidence intervals includes both benefit and harm), and 1 level for imprecision (small sample size of n = 267).
[b]Downgraded 1 level for study limitations (high risk of bias across multiple domains) and 1 level for imprecision (95% confidence intervals include both benefit and harm).
[c]Downgraded 1 level for study limitations (high risk of bias across multiple domains), 1 level for inconsistency (direction of effect varied across studies) and 1 level for imprecision (small sample size of n = 279).
[d]Downgraded 1 level for study limitations (high risk of bias across multiple domains), 1 level for inconsistency (direction of effect varied across studies and 1 level for imprecision (95% confidence intervals includes both benefit and harm).
[e]Downgraded 1 level for study limitations (high risk of bias across multiple domains), 1 level for imprecision (small sample size of n=202), and 1 level for imprecision (95% confidence intervals includes both benefit and harm).

BACKGROUND

Description of the condition

Autism spectrum disorder (ASD) is characterised by persistent deficits in social communication and social interaction across multiple contexts, as well as restricted repetitive patterns of behaviour, interests, or activities (DSM-5 2013). There are currently five diagnostic criteria used by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5 2013), for the diagnosis of ASD, including 1) persistent deficits in social communication and social interaction across multiple contexts; 2) restricted, repetitive patterns of behaviour, interests, or activities; 3) presentation of symptoms in the early developmental period; 4) symptoms that cause clinically significant impairment in important areas of current functioning; and 5) disturbances that are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay (DSM-5 2013).

Thirty years ago, research suggested that ASD was a rare categorical disorder with a prevalence of 4 in 10,000 (Baron-Cohen 2008); more recent prevalence studies show it to be a common condition with a prevalence of approximately 1% of the population across most countries (Arora 2018; Cleaton 2018; Elsabbagh 2012; Ritchie 2020). However, prevalence varies between countries, with higher rates in high-income countries such as the USA and UK, estimated to be 1% to 3%, whereas rates in lower-income countries are 0.5% or less (Cleaton 2018; Ritchie 2020).

Some have attributed this rise to a true increase in the problems seen in ASD. Others have disputed this, attributing the rise to factors such as earlier diagnosis, broadening of diagnostic criteria (May 2020; Tantam 2012) and changes in diagnostic attribution (May 2017; Turowetz 2015). The prevalence of ASD in men is reported to exceed that in women, although the exact ratio may be impossible to specify; a recent review reported an overall male to female ratio of 3:1 (Loomes 2017).

The lower prevalence of ASD in lower-income countries has been attributed to a relative lack of epidemiological studies in low-income countries (Matos 2022), and multiple factors including community awareness, cost and capacity of health and other services, information seeking, and socio-demographic factors (Zeidan 2022). In addition, some have suggested that due to financial restraints, low-income countries often use their own or other criteria compared to more widely-used criteria such as the DSM-5 2013 to diagnose ASD (Peiris 2022). Because various ASD criteria and diagnostic tools are being used, this may explain the lack of consistency particularly between low-income and high-income countries.

The authors of this review are aware that a substantial proportion of the autistic community prefer to describe themselves as autistic, an autistic person, or on the spectrum, rather than person with autism or ASD (Autism Spectrum Australia 2023; Autistic Self Advocacy Network 2023; National Autistic Society 2023). However, preferences vary and throughout this review the authors will be using standard notation of 'person with ASD'.

Behaviours of concern

The terms 'challenging behaviour' (Emerson 1995), and 'behaviours that challenge' (NICE 2015), are widely used in the literature to describe behaviours such as irritability, aggression, and self-injury. However, many behaviours seen as being challenging and framed as inherent to the person with autism could be better understood as legitimate responses to difficult environments and situations (Ramcharan 2009). 'Challenging behaviours', therefore, have also been described as reactive and responsive behaviours, distressed behaviours, expressions of unmet need, and in Australia, behaviours of concern. Throughout this review we use the term 'behaviours of concern', because it is a term that is increasingly being used internationally.

Irritability is an ambiguous term that is often not well-defined. Irritability is defined by the DSM-5 2013 as "persistent anger, a tendency to respond to events with angry outbursts or blaming others, an exaggerated sense of frustration over minor matters". Other emotions and behaviours such as anger and aggression are often associated with irritability, however, they are usually consequences of irritability rather than a trait of irritability (Benarous 2019; Toohey 2017).

In addition to the core symptoms, people with ASD may exhibit behaviours of concern. These can include behaviours such as agitation, aggression, self-injury, destruction to property, disruptive behaviour, sexual misconduct, or arson (NICE 2015; Sheehan 2015). Neurodevelopmental disorders included in the DSM-5 such as attention deficit hyperactivity disorder (ADHD), ASD, intellectual disability, specific learning disorders, or impairments in social interaction, communication, or movement are associated with behaviours of concern (Cleaton 2018; DSM-5 2013), with increasing severity of disability associated with an increased likelihood, frequency, and severity of behaviours of concern (Emerson 2001; Matson 2009; McTiernan 2011).

The reported prevalence of behaviours of concern varies. It is estimated that between 5% and 15% of people with ASD develop behaviours of concern (NICE 2015), with a higher prevalence of greater than 25% reported in children (Hill 2014; Kanne 2011; Soke 2016). Prevalence tends to also be higher in particular circumstances such as in hospitals, amongst teenagers, people in their early twenties, men and boys, people with comorbid psychiatric diagnoses (NICE 2015), and people with dual diagnoses of intellectual disability and ASD (Fitzpatrick 2016; Kanne 2011; Tyrer 2006).

There appears to be a high co-occurrence of other neurodevelopmental disorders with ASD, such as attention deficit hyperactivity disorder (ADHD; DSM-5 2013). People with co-occurring ASD and ADHD may have a higher incidence of behaviours of concern, which is not surprising given that such behaviours are reported in both disorders (Craig 2015; Ringer 2020). Furthermore, there is also co-occurrence of mental health disorders with ASD, notably anxiety and depression (Hollocks 2019; Koritsas 2015; Lord 2018). Approximately 40% of children and 27% of adults with ASD are reported to also have at least one anxiety disorder (Hollocks 2019; Van Steensel 2011). Over 20% of adults with ASD are reported to have a current diagnosis of depression (Van Steensel 2011). When there are co-occurring diagnoses, medications such as stimulants, anxiolytics or antidepressants may be prescribed to treat the co-occurring condition.

The presence of behaviours of concern add complexity to living with and supporting people with ASD. Not only can this result in families and informal carers experiencing high levels of stress, they can also

create barriers to adult independence and community involvement (Smith 2014).

Description of the intervention

Interventions that target core symptoms of ASD or co-occurring difficulties can be associated with positive outcomes in areas such as cognitive functioning, language skills, social behaviours, and reduction of behaviours of concern (Seida 2009; Weitlauf 2014).

For individuals with ASD, environmental modifications, non-pharmacological interventions (such as educational interventions and behavioural and psychological therapies) and pharmacological interventions (medication and other biological therapies) are commonly suggested treatments and can help reduce behaviours of concern such as irritability, aggression and self-injury (Perez 2012; Posey 2001; Sengupta 2017).

This review will focus solely on pharmacological interventions that are used to target irritability, aggression or self-injury in people with ASD. The major drug classes of interest were typical and atypical antipsychotics, ADHD-related medications, anticonvulsants, anti-dementia medications, antidepressants, antiparkinsonian medications, anxiolytics, neurohormones, and a number of drugs that did not fall into any of these classes and that we grouped under an 'experimental' category. These drug classes were based on the major classes listed in the review protocol (Livingstone 2015), as well as additional pharmacological classes identified from the search results (see Appendix 1 for search strategy).

Antipsychotics

Antipsychotics are medications that treat disorganised thinking and poor awareness of reality. The use of antipsychotics has also been associated with reduced irritability, social withdrawal, hyperactivity, and stereotypical behaviours in young people with ASD (Jesner 2007). First-generation or 'typical antipsychotics' such as haloperidol were first used in the 1950s to treat people with schizophrenia. Second-generation or 'atypical antipsychotics' such as aripiprazole and risperidone were introduced in the 1980s because of their reduced risk of long-term and irreversible adverse effects (AEs) when compared to typical antipsychotics. Antipsychotic medications are psychotropic agents frequently prescribed for people with ASD (Coury 2012; Howes 2018; Loy 2017; Madden 2017; Murray 2014; Rasmussen 2019), often in the absence of a diagnosed mental disorder (Cvejic 2018; Deb 2009; Deb 2015; Sheehan 2015). Large-scale studies have shown that around 5% to 15% of people with ASD are prescribed antipsychotics (Coury 2012; Howes 2018; Lake 2017; Murray 2014; Rasmussen 2019). Antipsychotics are commonly prescribed for hyperactivity, aggression, and other behaviours of concern (Dinnissen 2020; Henderson 2020), and antipsychotic prescribing is more prevalent amongst people with autism and/or intellectual disability compared to the general population (Glover 2015; Henderson 2020).

Although antipsychotics are not recommended for the treatment of core symptoms of ASD (Howes 2018), there is increasing evidence that antipsychotics decrease behaviours of concern in people with ASD (Howes 2018; Jesner 2007). Since publication of the protocol for this review (Livingstone 2015), seven systematic reviews reporting the effectiveness of antipsychotics on behaviours of concern in people with autism, predominantly children and adolescents, have been published (D'Alò 2021; Fallah 2019; Fung 2016; Hirsch 2016; Maneeton 2018a; Maneeton 2018b; Mano-Sousa 2021). Although results were mixed, the majority of evidence for the effectiveness of antipsychotic medications in reducing behaviours of concern was reported for the atypical antipsychotics, aripiprazole and risperidone.

There is some concern regarding the long-term health outcomes of antipsychotic use, such as significant weight gain (Alvarez-Jiménez 2008; Bak 2014; Lake 2017), increased risk of diabetes mellitus (Holt 2019), increased prevalence of cardiovascular disease such as stroke and heart attack (Zivkovic 2019), and increased risk of all-cause mortality (Simon 2015; Trifirò 2009). The National Institute for Health and Care Excellence (NICE) Guidelines recommend that antipsychotic medications should only be considered if behaviours of concern have not been reduced by psychological or other interventions, treatment for any co-existing psychiatric disorders and the person or others are at severe risk of harm (NICE 2015). Other guidelines recommend that antipsychotics are only a short-term option (up to 8 weeks) if non-pharmacological interventions did not reduce the behaviours of concern. Effectiveness should be reviewed after three or four weeks on the drugs before continuing (SIGN 2016), and only one drug should be trialled at any one time to determine its effectiveness (Deb 2009).

ADHD-related medications

ADHD-related medications are often prescribed to people with ASD who exhibit behaviours of concern, at least in part due to some similarities between ASD and ADHD such as hyperactivity, inattention and social or communication deficits, or both (Cortese 2012; Hanson 2013; Mikami 2019; Rosello 2018), as well as the high comorbidity rates of ADHD amongst people with ASD (Antshel 2013; Sokolova 2017). In the past, stimulant medications have been prescribed to people with ASD who show behaviours of concern and have hyperactivity (Cortese 2012; Hanson 2013; Mikami 2019; Rosello 2018). Since 2013, when a dual diagnosis of ADHD and ASD was permitted, a high prevalence of co-occurring ASD and ADHD has been reported (Antshel 2013; Sokolova 2017). Stimulants such as methylphenidate are the most commonly prescribed psychotropic medications for people with ASD aged six years and older, with prescribing rates up to 34% reported in large multinational studies (Houghton 2017; Hsia 2014; Murray 2014), and 17% in an Australian study (Rasmussen 2019).

Stimulants and non-stimulants have also been reported to reduce symptoms of irritability and aggression in people with ASD (Banas 2020; Handen 2008; Ming 2008), and are some of the most prescribed psychotropics for people with ASD (Madden 2017). Stimulants such as methylphenidate, have also been recommended as adjuncts to behavioural interventions for hyperactivity in children or young people with co-occurring ASD and ADHD (SIGN 2016). However, a narrative synthesis by Ghanizadeh 2019 concluded there was inadequate evidence to support or refute the effect of methylphenidate on irritability, while a Cochrane Review found no evidence that rates of treatment-emergent irritability were different in children and adolescents with ASD taking methylphenidate (Sturman 2017).

Anticonvulsants

Anticonvulsants are primarily used to reduce seizures (Wassenaar 2013; Wlodarczyk 2012). Seizures associated with epilepsy are caused by abnormal and asynchronous firing of neurons (nerve

cells) which usually end abruptly (DeLorenzo 2005; Geiger 2011; Kusmaker 2018; Proix 2018). Most anticonvulsants such as carbamazepine, phenobarbital and valproate block voltage-gated sodium channels to reduce the firing of neurons (Verrotti 2010). Some anticonvulsants such as levetiracetam, topiramate or valproate also have a role in the release or modulation of the inhibitory neurotransmitter GABA (Cortes-Altamirano 2016), decreasing the speed and firing of neurons. Some anticonvulsants are also used as mood stabilisers, for example, divalproex sodium, primarily in bipolar illness. Use of these medications has also been associated with reduction in affective instability, impulsivity and aggression in ASD (Hollander 2001).

In a systematic review of anticonvulsants for psychiatric disorders in children and adolescents, two trials of valproate and one of levetiracetam found no effect on aggression; however, an additional trial reported a decrease of irritability and aggression in the valproate group (Davico 2018). There was no difference in aggression in the remaining trial of participants with ASD, which compared to placebo. In another review of GABA modulators in autism by Brondino 2016, there was no difference in aggression and irritability in one study that evaluated valproate, while the other found valproate reduced irritability. Similarly, in the systematic review of the pharmacologic treatment of severe irritability and aggression in 2- to 17-year-olds with ASD by Fung 2016, one of the two small trials comparing valproate to placebo found it reduced the Aberrant Behaviour Checklist Irritability subscale (ABC-I; Aman 1985) scores, with no apparent effect in the other.

Antidementia medications

Antidementia medications include cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists, which are primarily used to treat individuals with Alzheimer's dementia. Previous studies have shown that the cholinesterase inhibitor donepezil, has been associated with changes in aberrant behaviours of children with ASD (Chez 2003). Research also indicates that the NMDA receptor antagonist, memantine, could improve social behaviour, self-stimulatory behaviours (Chez 2004), and irritability (Erickson 2007), in people with ASD.

Antidepressants

Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, are used to treat symptoms of depression, anxiety, and obsessionality and are commonly prescribed for people with ASD (Coury 2012; Howes 2018; Murray 2014); often in the absence of a diagnosed mental disorder (Cvejic 2018; Sheehan 2015; Tsouris 2013). Large-scale studies involving people with ASD have found that antidepressants are prescribed at similar rates to antipsychotics and stimulants, and often concurrently (up to 40%) with antipsychotics (Branford 2019; Cvejic 2018; Esbensen 2009). In addition, the use of antidepressants amongst people with ASD in large-scale studies is approximately eight times higher than in people without ASD (Madden 2017). However, there is no clear evidence of the effectiveness of antidepressants in reducing behaviours of concern in people with ASD (Branford 2019; Hurwitz 2012; Johnco 2015; Williams 2013).

Two Cochrane Reviews evaluated the effects of these two major classes of antidepressants on ASD. In one Cochrane Review of SSRIs for ASD (Williams 2013), there was limited evidence that citalopram reduced irritability but no evidence that fenfluramine and fluoxetine had an effect. In a Cochrane Review of tricyclic antidepressants for ASD in children and adolescents, there was no evidence that clomipramine and tianeptine improved irritability relative to placebo (Hurwitz 2012); however, the three included trials were very small. In an additional systematic review of antidepressant and antianxiety medications for people with ASD (Deb 2021), there was no evidence that citalopram, clomipramine, venlafaxine or fluoxetine decreased behaviours of concern, but one of two trials of fluvoxamine showed reduced aggression.

Antiparkinsonian medications

Antiparkinsonian medications are primarily used to treat individuals who have Parkinson's disease and Alzheimer's dementia. Some antiparkinsonian medications, such as amantadine, have been studied for the treatment of people with ASD to address symptoms of irritability and aggression. A double-blind, placebo-controlled trial of children with ASD aged 5 to 19 years found that symptoms of irritability and aggression were reduced in those receiving amantadine as the active medication (King 2001). Other studies have reported that they may improve language function, social behaviour, and self-stimulatory behaviours of some people with ASD (Chez 2004). A smaller improvement in irritability symptoms has also been reported (Erickson 2007). In a systematic review of pharmacologic treatment in 2- to 17-year-olds with ASD (Fung 2016), there was no evidence that amantadine decreased ABC-I scores in the one small identified placebo-controlled trial.

Anxiolytics

As anxiety is associated with behaviours of concern (Johnco 2015; Nadeau 2011; NICE 2015), anxiolytics may be effective in reducing behaviours of concern in people with ASD and anxiety (Bitsika 2016; Johnco 2015). Anxiolytics such as buspirone are commonly used to treat generalised anxiety disorder (Schmitt 2005). Compared to benzodiazepines, buspirone has a reduced risk of dependency, abuse and sedation, and so is sometimes considered a safer option for long-term management of anxiety disorders, particularly amongst the young or elderly populations (Crocco 2017; Schmitt 2005). Buspirone is also considered a treatment for older adults or children with aggression, irritability, or agitation (Aronson 2016; Howland 2015), and as such, may be effective in reducing behaviours of concern in people with ASD. In the systematic review by Deb 2021, one of two parallel trials of buspirone showed a decrease in irritability.

Neurohormones

Neurohormones are hormones produced by nerve cells and secreted into the circulation with varying mechanisms of action and sites of origin. Two neurohormones have been investigated in ASD, namely oxytocin and secretin. Secretin has been suggested as potentially beneficial in the management of ASD and related behaviours of concern (McQueen 2002; Tanaka 2018). However, in an earlier Cochrane Review of intravenous secretin compared to placebo treatment in children or adults diagnosed with ASD, there was no effect of secretin in any of the three studies that reported irritability (Williams 2012).

Experimental

Effects have previously been reported for a range of medications that do not fall into any of the previously mentioned categories. A systematic review of trials of GABA modulators in autism evaluated

acamprosate, arbaclofen, bumetanide, carnosine, flumazenil, riluzole and valproate (Brondino 2016). However, there was insufficient evidence to suggest that any of these medications were effective in people with autism (Brondino 2016). In a review of the drug riluzole, which also appears to regulate glutamate activity (De Boer 2019), two of three studies in children and young adults reported that single and adjunct use of riluzole decreased irritability, although there was no effect in the remaining trial. In a meta-analysis of n-acetylcysteine in ASD (Lee 2021), irritability scores were not different across all four identified studies, though a subgroup study indicated effects in one trial.

How the intervention might work

While each of these medications works differently, broadly speaking, medications may act by reducing co-occurring conditions, like ADHD, anxiety or depression, or will act directly to reduce behaviours of concern. However, there is limited evidence for the effectiveness of these medications at this stage.

Antipsychotics

ASD has been associated with abnormalities in both the dopaminergic system and serotoninergic systems (Nakamura 2010). Dopamine over-activation has also been linked with excessive motor activity and stereotyped behaviours, which are often observed in individuals with ASD (Previc 2007). Altered serotonin levels have been found to lead to changes in several psychological processes, which are also altered in individuals with ASD, including mood, irritability, and aggression (Young 2002). Typical or first-generation antipsychotics exert their action by blocking dopamine receptors. However, atypical (second-generation) antipsychotics also have a range of actions at other neurotransmitter systems, including systems that modulate serotonin and norepinephrine receptors.

Antidepressants

The two major classes of antidepressants prescribed for ASD (SSRIs and tricyclic antidepressants) have differing pharmacological actions. SSRIs exert their effects through increasing the availability of serotonin (Williams 2013), whereas tricyclic antidepressants increase the availability of the neurotransmitters serotonin and noradrenaline (Hurwitz 2012; Shojaie 2020). Altered serotonin levels have been found to lead to changes in several psychological processes, which are also altered in individuals with ASD, including mood, irritability, and aggression (Young 2002; Williams 2013). Antidepressants may be effective in treating some common comorbidities of ASD such as anxiety, depression, and obsessive compulsive disorder, which can in turn reduce behaviours of concern (Williams 2013; Zaboski 2018).

Anticonvulsants

The mechanism by which antiepileptic medications, such as carbamazepine and levetiracetam, could affect irritability and aggression remains unclear. What is known is that gabapentin reduces the excitability of nerve cells in the brain (Guglielmo 2013).

Anticonvulsants such as divalproex sodium are also used as mood stabilisers. It has been suggested that mood stabilisers, such as divalproex sodium, work by enhancing GABA, inhibiting glutamate, acting on serotonin and norepinephrine systems, and via limbic kindling (Hollander 2001).

ADHD-related medications

These include stimulants such as methylphenidate and dexamphetamine that increase dopamine and noradrenaline activity; and non-stimulants such as atomoxetine, clonidine and guanfacine, which primarily increase noradrenaline activity (Osland 2018).

Stimulant (Ghanizadeh 2019; Sturman 2017), and nonstimulant (Banas 2020; Ghanizadeh 2013; Patra 2019), ADHD-related medications have been administered to children with ASD with the aim of improving symptoms. It is thought that any effects on behaviours of concern with ADHD-related medications are likely to be secondary to improvements in attention, concentration and hyperactivity (Banas 2020).

ADHD is often associated with dopaminergic system dysfunction (Froehlich 2013; Huss 2016; Wu 2012). Dopamine plays an important role in planning, motor and motivational processes, which are abnormal in people with ADHD (Marinho 2018; Wu 2012). Stimulants such as amphetamine and methylphenidate are thought to improve symptoms of ADHD by increasing dopamine activity (Wu 2012).

The neurotransmitter, noradrenaline, may also decrease symptoms of ADHD as it has an important role in the prefrontal cortex, an area associated with attention and executive functioning (Patra 2019). Non-stimulants such as atomoxetine, clonidine and guanfacine, which primarily increase noradrenaline activity, are sometimes prescribed as an alternative to stimulant ADHD-related medications.

Atomoxetine is a dopamine and noradrenaline reuptake inhibitor (Froehlich 2013; Janak 2012). The increase in norepinephrine and dopamine in the pre-frontal cortex by atomoxetine is thought to improve ADHD symptoms such as impaired attention and reduced executive function (Patra 2019; Ulke 2019). Clonidine and guanfacine are alpha-2 adrenergic receptor agonists (Giovannitti 2015; Huss 2016), and are thought to improve ADHD symptoms by increasing noradrenergic activity in the prefrontal cortex (Caye 2019; Mechler 2022).

Antidementia medications

As described above, impairments in the dopaminergic system have been associated with behavioural characteristics of several neurodevelopmental disorders, including ASD (DiCarlo 2019). Amantadine is an NMDA receptor antagonist with an indirect dopaminergic agonist role (King 2001; Müller 2012).

The NMDA receptors play an important role in the cellular processes of the brain underlying learning and memory function (Chang 2021; Olivares 2012). NMDA also plays a role in regulating inflammation in the brain (Chang 2021), and it is thought that neuro inflammation is involved in neurological and neuropsychiatric disorders (Ricci 2013). The precise mechanisms by which NMDA receptor antagonists work is not well known, however, it has been found that people with ASD often have abnormally high glutamate and activity levels of NMDA receptors (Rojas 2014). Therefore, it is thought that NMDA receptor antagonists such as memantine may play a role in reducing the core symptoms of ASD.

Antiparkinsonian medications

Cholinergic neurotransmission, including nicotinic acetylcholine receptors, are involved in several functions including attention, memory, learning, social interactions, movement, and anxiety (Park 2022; Vallés 2021). The cholinergic system is thought to play a central role in Alzheimer's disease, particularly the associated cognitive decline (Sabri 2008), and nicotinic acetylcholine receptors are thought to have anti-inflammatory and neuroprotective properties (Park 2022).

According to recent studies, acetylcholine and nicotinic receptor activity may be lower in brain samples of people with ASD. It has been suggested, therefore, that acetylcholinergic enhancement through the use of donepezil hydrochloride — an acetylcholinesterase inhibitor — may improve some behaviours associated with ASD (Chez 2003).

Anxiolytics

People with ASD commonly have elevated levels of blood serotonin (Anderson 1987), however, people with ASD also have an increased risk of alterations to serotonin receptors and synthesis (Veenstra-VanderWeele 2012). Anxiolytics such as buspirone have a strong attraction to serotonin, both presynaptically and postsynaptically (Ceranoglu 2019; Poisbeau 2018), thereby increasing the availability of serotonin. Serotonin plays a role in regulating mood and sleep, and medications that increase serotonin are often prescribed for anxiety due to the anxiolytic effect of serotonin (Żmudzka 2018).

Neurohormones

Oxytocin is produced in the hypothalamus (Wilczyński 2019), with the primary role of promoting lactation, facilitating contractions, and promoting bonding between mother and infant (Andari 2010; Green 2010;Taylor 2018). Oxytocin has been found to be reduced in children with ASD (John 2021; Moerkerke 2021), and oxytocin is thought to have a role in ASD behaviours (Gottschalk 2017; Ooi 2017; Yamasue 2017; Yoon 2020). It has been suggested that increasing oxytocin will reduce ASD behaviours and this could lead to a reduction of behaviours of concern.

Secretin is produced in the gastrointestinal tract and has both digestive and neurological functions (Banko 2011; Welch 2004). Because secretin receptors are also located in areas of the brain associated with emotion and behaviour, such as in the amygdala, which regulates emotions and mood, and in the hippocampus, which is associated with memory formation (Banko 2011; Qi 2020), impairments or irregularities in brain neurohormones may be associated with ASD (Chaddad 2017; Gibbard 2018). Secretin has therefore been suggested as a potential intervention in the management of ASD (Krishnaswami 2011; McQueen 2002; Tanaka 2018).

Why it is important to do this review

To date, there have been five published Cochrane systematic reviews focusing on the use of pharmacological interventions in ASD. A review on risperidone found evidence that the medication may lead to significant improvements in irritability (Jesner 2007). Two reviews on aripiprazole also found evidence of improvements in irritability (Ching 2012; Hirsch 2016). A review of tricyclic antidepressants found small positive effects in children and adolescents with ASD, particularly in reducing irritability, although results were inconsistent (Hurwitz 2012). A review of SSRIs found evidence of improvement in an adult's aggression, but only from studies with a high risk of bias (Williams 2013). To date, no Cochrane Review has focused on any of the remaining pharmacological interventions that can be used to address behaviours of concern in ASD. These previously conducted reviews of single medications or single classes of medications have provided useful information regarding their effectiveness and safety, however, these reviews now require updating. Furthermore, this review includes studies of children and adults with ASD, whereas previous reviews had focused only on either children or adults.

Since the publication of the protocol (Livingstone 2015), 17 systematic reviews have been published. Seven of these were on antipsychotics, three each on anticonvulsants and 'experimental' interventions, and an additional four systematic reviews on antiparkinsonians, anxiolytics, dementia-related medications, and antidepressants respectively. Each of the systematic reviews reported on the effectiveness of only one class of drug.

The extent to which the age of the person receiving the treatment will affect the intervention's efficacy remains unclear. ASD is a lifelong condition, and therefore it is important to understand the effect of interventions, including medication, across the lifespan (Tantam 2012).

OBJECTIVES

To assess the effectiveness and AEs of pharmacological interventions for managing the behaviours of irritability, aggression, and self-injury in ASD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), including cross-over studies, that compare pharmacological interventions to an alternative drug, standard care, placebo, or wait-list control.

Types of participants

Studies were considered eligible for inclusion if they included participants of any age with a clinical diagnosis of ASD, who displayed one or more behaviours of concern at baseline assessment, specifically irritability, aggression and self-injury. People with reported comorbidities were included in the analysis. We will also include studies that identify a subset of people with ASD.

We included studies where participants were diagnosed according to the criteria of the *Diagnostic and Statistical Manual for Mental Disorders (DSM) Fourth* (DSM-IV (DSM-4 1994); or DSM-IV-TR (DSM-4-TR 2000)) and *Fifth* (DSM-5; DSM-5 2013) Editions, or the *International Classification of Diseases, 10th Revision* (ICD-10; ICD-10 2004); and those who had been diagnosed through use of a standardised diagnostic instrument, including the Autism Diagnostic Observation Schedule (ADOS; Lord 2000) or the Autism Diagnostic Interview Revised (ADI-R; Lord 1994).

Types of interventions

Any pharmacological intervention used to manage behaviours of concern in children, adolescents or adults with ASD, specifically irritability, aggression, or self-injury. Interventions may have been given at any dosage, for any duration, and any frequency of administration. Relevant pharmacological interventions included first-generation ('typical') antipsychotics such as haloperidol, second-generation ('atypical') antipsychotics such as risperidone and aripiprazole, ADHD-related medications, anticonvulsants, antidementia medications, antidepressants (including selective SSRIs and tricyclic antidepressants), antiparkinsonian medication, anxiolytics, neurohormones, and a number of other drugs that did not fall into any of these classes that we grouped under an experimental category.

It was possible that additional eligible interventions that review authors were not previously aware of may be identified in the course of the review. When we identified any pharmacological interventions that were not initially included, we considered them as eligible and included them in the review after assessing their comparability with those named above.

Because pharmacological interventions could be used in addition to non-pharmacological therapies, we included any studies in which participants received concurrent non-pharmacological therapies, provided that they were used in all intervention arms.

The interventions of interest for this review focus on the effectiveness and benefits and harms associated with pharmacological agents to address the behaviours of irritability, aggression and self-injury for people with ASD. Interventions with different foci such as sleep interventions were not included in this review.

Types of outcome measures

We classified outcome measures as either primary or secondary outcomes.

Lower scores indicate a more positive response for all outcomes and measures used apart from quality of life, where higher scores indicate an improved quality of life.

Where data were insufficient, we provided a narrative account of the outcomes.

Where feasible, we made comparisons at the following specific follow-up periods:

- short-term follow-up (less than 6 months);
- medium-term follow-up (6 to 12 months); and
- long-term follow-up (over 12 months).

Primary outcomes

Behaviours of concern

Behaviours of concern in ASD, specifically:

- irritability (including outcomes of irritability improvement and irritability relapse as defined by the study authors);
- aggression; and
- self-injury.

These outcomes needed to be measured by standardised instruments such as the 'irritability' subscale of the Aberrant Behaviour Checklist (ABC-I; Aman 1985). Where possible, preference was given to analysing each of these three specific challenging behaviours separately. Where this was not possible, we combined measures across studies to create a composite 'challenging behaviour' outcome. In the event that study authors reported several similar scales, we established a hierarchy of preferred scales/instruments where the ABC-I was the preferred scale. This hierarchy was established through discussion with the full review group.

Adverse effects

AEs (including sedation and weight gain)

Due to the wide range of AE data that we collected during this review, we made a postprotocol decision to categorise available data into the following groups:

- cardiovascular;
- gastrointestinal;
- immune;
- metabolic system;
- musculoskeletal;
- neurological;
- psychological;
- respiratory system;
- skin;
- urinary; and
- other.

Secondary outcomes

Quality of life

Quality of life for both the child and the parents or informal carers or family (as measured by standardised instruments such as the Pediatric Quality of Life Inventory (PedsQL; Varni 1999), or through quality-of-life questionnaires).

Tolerability and acceptability

Tolerability and acceptability of the intervention (as measured by self-reported or clinician-reported adherence to treatment).

Summary of findings tables

We used the following outcomes to populate the summary of findings tables for the main comparison:

- irritability;
- aggression;
- self-injury;
- AEs.

Search methods for identification of studies

We ran searches in 2020 using the search strategies in Appendix 2. We also ran updated searches in 2022, in which we made changes to the original MEDLINE search strategy by adding the MeSH term for neurodevelopmental disorders to the population section, and included more search terms for pharmacological interventions. We adapted the revised MEDLINE search for all databases (Appendix

1), and ran the searches from inception for each source before de-duplicating these with the records retrieved by the previous search.

Electronic searches

We searched all available years of the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2022, Issue 5), in the Cochrane Library. Searched 6 June 2022
- MEDLINE Ovid (1946 to 6 June 2022)
- MEDLINE In-Process and Other Non-indexed Citations Ovid (6 June 2022)
- MEDLINE Epub Ahead of Print Ovid (6 June 2022)
- Embase Ovid (1974 to 6 June 2022)
- CINAHL EBSCOhost (1937 to 6 June 2022)
- APA PsycINFO Ovid (1967 to 6 June 2022)
- ERIC EBSCOhost (1966 to 6 June 2022)
- Epistemonikos (www.epistemonikos.org/en/). Searched 6 June 2022
- Sociological Abstracts Proquest, 1952 to 6 June 2022
- Science Citation Index (SCI) Web of Science Clarivate (1970 to 6 June 2022)
- Conference Proceedings Citation Index – Science (CPCI-S) Web of Science Clarivate (1990 to 6 June 2022)
- *Cochrane Database of Systematic Reviews* (CDSR; 2020, Issue 11), in the Cochrane Library. Searched 6 June 2022
- Database of Abstracts of Reviews of Effects (DARE), in the Centre for Reviews and Dissemination (CRD) databases. Searched 6 June 2022
- LILACS (lilacs.bvsalud.org/en/). Searched 6 June 2022
- AutismData (autism.org.uk/autismdata). Not available 6 June 2022
- ClinicalTrials.gov (clinicaltrials.gov/). Searched 6 June 2022
- World Health Organization (WHO) International Clinical Trials Registry Platform (isrctn.com/). Searched 6 June 2022

We used search filters for RCTs where appropriate. We did not apply any language or date restrictions. We did not restrict by publication status, and we sought translation of documents where necessary.

Searching other resources

We scanned bibliographies of included and excluded studies for possible additional references of interest.

We contacted relevant pharmaceutical companies, authors, and key scholars to identify any additional ongoing or missed studies.

Data collection and analysis

The protocol of this review planned to conduct a network meta-analysis on the available data. After assessing the plausibility of the transitivity assumption, we decided that a network meta-analysis would not be appropriate with the available data.

This was due to the variation across studies in participants, interventions and comparators, that did not allow scope for linking nodes to produce a network for a network meta-analysis. It was felt that the heterogeneity would have led to issues with transitivity that would have rendered the network unstable.

Network meta-analyses may still be performed in future updates if more appropriate data become available. In the following sections, we have only reported the methods that were used in this version of the review. For unused methods, please refer to the published protocol for this review (Livingstone 2015), and Appendix 3.

Selection of studies

Two of the four review authors (DG, MI, MJ, NL) independently selected and assessed every study at abstract and title level and then full-text level to determine whether they met the inclusion criteria for this review. We resolved any disagreements between the authors through discussion with the full review group. The selection process is presented in two PRISMA diagrams (Figure 1; Figure 2; Moher 2009).

Figure 1. Original search November 2020

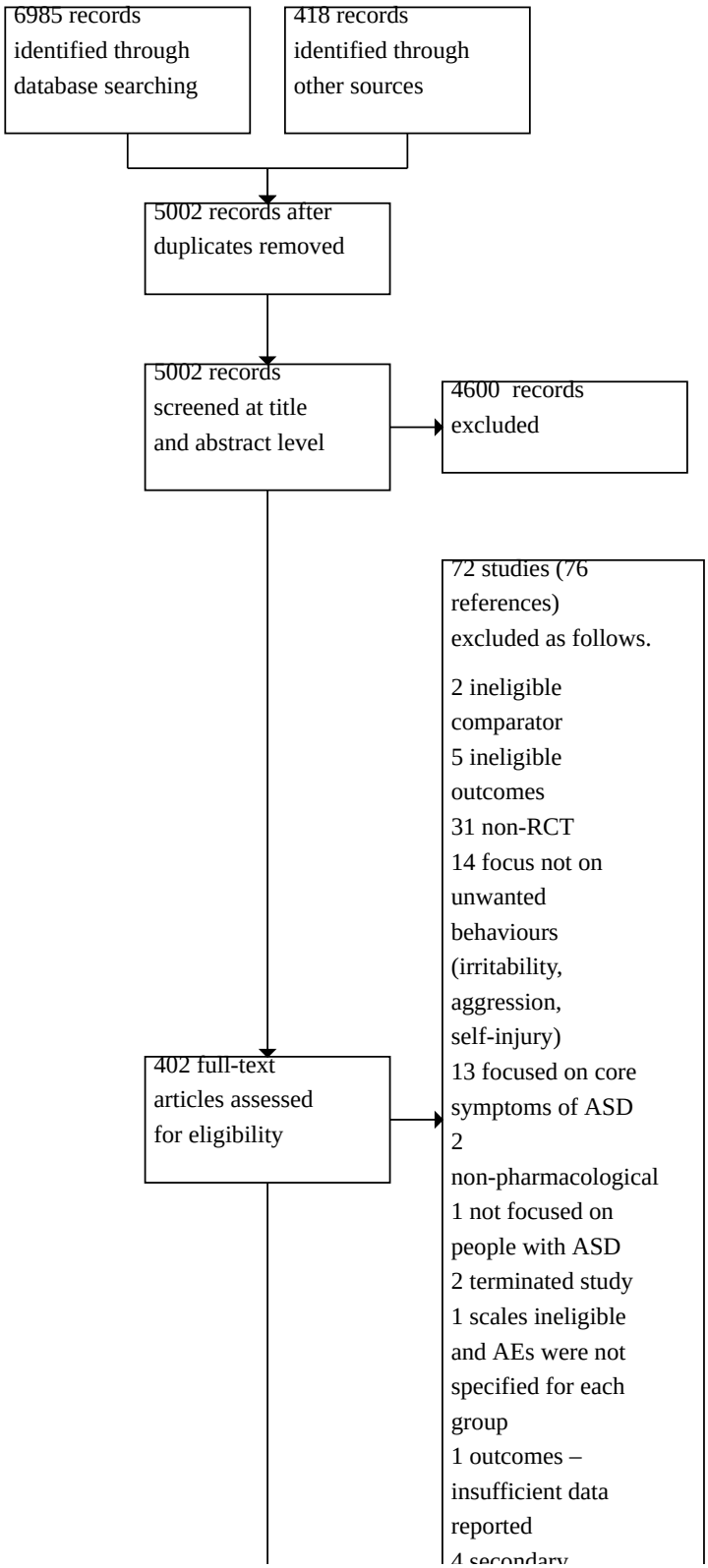


Figure 1. (Continued)

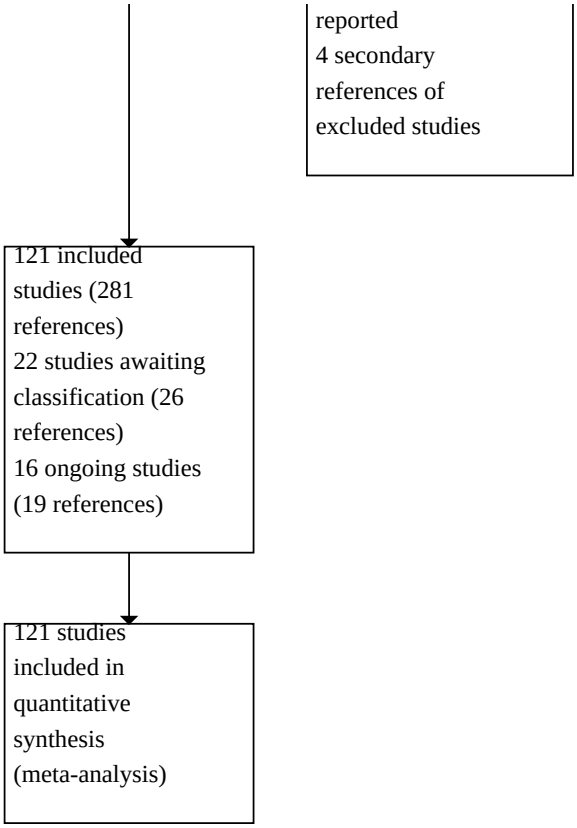


Figure 2. Search update June 2022

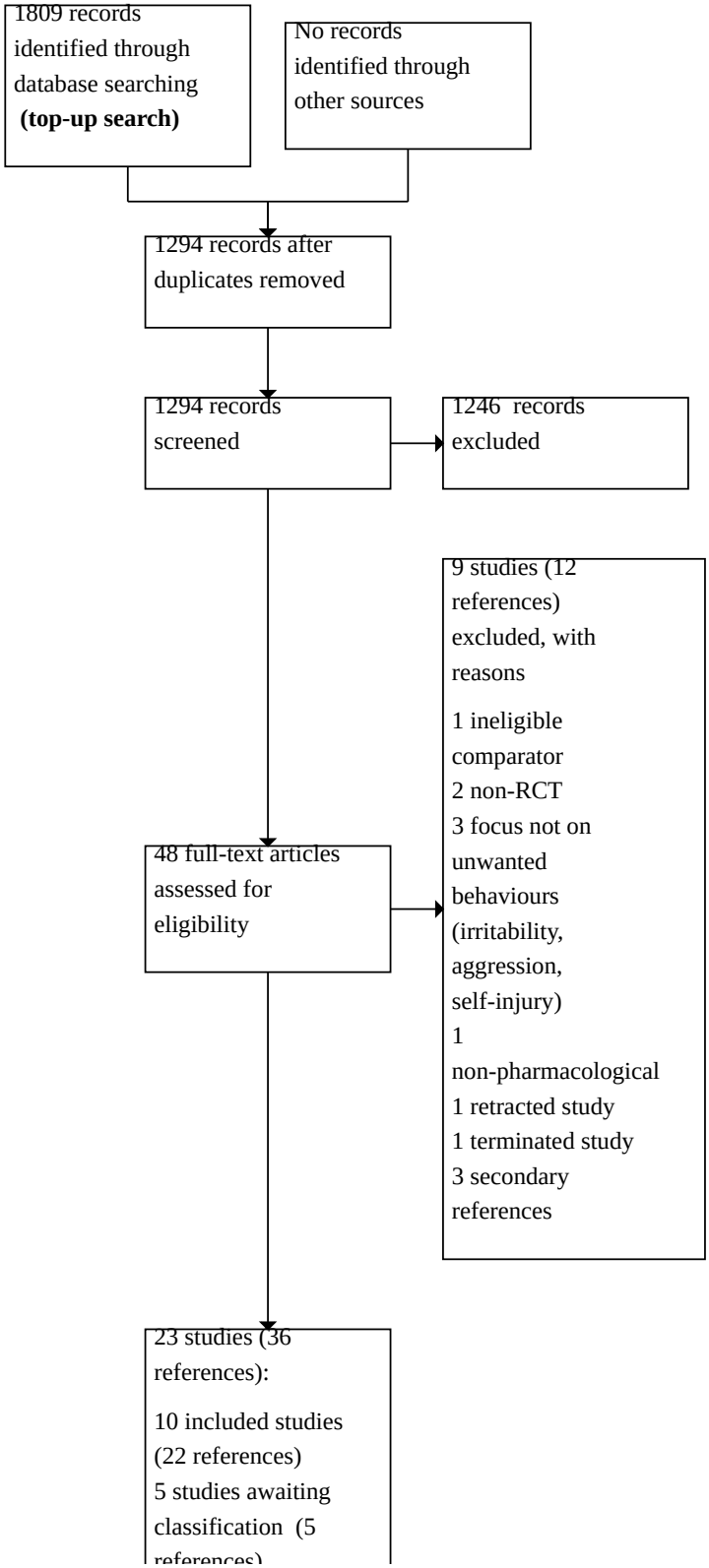
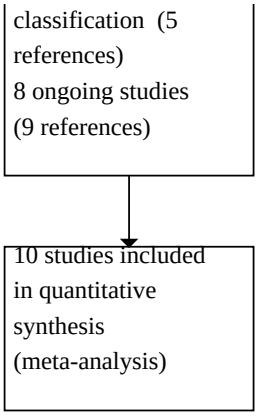


Figure 2. (Continued)



Data extraction and management

Two review authors (DG, MI, MJ, NL) extracted data independently and entered them into a piloted data extraction form. We resolved any disagreements between the review authors through discussion with the full review group. We extracted the following data.

Outcome data

From each included study, we extracted relevant details on all primary and secondary outcome measures used, as defined by the review authors; and length of follow-up and summary data, including means, standard deviations, confidence intervals and significance levels for continuous data, and proportions for dichotomous data. We extracted arm-level data.

Data on potential effect modifiers

From each included study, we extracted data on the following study, participant, intervention, and comparison characteristics that may have acted as effect modifiers.

- Study characteristics (study design, study duration, details of attrition, and risk of bias concerns)
- Participant characteristics (number randomised, age of participants, specific diagnosis, comorbidities, gender distribution, geographical location of study)
- Intervention characteristics (type of antidepressant or antipsychotic, dose, duration, frequency, age medication began, concurrent interventions)
- Comparison characteristics (form, frequency, and duration of 'standard care')

Other data

From each included study, we extracted data on the following additional information.

- Study author(s), year of publication, citation, and contact details
- Sources of funding and other potential commercial interests

Assessment of risk of bias in included studies

Two of the four review authors (DG, MI, MJ, NL) independently assessed the seven risk of bias domains for each study and assigned each domain to one of the following categories as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

- high risk of bias;
- low risk of bias; or
- unclear or unknown risk of bias.

When determining quality of evidence, the overall risk of bias of each trial was assessed independently by two of the review authors and then agreed by consensus or referral to a third review author. Assessments of risk of bias for each study were based on the following criteria as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

- Sequence generation (was the allocation sequence adequately generated?)
- Allocation concealment (was allocation adequately concealed?)
- Blinding of participants and personnel (was knowledge of the allocated intervention adequately prevented during the study?)
- Blinding of outcome assessors (was knowledge of the allocated intervention adequately prevented during the study?)
- Incomplete outcome data (were incomplete outcome data adequately addressed?)
- Selective outcome reporting (are reports of the study free of suggestion of selective outcome reporting?)
- Other sources of bias (was the study apparently free of other problems that could put it at a high risk of bias?)

We resolved any disagreements between the review authors through discussion with the full review group. We reached overall risk of bias judgements by considering the results from each relevant risk of bias domain for the outcome being considered.

Measures of treatment effect

Continuous data

We calculated standardised mean differences (SMDs) with 95% confidence intervals (CIs) for continuous outcome data (e.g. scores on standardised measures). We used Cohen's standards for interpreting effect sizes (small = 0.2, medium = 0.5, large = 0.8 (Cohen 1988)).

Dichotomous data

We estimated the pairwise relative treatment effects of the competing interventions by calculating effect sizes as odds ratios (ORs) with 95% CIs for dichotomous outcome data (e.g. adherence).

Unit of analysis issues

Cross-over trials

We included cross-over trials, in which all participants receive both the control and intervention treatment but in a random order. We had aimed only to use data reported during the first phase of the study, up to the point of the first cross-over, to avoid any carry-over effect from the first to second phase. However, the majority of studies did not differentiate data from first and second phases. Therefore, where first phase data were not reported in cross-over studies, we included reported data from the study but undertook a sensitivity analysis to identify whether inclusion of these data had a differential effect on meta-analytic estimates.

Multiple treatment groups

If two or more eligible intervention groups were compared to a single eligible control group, we split the sample size for the shared comparator group to prevent the same comparator participants being included twice. We clearly documented decisions made during this process in the review.

Dealing with missing data

We contacted the original investigators to request missing data. If we could not obtain the data, we made assumptions about whether the data appeared to be 'missing at random' or 'not missing at random' and followed the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a).

Data that are not missing at random are likely to be missing for reasons related to the outcomes of the missing data. For example, if a participant agrees to take part in a trial but is unhappy with the outcome of allocation, fails to adhere to the medication or experiences AEs as a result of the medication, then they may be unwilling to complete any follow-up assessments. In such a situation, where dichotomous data are missing, we imputed data on the assumption that the participants experienced the less favourable outcome (e.g. 'participant did not adhere to the treatment').

When studies provided insufficient information regarding the exact number missing from each group, data imputation was not possible, in which case we analysed only the available data. Where continuous data were missing, we analysed only the available data.

Where studies had missing summary data, such as missing standard deviations, we derived these where possible using calculations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a).

We specified the methods used to address any missing data in the Characteristics of included studies tables. If imputation was not possible, we outlined the reasons for this in the text.

Assessment of heterogeneity

We examined clinical heterogeneity within each pairwise comparison by inspecting each included study for variability in the participants, interventions or outcomes described. We examined methodological heterogeneity within each pairwise comparison by inspecting each included study for variability in the study design and risk of bias. We discussed in full any unexpected variability that arose. In pairwise analyses, we assessed statistically the presence of heterogeneity within each pairwise comparison using the Chi^2 statistic and its P value (Deeks 2022), and the I^2 statistic (Higgins 2003), and its 95% CI.

Assessment of reporting biases

We assessed publication bias and other reporting biases by visually inspecting the funnel plots of analyses with more than 10 trials and performing trim and fill analyses.

Data synthesis

We performed standard pairwise meta-analyses on the results when data from at least two included studies were available for any treatment comparison. Due to expected heterogeneity amongst the included studies, we performed a random-effects meta-analysis using an inverse variance weighting method (Chi^2 P value 0.05 or less) using Review Manager (RevMan) Web software (RevMan Web 2021). We used an inverse-variance approach to meta-analysis in order to increase the certainty of the pooled effect estimate, as larger studies with smaller standard errors are weighted more heavily than smaller studies with larger standard errors (Deeks 2022). When pooling the data was inappropriate, we provided a narrative description of the individual study results.

Subgroup analysis and investigation of heterogeneity

We conducted the following subgroup analyses for comparisons with a sufficient number of studies that provided specific details:

- the differential effects of interventions by the age at which the drug was first administered; for example, infant/toddler (birth to six years of age) versus school age (6 to 12 years of age) versus adolescent (12 to 18 years of age), versus adult (18 years of age and over);
- the differential effects of interventions by communication ability; for example, low communication ability versus high communication ability;
- the differential effects of interventions by cognitive ability; for example, low cognitive ability versus high cognitive ability;
- the differential effects of interventions by the gender of the participant; for example, male versus female.

Because most studies did not specify the ages of children, the subgroup analyses we conducted were children (up to 17 years of age) compared to children and adults, and adult-only samples.

We also undertook subgroup analyses that were not planned in the protocol. This was because we wanted to identify whether there were differences within subclasses of each pharmacological class that had differing mechanisms of action, that is, each of the atypical antipsychotics that have differing mechanisms of action, stimulant versus non-stimulant ADHD-related medications, SSRI versus dibenzoxazepine antidepressants, different neurohormones, and between each of the different experimental drugs.

Sensitivity analysis

In the protocol (Livingstone 2015), we stated our aim to perform sensitivity analyses to assess whether the findings of this review were robust to the following:

- reanalysis excluding studies according to study quality issues, including those with low sample size, high risk of bias, or high attrition;
- reanalysis without imputing data for the missing participants;
- reanalysis using a fixed-effect model.

In addition, as the majority of cross-over studies did not differentiate data from first and second phases, we aimed to undertake sensitivity analyses to identify whether inclusion of these data had a differential effect on meta-analytic estimates.

We used the primary outcome irritability for the comparisons where there were significant differences between intervention and placebo groups.

We were only able to undertake sensitivity analyses on the comparisons of antipsychotics versus placebo, and neurohormone versus placebo as there were inadequate data for other comparisons. We were unable to do sensitivity analyses for cross-over studies in atypical antipsychotics as there were no cross-over studies included in those comparisons. Also, we did not use imputed data, therefore we undertook sensitivity analysis excluding studies at:

- high risk of attrition bias;
- high risk of other bias; and
- with a sample size less than 50.

Summary of findings and assessment of the certainty of the evidence

We created summary of findings tables using the system developed by the GRADE Working Group (Schünemann 2013).

We used GRADEpro GDT to import data from RevMan Web to create summary of findings tables for the main comparisons and outcomes indicated under 'Types of outcome measures' (RevMan Web 2021).

Three review authors (NL, MI, DG) independently assessed the certainty of the evidence using GRADE. We resolved any disagreements through discussion.

For information regarding the GRADE approach, and factors that influence the assessment, see chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022).

The main comparisons in this review as judged by clinical experts and for which we created summary of findings tables were as follows.

- Atypical antipsychotics versus placebo
- Neurohormones versus placebo
- ADHD-related drugs versus placebo
- Antidepressants versus placebo

We used the following outcomes to populate the summary of findings tables for the main comparisons.

- Irritability (short-term)
- Aggression (short-term)
- Self-injury (short-term)
- AEs (metabolic, musculoskeletal, neurological, and psychological; short-term)

During the course of this review, many different types of AEs were found to be reported by the included studies. To make the summary of findings tables more readable and useful, the clinical content experts on the review team were asked to prioritise the list of available AEs, to decide which should be presented in the summary of findings tables. The clinical experts were blinded to the type or availability of evidence available for each type of AE when they made this decision, to ensure their choice was based on clinical importance and not data availability. As a result of this prioritisation exercise, the decision was made to present a narrative summary of the most important AEs in the four most clinically important categories of AEs - metabolic, musculoskeletal, neurological, and psychological.

RESULTS

Description of studies

For more information please see Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification; and Characteristics of ongoing studies.

Results of the search

An electronic search conducted in November 2020 yielded 7403 possible references. This was reduced to 5002 possible references once duplicates were removed. These 5002 references were screened at the title and abstract level; 4600 were irrelevant, and we excluded them for reasons such as they were not RCTs, they used an ineligible study design, were reviews, involved an irrelevant population or were non-pharmacological interventions. This left 402 full-text articles (376 studies) to screen, after which we excluded 76 references (as 72 studies), leaving 326 references: 281 references (121 studies) included in the analysis; 26 references (22 studies) awaiting classification; and 19 references (16 studies) for ongoing studies (Figure 1).

A top-up electronic search was conducted in June 2022, which yielded 1809 possible references. This was reduced to 1294 possible references once duplicates were removed. After initial screening, this was reduced to 48 full-text records that needed screening, after which we excluded 12 references (9 studies), leaving 36 references (as 23 studies). These were 10 included studies, five studies 'awaiting classification', eight 'ongoing studies' and 13 secondary references of these studies. See Figure 2 for a flow diagram of the search process.

We also contacted a number of study authors to request further information. See Table 2 for information about the studies and contact person.

Included studies

We have included 131 studies (291 reports and 149 datasets) involving 7014 participants in this review. We identified 25 studies as awaiting classification (see Studies awaiting classification) and 25 ongoing studies (see Ongoing studies). All included studies

compared a pharmacological intervention to a placebo or to another pharmacological intervention.

The number of participants in each study ranged from 8 to 321 and most studies involved children, although some studies involved children and adults and some only adults; 53 studies involved only children under 13 years, 37 studies involved children and adolescents, two involved adolescents only, 16 involved children and adults, and 23 involved only adults.

Antipsychotics by comparison

Atypical or typical antipsychotics versus placebo or alternative medication class

Twenty-four studies (59 reports, 1225 participants, 29 datasets) compared an atypical or typical antipsychotic to a placebo or other treatment (see Table 3 for further information). The number of participants ranged from nine (Dollfus 1992), to 128 (Loebel 2016), with an average age of 10.4 years. Apart from three studies that included a total of 44 adults (Mace 2001; McDougle 1998; Remington 2001), all participants were children (< 18 years). All the studies were short-term (less than 6 months) and ranged from 34 days (Mace 2001), to 16 weeks (Findling 2014), although the average duration was between eight and 10 weeks. All trials were parallel RCTs apart from Dollfus 1992 and Remington 2001, which were cross-over studies.

- Interventions: 16 studies compared an atypical antipsychotic to a placebo, two studies compared one atypical antipsychotic to another atypical antipsychotic, two studies compared a typical antipsychotic to a placebo, and two studies compared an atypical antipsychotic to a typical antipsychotic. A further two studies compared an atypical antipsychotic to an anti-dementia drug and an atypical antipsychotic to an antiparkinsonian drug, respectively. Further information can be found in Table 3.
- Setting: most (17) of the studies were conducted in the USA apart from Ghanizadeh 2014; and Nikvarz 2017, which were conducted in Iran, Ichikawa 2017 and NCT01624675 in Japan, Miral 2008 in Turkey, Remington 2001 in Canada, and Dollfus 1992 in France.
- Inclusion criteria: all studies required a clinical diagnosis of ASD and some studies (DeVane 2019; Ichikawa 2017; Marcus 2009; McCracken 2002), also required co-occurring behaviours of concern such as aggression, agitation, irritability, or self-injury to be assessed at baseline.
- Exclusion criteria: all studies excluded people with other DSM diagnoses or neurological disorders including schizophrenia, pervasive developmental disorder not otherwise specified (PDD-NOS), Rett syndrome, psychosis, unstable seizure disorders, or other significant cardiac, renal or endocrine disorders. Some studies also excluded people who had previously been treated with the intervention or interventions of interest.
- Participant intellectual ability: the intellectual ability of participants varied between trials, with some trials not providing specific details (DeVane 2019; Kent 2013). Most studies required participants to have a mental age of at least 18 months. Some studies included up to 83% of participants with an intellectual disability of varying severity (Ichikawa 2017; Malone 2001; McCracken 2002; Shea 2004).
- Concomitant medications: most studies required participants to cease taking all psychotropic medications before commencing in the trial except for Findling 2014, which allowed the use of sleep medications, Troost 2005, which allowed stimulant use for co-occurring ADHD, and Research Units 2005 and Hollander 2006b, both of which allowed anticonvulsants for participants with stable epilepsy.

Interventions

- Amisulpride: one study compared amisulpride to an antiparkinsonian (bromocriptine; Dollfus 1992). Further details are provided below.
- Aripiprazole: eight studies compared aripiprazole to a placebo or another atypical antipsychotic. Most studies administered the doses once daily in either a fixed or flexibly-dosed manner to a maximum of 15 mg/day. The mean daily dose of aripiprazole was between 0.172 mg/day and 0.354 mg/kg/day.
- Lurasidone: one study compared lurasidone to a placebo (Loebel 2016). Participants received either 20 mg or 60 mg once daily.
- Olanzapine: two studies compared olanzapine to a placebo (Hollander 2006b), or a typical antipsychotic (Malone 2001). Participants who weighed less than 40 kg received a maximum of 2.5 mg of olanzapine once daily, and children 40 kg or heavier received a maximum of 5 mg of olanzapine once daily (Hollander 2006b). Malone 2001 administered olanzapine at 2.5 mg every second day for children who weighed 40 kg or less, and 2.5 mg once daily for children 41 kg and above with a maximum daily dose of 5 mg.
- Risperidone: a total of 10 studies compared risperidone to a placebo or other treatment. Nine studies compared risperidone to a placebo, one study (Nikvarz 2017), compared risperidone to an antidementia medication, and one study compared risperidone to haloperidol (Miral 2008). Apart from the two discontinuation studies that required the intervention to be administered twice daily, doses were administered once daily. Mean daily dosage of risperidone for children who weighed less than 40 kg was 1.58 mg/day, 2.27 mg/day for children 40 kg or heavier, and 3.25 mg/day for adults.
- Haloperidol: two studies (Mace 2001; Remington 2001), compared haloperidol (a typical antipsychotic) to a placebo. Both studies administered haloperidol two to three times daily, however, Remington 2001 used fixed doses (mean daily dose of 1.3 mg) while Mace 2001 initiated haloperidol at 0.25 mg/day for children who weighed 40 kg or less, and 0.5 mg/day for children who weighed 40 kg or more up to a maximum of 5 mg/day (mean daily dose 1.4 mg).

Comparator

- Placebo: the majority of antipsychotic studies compared to a placebo, however, apart from NCT00468130, which used sugar pills, the study authors did not provide details regarding the ingredients of the placebo.
- Haloperidol: two studies (Malone 2001; Miral 2008), compared an atypical antipsychotic (olanzapine and risperidone respectively) to haloperidol. Mean dose of haloperidol was 1.4 mg/day to 2.6 mg/day. Haloperidol was given up to twice daily.
- Bromocriptine: one study (Dollfus 1992), compared amisulpride to bromocriptine. Bromocriptine was administered at 0.15 mg/kg/day to 0.20 mg/kg/day for all participants.

Primary outcomes

- Irritability: 16 of the studies reported irritability; the majority used the ABC-I subscale (Aman 1985). The exceptions were McDougle 1998 and Miral 2008, which both used the Ritvo Freeman Real Life Rating Scale (RFRLRS; Freeman 1986), to report irritability.
- Improvement and relapse: amongst those taking risperidone (Kent 2013; McCracken 2002), or aripiprazole (Marcus 2009; Owen 2009), improvement was defined as a minimum of 25% improvement in ABC-I (Kent 2013), in addition to a rating of much improved or very much improved on the Clinician Global Impression-Irritability (CGI-I) scale (Marcus 2009; McCracken 2002; Owen 2009). The two discontinuation studies (Research Units 2005; Troost 2005), reported relapse, defined as a minimum increase of 25% in ABC-I scores during the discontinuation phase.
- Aggression: one study (Shea 2004), reported aggression using the Nisonger Child Behavior Rating Form (conduct problem subscale; Aman 1996).
- Self-injury: three studies reported self-injurious behaviour. One study (McDougle 1998), used the Self-Injurious Behaviour Questionnaire (SIB-Q; Gualtieri 2002), to measure self-injurious behaviour, Shea 2004 used the Nisonger Child Behaviour Rating Form (Self-injurious/ stereotypic subscale; Aman 1996), and Mace 2001 used their own scale to rate self-injurious behaviour (self-injurious behaviour per hour).
- AEs: apart from three studies (Mace 2001; Research Units 2005; Troost 2005), all studies reported AEs. AEs were analysed and reported based on major categories including cardiovascular, metabolic, gastrointestinal, immune system, neurological, psychological, respiratory, skin, and urinary AEs. We could not include data from three studies in the analysis (Malone 2001; Marcus 2009; Owen 2009). Further details can be found in Effects of interventions.

Secondary outcomes

- Quality of life: three trials comparing aripiprazole to a placebo reported quality-of-life outcomes (Findling 2014; Marcus 2009; Owen 2009). Each study used the Pediatric Quality of Life Inventory (PedsQL; Varni 2001).
- Tolerability and acceptability (loss to follow-up): 231 participants withdrew from studies involving an atypical antipsychotic versus a placebo and were not included in the relevant study analyses. Reasons for withdrawing included lack of efficacy (75), AEs (44), withdrew consent (32), other/ not specified (18), lost to follow-up (14), noncompliance (6), increased behaviours of concern or exacerbation of medical condition (5), missed visits (4), and physician decision (3).

Neurohormones versus placebo or other treatment

Twenty-four studies (46 reports, 1640 participants, 27 datasets) compared a neurohormone to a placebo. Seven studies involved adult participants only (Anagnostou 2012; Bernaerts 2020; Jacob 2022; NCT01337687; NCT02940574; Squassante 2018; Yamasue 2020), one study involved adolescents and adults (15 to 45 years; Munesue 2016), one study involved children three to eight years of age (Le 2022), one study involved adolescents (12 to 18 years; Guastella 2015a), and fourteen studies involved only children (< 18 years). Fifteen studies were parallel trials and nine were cross-over studies. Study duration ranged from four weeks to 24 weeks (Hollander 2020b; Jacob 2022; Sikich 2021). All but nine studies were conducted in the USA. The other studies were conducted in Australia, Belgium, China, two in Canada, the Netherlands, and three in Japan (Guastella 2015a; Bernaerts 2020; Le 2022; NCT01908205; NCT02940574; Buitelaar 1990; Munesue 2016; Takamitsu 2015a; Yamasue 2020) respectively.

- Interventions
  - Adrenocorticotrophic hormone: one study involving 14 participants compared adrenocorticotrophic hormone to a placebo (Buitelaar 1990). Doses of either adrenocorticotrophic hormone or placebo were fixed (20 mg/ day).
  - Balovaptan (RG7314): three studies involving 657 adult participants compared balovaptan to a placebo (Hollander 2020b; Jacob 2022; Squassante 2018). Doses were either 1.5 mg, 4 mg or 10 mg once daily of balovaptan in capsule form.
  - Oxytocin: 13 studies involving 709 participants compared oxytocin to a placebo. All but four studies required participants to take 12 IU of oxytocin twice daily (total of 24 IU daily). Munesue 2016 had a maximum of 8 IU of oxytocin twice daily, Guastella 2015a and Sikich 2013 had varying levels of oxytocin based on age (Guastella 2015a 18 IU twice daily for children < 16 years, and 24 IU twice daily for participants 16 to 18 years; Sikich 2013 administered up to 24 IU for children 3 to 10 years and a maximum of 32 IU for children 11 to 17 years), NCT01908205 involved 0.4 IU/kg taken twice daily up to a maximum of 24 IU per dose.
  - Secretin: five studies involving 211 participants compared secretin to a placebo. All studies were either single-dose (Carey 2002; Levy 2003; Owley 2001; Unis 2002), or two doses separated by two months (Handen 2005). All studies used 2 IU/kg per infusion.
  - Vasopressin: two studies (Parker 2019; Umbricht 2017), involving 67 participants compared vasopressin to a placebo. Parker 2019 was a four-week parallel study with vasopressin doses ranging from 4 IU to a maximum of 12 IU twice daily for children up to 12.9 years of age, and maximum of 16 IU twice daily for children over 12.9 years of age. Umbricht 2017 was a 20-mg single-dose cross-over study involving male adults.
- Comparators: all studies compared a neurohormone to a placebo. Apart from four studies that used saline solution (Anagnostou 2012; Carey 2002; NCT01337687; Owley 2001), the ingredients of placebo were not outlined.
- Inclusion criteria: all studies required a clinical diagnosis of ASD, Asperger's, or PDD-NOS to participate in the trial. Six studies also required a CGI severity score (Schopler 2009), above 4, four studies restricted participation to male participants only (Bernaerts 2020; Squassante 2018; Takamitsu 2015a; Yamasue 2020), four studies required participants to have an IQ above 70 (Munesue 2016; Sikich 2013; Squassante 2018; Yamasue 2020), and some required participants to either be on stable concomitant medication (Anagnostou 2012; Munesue 2016; Owley 2001; Sikich 2013), or not to have trialled the intervention previously (Carey 2002).
- Exclusion criteria: most studies excluded people with a clinical diagnosis of psychosis, other mental disorders, or significant neurological or other medical conditions. Additional exclusion criteria included previous use of the intervention (Parker 2017; Parker 2019; Unis 2002), or use of psychotropic or other prohibited medications in the period before and during the trial.

- Setting: apart from one study conducted in Australia (Guastella 2015a), two in Belgium (Bernaerts 2020; NCT02940574), one in Canada (NCT01908205), one in China (Le 2022), one in the Netherlands (Buitelaar 1990), and three in Japan (Munesue 2016; Takamitsu 2015a; Yamasue 2020), all studies were conducted in the USA. Studies were conducted at either outpatient clinics, hospitals or clinics and research centres associated with universities.
- Concomitant medications: six studies provided details of concomitant medications. Bernaerts 2020 reported that 27% and 11% of those in the intervention and placebo groups respectively were taking psychostimulants concomitantly, as well as other medications including antidepressants, risperidone and aripiprazole. Guastella 2015a reported that approximately 35% of participants in both groups were taking other psychotropic medications. Levy 2003 reported that 10 participants out of 62 were taking one concurrent medication, including guanfacine, methylphenidate, fluoxetine (Prozac), and risperidone, and one participant was taking both guanfacine and Prozac concurrently. Squassante 2018 reported that antipsychotics were being taken concurrently by 15% to 28% of participants and concurrent stimulant use by 13% to 26% of participants. Parker 2017 reported concomitant medication use of up to 17% and included SSRIs, benzodiazepines, stimulants, anticonvulsants, and guanfacine, and Yamasue 2020 reported antidepressants, antipsychotics, anticonvulsants or hypnotics were being taken concurrently by 12 participants.
- Participant cognitive status: reported IQ varied greatly between studies and ranged from 35 to 120.
- Length of follow-up: study duration ranged from four weeks to 12 weeks (Squassante 2018), although Guastella 2015a reported three-month follow-up data for primary and secondary outcomes.

Primary outcomes

- Irritability: 10 of the studies reported irritability. All but one study used the ABC-I scale (Aman 1985), whereas Levy 2003 used the Ritvo-Freeman Real Life Rating Scale (affectual responses subscale; Freeman 1986) to measure irritability. Umbricht 2017 reported baseline ABC-I (Aman 1985) but did not report endpoint data.
- Self-injury: Guastella 2015a reported self-injurious behaviour using the Repetitive Behaviour Scale - Revised (self-injurious subscale) (Bodfish 2000).
- AEs: 14 studies reported AEs, although Levy 2003 did not report AEs for both groups and therefore, the AE data from Levy 2003 could not be included.

Secondary outcomes

- Quality of life: five studies (Anagnostou 2012; Bernaerts 2020; NCT01908205; Parker 2019; Takamitsu 2015a), reported quality of life. Anagnostou 2012, Bernaerts 2020 and Takamitsu 2015a used the WHO Quality of Life scale (WHOQoL; WHO 1998) and NCT01908205 and Parker 2019 used the Pediatric Quality of Life (PedQL) inventory (parent-rated; Varni 2001).
- Tolerability and acceptability (loss to follow-up): 67 participants (7.6%) withdrew and were not included in the relevant study analyses. Reasons included withdrawing consent (26), loss to follow-up (12), AEs (12), other (5), poor/non-compliance (3), protocol violation (3), worsening of behaviours of concern (2), physician decision (1), and an administrative error (1).

ADHD-related medications versus placebo or other treatment

Thirteen studies (28 reports, 482 participants, 18 datasets) compared an ADHD-related medication to a placebo or other intervention. All studies included children (< 18 years) with study duration ranging from two weeks (Quintana 1995), to 11 weeks (NCT03242772); the mean was 5.5 weeks. Seven of the studies were cross-overs and six were parallel (Eslamzadeh 2018; Handen 2015; Harfterkamp 2014;NCT03242772; NCT00498173; Scahill 2015).

- Interventions
  - Amphetamine: one study involving 18 participants compared amphetamine to a placebo (NCT03242772). Amphetamine was initiated at 3.1 mg once daily for 11 weeks and titrated upwards if tolerated.
  - Atomoxetine: five studies involving 274 participants compared atomoxetine to a placebo (Arnold 2006; Eslamzadeh 2018; Handen 2015; Harfterkamp 2014; NCT00498173). Atomoxetine commenced at 0.3 mg/kg/day to 0.5 mg/kg/day up to a maximum of 1.8 mg/kg/day. Mean final doses were 1.2 mg/kg/day administered once daily (Harfterkamp 2014), 1.2 mg/kg/day twice daily (Eslamzadeh 2018), and 1.38 mg/kg/day administered twice daily (Handen 2015).
  - Clonidine: two studies (17 participants) compared clonidine to a placebo. Fankhauser 1992 administered clonidine via a weekly transdermal patch (approx 0.005 mg/kg/day) and Jaselskis 1992 administered 0.15 mg/kg/day to 0.20 mg/kg/day across three doses per day.
  - Guanfacine: two studies (73 participants) compared guanfacine to a placebo. The maximum daily dose of guanfacine was 3.0 mg/day across three daily doses (mean daily dose 2.68 mg/day; Handen 2008) or a maximum of 3 mg/day for children less than 25 kg and maximum 4 mg/day for children 25 kg or more (Scahill 2015).
  - Methylphenidate: three studies (7 datasets, 100 participants) compared methylphenidate to a placebo. Methylphenidate was administered two to three times daily using fixed doses. All studies were cross-over studies: Posey 2005 administered three different doses (3 datasets) based on bodyweight (0.125 mg/kg/day, 0.250 mg/kg/day, 0.500 mg/kg/day); Quintana 1995 administered a mean methylphenidate dose of 0.397 mg/kg/day; and Pearson 2013 had mean doses of 0.21 mg/kg, 0.35 mg/kg and 0.48 mg/kg for low, medium and high doses respectively.
- Comparators: all studies compared an ADHD-related medication to a placebo. Only one study (Handen 2015), provided details of the placebo (sugar pill).
- Inclusion criteria: all studies required participants to meet the DSM criteria for ASD, Asperger's or PDD-NOS. Other criteria included a minimum mental age of 24 months, and symptoms of hyperactivity or impulsiveness for at least six months.
- Exclusion criteria: prior exposure to ADHD-related medication in the past two years, adverse reaction to the intervention, concurrent psychotropic medication use, other significant neurological, psychiatric, or medical conditions that may require medical management

- Setting: apart from two trials that were conducted in Iran and the Netherlands respectively (Eslamzadeh 2018; Harfterkamp 2014), all studies were conducted in the USA, with participants recruited from either outpatient clinics or clinics and research centres associated with universities.
- Concomitant medications: all studies required participants to be free of all psychotropic medications for up to one month prior to starting the study apart from Pearson 2013, which allowed stable (> 3 months) medications to be continued during the trial.
- Participant cognitive status: the reported IQ ranged from severe intellectual disability to over 90.
- Length of follow-up: study duration was between one week (Pearson 2013), and 10 weeks (Handen 2015).

Primary outcomes

- Irritability - all studies apart from Eslamzadeh 2018 and NCT03242772 reported irritability. All studies apart from one used the ABC-I (Aman 1985), however, Posey 2005 did not report endpoint ABC-I scores. Fankhauser 1992 used the Ritvo-Freeman Real Life Rating Scale (Freeman 1986).
- Self-injury - only one study (Arnold 2006), reported self-injurious behaviour using the Repetitive Behaviour Scale - Revised (self-injury subscale; Bodfish 2000).
- AEs - nine of the studies reported AEs.

Secondary outcomes

- Tolerability and acceptability (loss to follow-up)

Antidepressants versus placebo or other treatment

Ten studies (22 reports, 662 participants, 10 datasets) compared an antidepressant to a placebo or another intervention. An additional study (Remington 2001) compared clomipramine to a placebo, however, those numbers have already been included in a previous comparison. Three studies involved children only (< 12 years), four studies included children and adolescents (< 18 years), two studies included children, adolescent and adult participants (Gordon 1993; Remington 2001), and two studies included only adult participants (Hollander 2012; McDougle 1996). Seven studies were parallel and four were cross-over studies (Gordon 1993; Hollander 2005; Niederhofer 2003; Remington 2001). Study duration ranged from five weeks (Gordon 1993) to 12 months (NCT00183339).

- Interventions
  - Citalopram: one study involving 149 participants compared citalopram to a placebo (King 2009). Maximum citalopram was 20 mg/day (mean maximum dose was 16.5 mg/day (+/-6.5 mg)).
  - Clomipramine: two studies compared clomipramine to a placebo. Remington 2001 (48 participants) commenced clomipramine at 25 mg once daily and increased incrementally up to 50 mg twice daily. Gordon 1993 (12 participants) commenced clomipramine at 25 mg/day up to a maximum of 5 mg/kg/day or maximum of 250 mg/day. The participants involved with Remington 2001 had previously been counted, so only the 12 participants from Gordon 1993 are included in the official count.
  - Fluoxetine: five studies involving 401 participants compared fluoxetine to a placebo (Herscu 2020; Hollander 2005; Hollander 2012; Mouti 2014; NCT00183339). Four of the studies involved only children (Herscu 2020; Hollander 2005; Mouti 2014; NCT00183339). They initiated fluoxetine at 2.0 mg/day to 8.0 mg/day depending on weight up to a maximum of 0.8 mg/kg/day (mean final dose 9.9 mg/day; Hollander 2005), a maximum of 20 mg/day and 30 mg/day for children under 40 kg and 40 kg and above (Mouti 2014; NCT00183339), or a maximum of 18 mg/day (mean final dose 11.8 mg ± 6.5; Herscu 2020). Hollander 2012, which involved adults, followed fixed doses of fluoxetine starting with 10 mg/day up to a maximum of 80 mg/day (mean final dose 64.76 mg/day). Most studies required participants to take fluoxetine once daily.
  - Fluvoxamine: one study involving 30 participants compared fluvoxamine to a placebo (McDougle 1996). Fluvoxamine was initiated at 50 mg once daily, increasing to a maximum of 300 mg/day if tolerated.
  - Sertraline: one study involving 58 participants compared sertraline to a placebo (Hagerman 2018). Sertraline was administered using fixed doses of 2.5 mg/day for children under four years of age, and 5.0 mg/day for children four years and over.
  - Tianeptine: one study involving 12 participants compared tianeptine to a placebo (Niederhofer 2003). Fixed doses of 37.5 mg/day were administered.
- Comparators: all studies compared an antidepressant to a placebo. Details of placebo ingredients were not provided except for McDougle 1996, which described placebo as "lactose in identical-looking tablets".
- Inclusion criteria: all studies required participants to meet the DSM criteria for ASD, Asperger's or PDD-NOS. Other criteria included being free of psychotropic medications for up to six weeks prior to the study (Hollander 2012; Niederhofer 2003; Remington 2001), and free of significant medical conditions (Niederhofer 2003).
- Exclusion criteria: three studies excluded people with other DSM diagnoses or significant medical conditions including schizophrenia, hypersensitivity to or previous use of the intervention (Herscu 2020; Hollander 2005; Hollander 2012), three studies excluded people for concurrent use of psychotropic medications (Herscu 2020; Mouti 2014; Remington 2001), and two studies excluded people for positive serum pregnancy test results (McDougle 1996; Mouti 2014).
- Setting: all studies were conducted in the USA apart from Mouti 2014 and Niederhofer 2003, which were conducted in Australia and Italy respectively. Participants were recruited from academic medical centres, tertiary hospitals, or research centres associated with universities.
- Concomitant medications: three studies reported that some participants were taking medications such as anticonvulsants and stimulants concurrently (Hagerman 2018; Mouti 2014; Remington 2001), however, most studies did not permit concurrent medication use apart from sleep or antiparkinsonian medications (King 2009; Remington 2001).
- Participant cognitive status: three of the studies reported that participants had an IQ of over 70, two studies reported that either all or some participants had an IQ of under 70 (Niederhofer 2003; Mouti 2014), one study included only adults who had an average IQ of over 100 (McDougle 1996), and the other four studies did not report cognitive status.
- Length of follow-up: ranged from seven weeks (Remington 2001), to 12 months (NCT00183339).

Primary outcomes

- Irritability: all the studies reported irritability using the ABC-I subscale (Aman 1985), except McDougle 1996.
- Aggression: McDougle 1996 was the only study that reported aggression. The Brown Aggression Scale was used to measure aggression (Brown 1979).
- Self-injury: two studies (King 2009; Mouti 2014), reported self-injurious behaviour using the Repetitive Behaviour Scale-Revised (Bodfish 2000).
- AEs: all the studies reported AEs.

Secondary outcomes

- Tolerability and acceptability (loss to follow-up): 159 participants (23.08%) withdrew and were not included in the relevant study analyses. Reasons included withdrew consent (66), loss to follow-up (23), lack of efficacy (5), AEs (38), other/reason unknown (16), non-compliance (3), protocol violation (3), clinician decision (4), and no longer met study criteria (1).

Atypical antipsychotic versus another atypical antipsychotic

Two studies involving 110 participants compared risperidone to aripiprazole (DeVane 2019; Ghanizadeh 2014). Participants were all children (< 18 years). The mean age was 9.6 and 9.5 years for aripiprazole and risperidone respectively. Both studies were parallel RCTs and were 10 weeks (DeVane 2019) and eight weeks (Ghanizadeh 2014) in duration.

- Interventions
  - Risperidone: both studies used twice-daily doses based on bodyweight. DeVane 2019 required participants who weighed 20 kg to 44 kg to take a maximum of 2.5 mg/day, and children 45 kg or more were allowed a maximum of 3 mg/day. Ghanizadeh 2014 required children up to 39 kg to take a maximum of 2 mg/day of risperidone, and children 40 kg and above a maximum of 3 mg/day (mean dose 1.12 mg/day).
  - Aripiprazole: Ghanizadeh 2014 allowed a maximum of 10 mg/day for children who weighed under 40 kg, and 15 mg/day for children who weighed 40 kg or more (mean dose 5.5 mg/day). DeVane 2019 allowed a maximum of 15 mg/day of aripiprazole regardless of weight.
- Inclusion criteria: both studies required a clinical diagnosis of ASD and DeVane 2019 required participants to have an ABC-I (Aman 1985), subscale score of > 18 at baseline, a CGI Severity score of 4 or greater (Guy 1976), and a mental age of at least 18 months.
- Exclusion criteria: participants with a history of or current unstable medical conditions, prior use of risperidone or aripiprazole for more than two weeks within the last three years, medical conditions that may increase the risk of AEs including liver, renal or cardiovascular conditions, psychiatric disorders that are currently managed by psychotropic medications, or seizures within the past six months
- Setting: DeVane 2019 was conducted in the USA whilst Ghanizadeh 2014 was conducted in Iran. All participants were recruited from either outpatient clinics, or clinics and research centres associated with universities.
- Concomitant medications: one study (Ghanizadeh 2014), required participants to be off aripiprazole and risperidone for at least two weeks prior to and during the study, although other concomitant medications were allowed during the trial provided they were stable and commenced at least two weeks prior to the trial, while DeVane 2019 did not explicitly state medication requirements except that participants could not have taken either intervention for longer than two weeks in the last three years (DeVane 2019).
- Participant cognitive status: neither study reported the cognitive status of participants.
- Length of follow-up: DeVane 2019 and Ghanizadeh 2014 were 10 and 8 weeks in duration respectively. Neither study followed up after the endpoint.

Primary outcomes

- Irritability: both studies reported irritability using the ABC-I subscale (Aman 1985). The baseline ABC-I scores of all participants were above 20.
- AEs: both studies reported AEs.

Secondary outcomes

- Tolerability and acceptability (loss to follow-up): 16 participants (14.5%) withdrew from their respective interventions and were not included in the relevant study analyses. Reasons for withdrawing from the risperidone groups included AEs (9), missed visits (4), increased behaviours of concern or exacerbation of medical condition (2), or physician decision (1).

Atypical antipsychotic versus an antidementia drug

One, eight-week, parallel study involving 34 participants compared risperidone to memantine (Nikvarz 2017). Participants were all under 18 years (mean 6.7 years).

- Interventions: once-daily doses of risperidone commenced at 0.02 mg/kg/day, increasing to a maximum of 0.08 mg/kg/day or 3 mg/day. Memantine was administered in once-daily doses of 20 mg if tolerated (mean daily dose of 0.4 mg/kg/day).
- Inclusion criteria: participants were 5 to 17 years of age with a clinical diagnosis of ASD and had not received any pharmacological treatments for ASD or the treatments had been ineffective.
- Exclusion criteria: people with a neurological disorder except for controlled epilepsy (defined as experiencing no seizures for at least one month prior to the study), history of substance abuse, any other significant medical conditions including cardiac, liver or kidney failure, pregnant or breastfeeding, previous allergic reactions to either risperidone or memantine, and currently taking stimulants.
- Setting: an outpatient child and adolescent clinic associated with a university in Iran
- Concomitant medications: details were not provided.
- Participant cognitive status: details were not provided.

Primary outcomes

- Irritability: irritability was reported using the ABC-I subscale (Aman 1985). The baseline ABC-I scores of all participants were above 20.
- AEs: AEs were not reported fully for both groups apart from somnolence, which we included in the analyses.

Secondary outcomes

- Tolerability and acceptability (loss to follow-up): four participants (11.76%) withdrew and were not included in the relevant study analyses. Reasons included changing psychiatrist (1) and lack of efficacy (3).

Atypical antipsychotic versus an antiparkinsonian drug (bromocriptine)

One study involving nine participants compared amisulpride to bromocriptine (Dollfus 1992). The four-week cross-over study was conducted in France and involved children aged between 4 and 13 years of age.

- Intervention (amisulpride plus placebo): amisulpride was administered at 1.5 mg/kg/day over a four-week period with a six-week washout period between the two phases.
- Comparator (bromocriptine plus placebo): bromocriptine was administered at 0.15 mg/kg/day to 0.20 mg/kg/day plus placebo over a four-week period with a six-week washout period between the two phases.
- Inclusion criteria: children aged 4 to 13 years with a clinical diagnosis of ASD, and a Childhood Autism Rating Scale (Schopler 2009), score of at least 36 indicating 'severely autistic'.
- Exclusion criteria: no neuroleptic or other psychotropic medications were allowed during the trial, except for benzodiazepine, niaprazine, or hydroxyzine for severe sleep disorders.
- Concomitant medications: three out of nine children were taking other permitted medications during the trial, including one child who was taking three different medications.

Outcomes

- AEs was the only relevant outcome reported in this study.

Anticonvulsants versus placebo or other treatment

Six studies (12 reports, 165 participants, 6 datasets) compared an anticonvulsant to a placebo. All participants were children (< 18 years) apart from one adult in Hollander 2006a. All trials were parallel studies, with study duration ranging from eight to 18 weeks (Belsito 2001), (mean 10 weeks) and apart from one study (Rezaei 2010 (Iran)) all trials were conducted in the USA.

- Interventions
  - Divalproex sodium: two trials involving 40 participants compared divalproex sodium to a placebo. Hollander 2010 commenced divalproex sodium at 125 mg/day once to twice daily for children up to 40 kg, and a maximum of 250 mg/day for children over 40 kg. Hollander 2006a increased divalproex sodium from 125 mg/day to a maximum of 30 mg/kg/day (mean final dose 822.92 mg/kg/day).
  - Lamotrigine: one study involving 35 participants compared lamotrigine to a placebo. Lamotrigine commenced at 0.5 mg/kg twice daily up to a maximum of 5.0 mg/kg twice daily (Belsito 2001).
  - Levetiracetam: one study involving 20 participants compared levetiracetam to a placebo. Wasserman 2006 commenced levetiracetam at 125 mg/day up to a maximum of 20 mg/kg/day to 30 mg/kg/day (mean maximum dose 862.50 mg/day).
  - Topiramate: one study involving 40 participants compared risperidone plus topiramate to risperidone plus placebo (Rezaei 2010). The analysis for this study is topiramate versus placebo. The maximum dose of topiramate was 100 mg/day for children under 30 kg or three to six years of age, and maximum of 200 mg/day for children 30 kg or more, or 7 to 12 years of age.
  - Valproate: one study involving 30 participants compared valproate to a placebo (Hellings 2005). The maximum valproate dose was 20 mg/kg/day.
- Comparators: all studies compared an anticonvulsant to a placebo. Further details regarding placebo ingredients were not provided.
- Inclusion criteria: all studies required participants to have a clinical diagnosis of ASD, Asperger's or PDD-NOS, be free of other medications for at least two weeks prior to the study, and six of the studies required significant overactivity or inattention or a dual diagnosis of ADHD and ASD.
- Exclusion criteria: most studies excluded people with unstable seizure disorders or other significant medical conditions including past or present psychotic disorders, and the concomitant use of psychotropic medications during the study.
- Setting: apart from Rezaei 2010, all studies were conducted in the USA at either outpatient clinics, hospitals or clinics and research centres associated with universities. Rezaei 2010 was conducted at a hospital associated with a university in Iran.
- Concomitant medications: all but two studies did not allow the use of psychoactive medications during the study. Handen 2008 had eight participants who were taking a range of psychotropic medications, including methylphenidate, risperidone, and anticonvulsants. Handen 2015 allowed the use of a single anticonvulsant for seizure disorders provided that seizures were stable, and the participant had been seizure-free for at least six months.
- Participant cognitive status: five of the studies reported IQ, all of which had a mean IQ of less than 90.
- Length of follow-up: length of follow-up ranged from eight to 18 weeks (mean 10 weeks).

Primary outcomes

- Irritability: all studies apart from one (Hollander 2006a), reported irritability. All studies used the ABC-I subscale to measure irritability, however, Wasserman 2006 only reports baseline ABC-I data.
- Aggression: one study (Hellings 2005), reports aggression. The Overt Aggression Scale (parent-rated; Yudofsky 2003), was used to measure aggression.
- AEs: all six studies reported AEs.

Secondary outcomes

- Tolerability and acceptability (loss to follow-up): 21 participants (12.73%) withdrew and were not included in the relevant study analyses. Reasons included withdrawing consent (9), difficulty administering the medication (1); increased behavioural difficulties (4); increased symptoms associated with ASD (3); lack of efficacy (2); seizures (1); and skin rash (1).

Antidementia interventions versus placebo or other treatments

Eight studies (641 participants, 17 reports, 9 datasets) compared an antidementia intervention to a placebo or other treatment. Four studies compared memantine to a placebo, one study compared

piracetam, one galantamine, and one compared donepezil to a placebo. All studies were parallel trials, were either 10 or 12 weeks in duration, and involved children (< 18 years). Four studies were conducted in the USA (Aman 2017; Handen 2011; NCT01972074; Soorya 2021), one study was conducted in multiple countries (Hardan 2019), and the other three were conducted in Iran. Most studies included children up to twelve years of age only, apart from Handen 2011 and NCT01972074, which involved children up to 17 years of age.

- Interventions
  - Memantine: five studies involving 527 participants compared memantine to a placebo (Aman 2017; Ghaleiha 2013a; Hardan 2019; NCT01972074; Soorya 2021). All studies administered memantine once daily apart from NCT01972074, which involved twice-daily doses. Two studies had maximum memantine doses of 15 mg/day (Ghaleiha 2013a; Hardan 2019), Aman 2017 administered 3 mg/day to 18 mg/day, depending on bodyweight, and children in NCT01972074 received a maximum of 20 mg/day.
  - Piracetam: one study involving 40 participants compared piracetam to a placebo (Akhondzadeh 2008). Piracetam was administered up to 800 mg/day in addition to 2 mg/day of risperidone for children up to 40 kg, and 3 mg/day for children 41 kg and above.
  - Galantamine: one study involving 40 participants compared galantamine to a placebo (Ghaleiha 2014). Galantamine was administered up to 12 mg/day for children up to 19 kg, 16 mg/day for children 20 kg to 30 kg, 20 mg/day for children 31 kg to 40 kg, and 24 mg/day for children over 40 kg. Risperidone was also administered up to 1 mg/day for children less than 20 kg, and 2 mg/day for children 20 kg and above.
  - Donepezil: one study involving 34 participants compared donepezil to a placebo (Handen 2011). The trial involved 5 mg/day of donepezil for four weeks and progressed to a maximum of 10 mg/day of donepezil for another four weeks if tolerated.
- Comparators: three studies compared the intervention to a placebo plus risperidone, however, the analysis for these studies only included intervention versus placebo because risperidone was also added to the intervention (Akhondzadeh 2008; Ghaleiha 2013a; Ghaleiha 2014). None of the studies provided details of the placebo.
- Inclusion criteria: all studies required participants to have a clinical diagnosis of ASD based on DSM criteria; two studies specified a minimum ABC-I score of 12 (Ghaleiha 2013a; Ghaleiha 2014), and a maximum ABC-I score of 16 (Hardan 2019). Two studies required either a minimum of 5 on the CGI-Severity scale (NCT01972074), or presentation of severe symptoms related to ASD (Akhondzadeh 2008).
- Exclusion criteria: most studies excluded people with co-occurring psychiatric disorders, history of or current significant medical conditions including renal, cardiovascular, neurological, current or recent treatment with psychotropic medications or other medications prohibited for use during the study, and two studies excluded people with severe intellectual disabilities (Akhondzadeh 2008; Ghaleiha 2014).
- Setting: four studies were primarily based in the USA at clinics and hospitals, three studies in Iran at clinics and hospitals associated with a university, and one study was conducted in 15 countries (Hardan 2019).
- Concomitant medications: two studies provided details of concomitant medication use (Handen 2011; Hardan 2019). Handen 2011 allowed medications that did not interact with donepezil. Concurrent medication use included atomoxetine (1 participant in each group), stimulants (2 participants in each group), and sertraline (1 participant in intervention group) and citalopram (1 participant in intervention group). Hardan 2019 reported that approximately 10% of participants were taking risperidone, amongst other supplements and medications.
- Participant cognitive status: not reported
- Length of follow-up: all studies were either 10 weeks or 12 weeks in duration and none of the studies followed up after the endpoint of the trial.

Primary outcomes

- Irritability: three studies reported irritability (Ghaleiha 2013a; Ghaleiha 2014; Handen 2011). Two studies used the ABC-I subscale (Aman 1985), to report irritability, while Handen 2011 used the Ritvo-Freeman Real Life Rating Scale (affectual responses subscale; Freeman 1986) to report irritability.
- Aggression: Handen 2011 reported aggression using the Child Behaviour Checklist (CBCL) (Achenbach 2000).
- AEs: apart from Handen 2011, which reported no AEs associated with donepezil, all studies reported AEs.

Secondary outcomes

- Tolerability and acceptability (loss to follow-up): 54 participants (8.7%) withdrew from the studies and were not included in the relevant study analyses. Reasons included withdrawing consent (15); AEs (15), protocol violations (5); lost to follow-up (4); lack of efficacy (5); no longer met inclusion/exclusion criteria (2); other (7); tolerability (2); and increased behaviours of concern (1).

Antiparkinsonian interventions versus placebo or other treatments

Two studies (3 reports, 79 participants, 2 datasets) compared an antiparkinsonian intervention to a placebo (King 2001; Mohammadi 2013). Both studies compared amantadine to a placebo, however, Mohammadi 2013 compared amantadine plus risperidone to placebo plus risperidone. The analysis for Mohammadi 2013 only included amantadine versus placebo. Both studies were parallel. King 2001 was five weeks in duration and was conducted in the USA at medical centres associated with universities. Mohammadi 2013 was 10 weeks in duration and was conducted in Iran at a hospital associated with a university. All participants were children and were approximately the same age (mean age 7.0 years).

- Interventions: King 2001 required children to take 5 mg/kg/day of amantadine over two daily doses regardless of weight, whilst Mohammadi 2013 required children who weighed 30 kg to take 100 mg/day of amantadine or 150 mg/day over two daily doses for children 30 kg or over.
- Comparators: both studies compared amantadine to a placebo however neither study described the ingredients of the placebo. Mohammadi 2013 compared amantadine to a placebo plus risperidone, although the analysis is only amantadine versus placebo.
- Inclusion criteria: both studies required participants to have a diagnosis of ASD based on the DSM criteria and a score of 12 or

higher on the ABC-I subscale. Mohammadi 2013 also required presentation of severely disruptive symptoms associated with ASD.

- Exclusion criteria: both studies excluded people with significant medical conditions requiring medications, allergies to the intervention, and psychotropic use in the six weeks prior to enrolment (Mohammadi 2013), or taking neuroleptic, anticonvulsant or stimulants (King 2001).
- Concomitant medications: King 2001 allowed the use of SSRIs provided the dose had been stable for at least one month prior to the trial and the dose did not change during the trial. Mohammadi 2013 did not allow the use of any psychotropic medications.
- Participant cognitive status: neither study provided details.
- Length of follow-up: King 2001 was five weeks and Mohammadi 2013 10 weeks in duration. Neither study followed up after the endpoint of the trial.

Primary outcomes

- Irritability: both studies reported irritability using the ABC-I subscale (Aman 1985), however, King 2001 did not report endpoint ABC-I data (only baseline). Participants in both studies had baseline ABC-I scores of at least 18.
- AEs: both studies reported AEs.

Secondary outcomes

- Tolerability and acceptability (loss to follow-up): Mohammadi 2013 excluded one participant (1.3%) from the analysis but did not provide the reason.

Anxiolytic interventions versus placebo or other treatment

Two studies (4 reports, 200 participants, 3 datasets) compared an anxiolytic to a placebo (Chugani 2016; Ghanizadeh 2015). Both studies compared buspirone, however, Ghanizadeh 2015 compared buspirone plus risperidone to placebo plus risperidone. The analysis for Ghanizadeh 2015 was buspirone versus placebo. Both studies were parallel, however Chugani 2016 was 24 weeks in duration and was based at six academic medical centres in the USA, and Ghanizadeh 2015 was eight weeks in duration and was conducted at a child and adolescent psychiatry clinic associated with a university in Iran. All participants were under 18 years old, however Chugani 2016 only included children under six years of age and Ghanizadeh 2015 included children up to 17 years of age.

- Interventions: Chugani 2016 required participants to take buspirone twice daily at either 2.5 mg/dose (5 mg/day) or 5 mg/dose (10 mg/day). Ghanizadeh 2015 required children who weighed less than 40 kg to have a maximum of 5 mg twice daily (10 mg/day), or a maximum of 10 mg twice daily (20 mg/day) for children who weighed 40 kg or more.
- Comparators: both studies compared buspirone to a placebo however Ghanizadeh 2015 compared buspirone plus risperidone to placebo plus risperidone. As mentioned previously, the analysis only involved buspirone versus placebo.
- Inclusion criteria: both studies required participants to meet the DSM-IV criteria for ASD; Ghanizadeh 2015 required participants to have at least a moderate rating on the CGI-Severity score.
- Exclusion criteria: both studies excluded people who had unstable medical conditions that required medication, including neurological, liver, kidney, cardiac or psychotic disorders. Chugani 2016 excluded people who were taking medications such as anticonvulsants, antidepressants, benzodiazepines, or neuroleptics in the six weeks prior to the trial, Ghanizadeh 2015 excluded people who had taken antipsychotics in the two months prior to the study.
- Concomitant medications: Ghanizadeh 2015 allowed participants to take stable medications apart from antipsychotics provided that they were maintained at a constant dose throughout the trial.
- Participant cognitive status: neither study provided details regarding cognitive status.
- Length of follow-up: Chugani 2016 was 24 weeks in duration and Ghanizadeh 2015 was eight weeks in duration.

Primary outcomes

- Irritability: Ghanizadeh 2015 reported irritability using the ABC-I subscale (Aman 1985). Baseline ABC-I scores were above 24.
- AEs: Chugani 2016 reported AEs.

Secondary outcomes

- Tolerability and acceptability (loss to follow-up): 30 participants (15%) withdrew and were not included in the relevant study analyses. Reasons included withdrawing consent (6); AEs (13), lost to follow-up (5); no longer met inclusion/exclusion criteria (2); clinical decision (2); participant moved(1); other (1).

Experimental interventions versus placebo or other treatment:

Forty-two studies (72 reports, 1920 participants, 43 datasets) compared an experimental interventional drug to a placebo. The majority of studies only included children, however, five studies included only adults (Chez 2020; Danforth 2018; Hollander 2020a; Lewis 2018; Willemsen-Swinkels 1995), two studies included both adolescents (12 years and over) and adults (Veenstra-VanderWeele 2017; Wink 2018), one study included only adolescents (11 to 17 years; Ayatollahi 2020), and one study involved children and adults up to 21 years of age (Aran 2021). Study duration ranged from seven days (Lewis 2018), to six months (Danfors 2005), with a mean duration of 10 weeks. Eighteen studies were conducted in Iran, 14 were conducted in the USA, four in the Netherlands (Sprengers 2021; VanAndel 2022; Willemsen-Swinkels 1996; Willemsen-Swinkels 1995), one in Israel (Aran 2021), China, Sweden, Australia, France and Austria respectively (Dai 2021; Danfors 2005; Dean 2019; Lemonnier 2017; Niederhofer 2002). All were parallel studies apart from 10, which were cross-over studies.

- Interventions
  - Arbaclofen: one study involving 150 participants compared arbaclofen to a placebo (Veenstra-VanderWeele 2017). Mean age of participants was 11.6 years (range 5 years to 21 years). Arbaclofen was administered twice daily, up to maximum of 10 mg/day for children under 12 years and a maximum of 15 mg for participants 12 years and above.
  - Baclofen plus risperidone: one study involving 58 participants 4 to 12 years of age compared baclofen (plus risperidone) to a placebo (plus risperidone; Mahdavinasab 2019). Risperidone commenced at 0.5 mg/day to a maximum of 1.5 mg/day and baclofen was administered three times daily at 0.6 mg/kg. The analysis was baclofen compared to placebo.

- Bumetanide: four studies involving 335 participants up to 18 years of age compared bumetanide to a placebo (Dai 2021; Lemonnier 2017; Sprengers 2021; VanAndel 2022). Participants in Lemonnier 2017 were allocated to either 0.5 mg, 1 mg, or 2 mg of bumetanide twice daily. Sprengers 2021 administered bumetanide in liquid form twice daily with a mean dose of 0.0482 mg/kg/day, and Dai 2021 administered 0.5 mg of bumetanide twice daily.
- Cannabidiol: one cross-over study involving 88 participants aged 5 to 21 years compared cannabidiol to a placebo (Aran 2021). Participants received 1 mg/kg of cannabidiol per day for 12 weeks.
- Celecoxib plus risperidone: one study involving 40 participants compared celecoxib to a placebo (Asadabadi 2013). Maximum celecoxib was 200 mg/day plus 2 mg/day of risperidone for children who weighed 10 kg to 30 kg, and 30 mg/day of celecoxib plus 3 mg/day of risperidone for children 31 kg and over. Equivalent placebo plus risperidone was provided to participants in the placebo group. The analysis for this study is celecoxib versus placebo.
- Cyproheptadine plus haloperidol: one study involving 40 participants compared cyproheptadine plus haloperidol to a placebo plus haloperidol (Akhondzadeh 2004). Maximum cyproheptadine was 0.2 mg/kg/day and maximum haloperidol was 0.05 mg/kg/day. The analysis for this study was cyproheptadine versus placebo.
- D-cycloserine plus social skills training: one study involving 67 participants compared D-cycloserine plus social skills training to a placebo plus social skills training (Minshawi 2016). Participants received 50 mg of D-cycloserine or placebo 30 minutes prior to weekly social skills training sessions.
- Dextromethorphan: one study involving eight participants compared dextromethorphan to a placebo (sweetened syrup; Woodard 2007). Children aged 6 to 12 years and 13 years and over received 30 mg or 60 mg of dextromethorphan, respectively, every 12 hours.
- Dextromethorphan plus quinidine: one study involving 14 participants compared dextromethorphan plus quinidine (Chez 2020). Participants received 20 mg of dextromethorphan plus 10 mg of quinidine in tablet form (Nuedexta) once daily for the first week and then twice daily for the following seven weeks.
- Fenfluramine: one study involving 11 participants compared fenfluramine to a placebo (Campbell 1987). Fenfluramine was initiated at 1.0 mg/kg/day across two daily doses, increasing to a maximum of 60 mg/day.
- Folinic acid plus risperidone: one study involving 55 participants compared folinic acid plus risperidone to a placebo plus risperidone (Batebi 2021). Folinic acid was administered at 2 mg/kg up to a maximum of 50 mg/day. Maximum risperidone for children who weighed up to 19 kg and 20 kg and over was 1 mg/day and 2 mg/day respectively. The analysis for this study was folinic acid versus placebo.
- L-carnosine plus risperidone: one study involving 42 participants compared L-carnosine plus risperidone to a placebo plus risperidone (Hajizadeh-Zaker 2018). Participants received 400 mg of L-carnosine twice daily plus a maximum of 1 mg/day of risperidone (children under 20 kg) or 2 mg/day of risperidone (children over 20 kg). The analysis for this study was L-carnosine versus placebo.
- Lofexedine: one study involving 12 participants compared lofexedine to a placebo (Niederhofer 2002). Lofexedine commenced at 0.4 mg/day up to a maximum of 1.2 mg/day over three daily doses.
- MDMA (methylenedioxymethamphetamine) plus psychotherapy: one study involving 12 adults compared MDMA plus psychotherapy to a placebo plus psychotherapy (Danforth 2018). Following three 60- to 90-minute psychotherapy sessions, participants received either 75 mg to 125 mg of MDMA or placebo on two occasions approximately one month apart.
- Mecamylamine: one study involving 20 participants compared mecamylamine to a placebo (Arnold 2012a). Mecamylamine was administered in fixed doses starting at 0.5 mg/day up to 5 mg/day if tolerated.
- Minocycline plus risperidone: one study involving 46 participants compared minocycline plus risperidone to a placebo plus risperidone (Ghaleiha 2016). Minocycline was administered in fixed doses of 100 mg/day plus risperidone 1 mg/day (children under 20 kg) or 2 mg/day (children over 20 kg). The analysis for this study was minocycline versus placebo.
- N-acetylcysteine plus risperidone: two studies involving 71 participants compared N-acetylcysteine plus risperidone to a placebo plus risperidone (Ghanizadeh 2013; Nikoo 2015).
- N-acetylcysteine: three studies involving 156 participants compared N-acetylcysteine to a placebo (Dean 2019; Hardan 2012; Wink 2016).
- Naltrexone: three studies involving 93 participants compared naltrexone to a placebo (Campbell 1993; Willemsen-Swinkels 1995; Willemsen-Swinkels 1996).
- Nicotine: one study involving seven adult participants compared nicotine to a placebo (Lewis 2018). Participants applied 7 mg of nicotine or placebo daily via skin patches.
- Palmitoylethanolamide plus risperidone: one study involving 62 participants compared palmitoylethanolamide plus risperidone to a placebo plus risperidone (Khalaj 2018); 600 mg of palmitoylethanolamide was administered twice daily in addition to 1 mg/day of risperidone (children under 20 kg) or 2 mg/day (children over 20 kg). The analysis for this study was palmitoylethanolamide versus placebo.
- Pentoxifylline plus risperidone: one study involving 40 participants compared pentoxifylline plus risperidone to a placebo plus risperidone (Akhondzadeh 2010). Maximum pentoxifylline was 400 mg/day for children who weighed up to 40 kg, or a maximum of 600 mg/day for children 41 kg and above. Risperidone was administered up to 2 mg/day for children who weighed up to 40 kg, or a maximum of 3 mg/day for children above 40 kg. The analysis for this study was pentoxifylline versus placebo.
- Pioglitazone plus risperidone: one study involving 44 participants compared pioglitazone plus risperidone to a placebo plus risperidone (Ghaleiha 2015); 15 mg of pioglitazone was administered twice daily in addition to an initial 0.5 mg/day of risperidone, increasing to 1 mg/day (children under 20 kg) or 2 mg/day (children over 20 kg). The analysis for this study was pioglitazone versus placebo.

- Prednisolone plus risperidone: one study involving 26 participants compared prednisolone plus risperidone to a placebo plus risperidone (Malek 2020). Prednisolone was administered at 1 mg/kg/day in addition to an initial 0.5 mg/day of risperidone, increasing to 1 mg/day (children under 20 kg) or 2 mg/day (children over 20 kg). The analysis for this study was prednisolone versus placebo.
- Pregnenolon plus risperidone: one study involving 59 participants compared pregnenolon plus risperidone to a placebo plus risperidone (Ayatollahi 2020). Pregnenolon was administered in fixed doses of 100 mg twice daily. Risperidone was administered at maximum doses of 2.5 mg/day for children who weighed 20 kg to 45 kg, or a maximum of 3.5 mg/day for children who weighed above 45 kg. The analysis for this study was pregnenolone versus placebo.
- Propentofylline plus risperidone: one study involving 48 participants compared propentofylline to a placebo (Behmanesh 2019). Propentofylline commenced at 300 mg once daily and increased to 300 mg twice daily (children under 45 kg) or propentofylline increased to 300 mg three times daily (children 45 kg or over). Risperidone commenced at 0.5 mg/day and increased to 1 mg/day for children who weighed under 20 kg or 2 mg/day for those who weighed 20 kg or above. The analysis for this study was propentofylline versus placebo.
- Resveratrol plus risperidone: one study involving 62 participants compared resveratrol plus risperidone to a placebo plus risperidone (Hendouei 2019). Resveratrol was administered as a fixed dose of 250 mg twice daily in addition to risperidone (initial dose of 0.5 mg/day increasing by 0.5 mg/day each week for the first three weeks). The analysis for this study was resveratrol versus placebo.
- Riluzole: one study involving seven participants compared riluzole to a placebo (Wink 2018). Riluzole commenced at 50 mg/day and increased to 100 mg twice daily.
- Riluzole plus risperidone: one study involving 40 participants compared riluzole plus risperidone to a placebo plus risperidone (Ghaleiha 2013b). Riluzole was administered 25 mg/day to 50 mg/day for children who weighed 10 kg to 40 kg, or a maximum of 100 mg/day for children over 40 kg. Maximum risperidone was 2 mg/day for children who weighed up to 40 kg and a maximum of 3 mg/day for children 41 kg and above.
- Simvastatin plus risperidone: one study involving 66 participants compared simvastatin plus risperidone to a placebo plus risperidone (Moazen-Zadeh 2018). Simvastatin was administered at either 20 mg/day for children under 10 years of age or 40 mg/day for children 10 years and over. The analysis for this study was simvastatin versus placebo.
- Sulforaphane plus risperidone: one study involving 60 participants compared sulforaphane plus risperidone to a placebo plus risperidone (Montazmenesh 2020). Sulforaphane was administered at 50 µmol /day for children who weighed less than 45 kg, or 100 µmol for children 45 kg to 90 kg. Risperidone was administered at a maximum of 1 mg/day for children under 20 kg, 2.5 mg/day for children 20 kg to 45 kg, and 3.5 mg/day for children who weighed over 45 kg.
- Tetrahydrobiopterin: two studies involving 58 participants compared tetrahydrobiopterin to a placebo (Danfors 2005; Klaiman 2013). Danfors 2005 administered tetrahydrobiopterin at a maximum of 3 mg/kg/day across two daily doses, while Klaiman 2013 administered tetrahydrobiopterin in tablet form at 20 mg/kg once daily (mean final dose was 385 mg/day).
- *Trichuris suis* ova: one study involving 10 adult participants compared *Trichuris suis* ova to a placebo (Hollander 2020a). Participants received a dose of 2500 ova every two weeks.

- Comparators: all studies compared an experimental intervention to a placebo, although 16 of the studies were compared to a placebo plus risperidone, one study was compared to a placebo plus haloperidol (Akhondzadeh 2004), and one study compared to placebo plus psychotherapy (Danforth 2018). Only three studies provided details of the placebo, sugar pill (Hardan 2012; Minshawi 2016) or sweetened syrup (Woodard 2007).
- Inclusion criteria: all studies required participants to have a clinical diagnosis of ASD, and additional criteria included a minimum of 15 on the ABC-I subscale (Asadabadi 2013; Ayatollahi 2020; Lewis 2018; Wink 2018; Woodard 2007), or a score of moderate or higher on the CGI-Severity score (Minshawi 2016; Veenstra-VanderWeele 2017), or the presentation of aggressive and disruptive behaviours (Akhondzadeh 2004; Akhondzadeh 2010; Behmanesh 2019; Ghaleiha 2015; Ghaleiha 2016; Malek 2020).
- Exclusion criteria: the majority of studies excluded people with a history of or current medical or psychiatric conditions and also people who had been taking psychotropic medications or other prohibited medications in the period leading up to the trial. Some studies also excluded people with severe intellectual disabilities (Akhondzadeh 2010; Asadabadi 2013; Batebi 2021; Ghaleiha 2013b; Ghaleiha 2016; Hajizadeh-Zaker 2018; Khalaj 2018; Montazmenesh 2020; Moazen-Zadeh 2018), were pregnant or breastfeeding (Hollander 2020a), currently using tobacco or nicotine products (Lewis 2018), or had an allergy or intolerance to the intervention (Ayatollahi 2020; Behmanesh 2019; Nikoo 2015; Veenstra-VanderWeele 2017).
- Concomitant medications: studies required participants to have been off medications for at least one month and six months prior to the study (Niederhofer 2002; Batebi 2021), remain on stable psychotropic medications for at least three months (Arnold 2012a; Hollander 2020a), and two weeks prior to randomisation respectively (Campbell 1987; Hardan 2012; Minshawi 2016), or stable medication with no changes in the past 14 days (Lewis 2018). One study allowed the use of anticonvulsants, supplements, or sleep medications, however, any other psychotropic medications were not allowed (Klaiman 2013).
- Participant cognitive status: most studies did not report the average IQ of participants apart from seven studies (Arnold 2012a; Danfors 2005; Dean 2019; Minshawi 2016; Niederhofer 2002; Sprengers 2021; Wink 2016). IQ ranged from 53 to 100 across these studies.
- Length of follow-up: study duration ranged from seven days (Lewis 2018), to six months (Danfors 2005). Mean duration was 9.6 weeks.

Primary outcomes

- Irritability: 32 of the studies reported irritability and all used the ABC-I subscale (Aman 1985), to measure irritability. Most studies required participants to have a minimum baseline ABC-I of 12

or higher while some studies required a baseline ABC-I of 15 or higher (Ayatollahi 2020; Lewis 2018; Mahdavinasab 2019; Wink 2018).

- Self-injury: five studies reported self-injurious behaviour (Dai 2021; Dean 2019; Hardan 2012; Hollander 2020a; VanAndel 2022). Each study used the Repetitive Behaviour Scale - Revised (self-injury subscale; Bodfish 2000) to measure self-injurious behaviour.
- AEs: apart from five studies, all studies reported AEs (Chez 2020; Lewis 2018; Mahdavinasab 2019; Malek 2020; Willemsen-Swinkels 1996).

Secondary outcomes

- Tolerability and acceptability (loss to follow-up): 230 participants (13%) withdrew and were not included in the relevant study analyses. Reasons included withdrawing consent (103); AEs (32), lost to follow-up (23) ; poor/non-compliance (20), protocol violations (10); lack of efficacy (9); due to an error (4); no longer met inclusion/exclusion criteria (4); clinical decision (2); participant moved (1); other (22).

Excluded studies

The full-text screening resulted in 88 references (as 81 studies) being excluded due to ineligible criteria. Full-text copies of the studies listed in this section were reviewed as it was not clear whether they met the inclusion criteria for the review based on title and abstract. Further screening of the full-text reports of these studies found that they did not meet our inclusion criteria. Reasons for exclusion included: did not focus on population of interest; did not have a focus on unwanted behaviours (irritability, aggression, self-injury); ineligible study design (non-RCT); non-pharmacological intervention; irrelevant comparator; and terminated studies.

Risk of bias in included studies

See Figure 3 for a risk of bias summary, and Figure 4 for a risk of bias graph.

Figure 3. Risk of bias in included studies

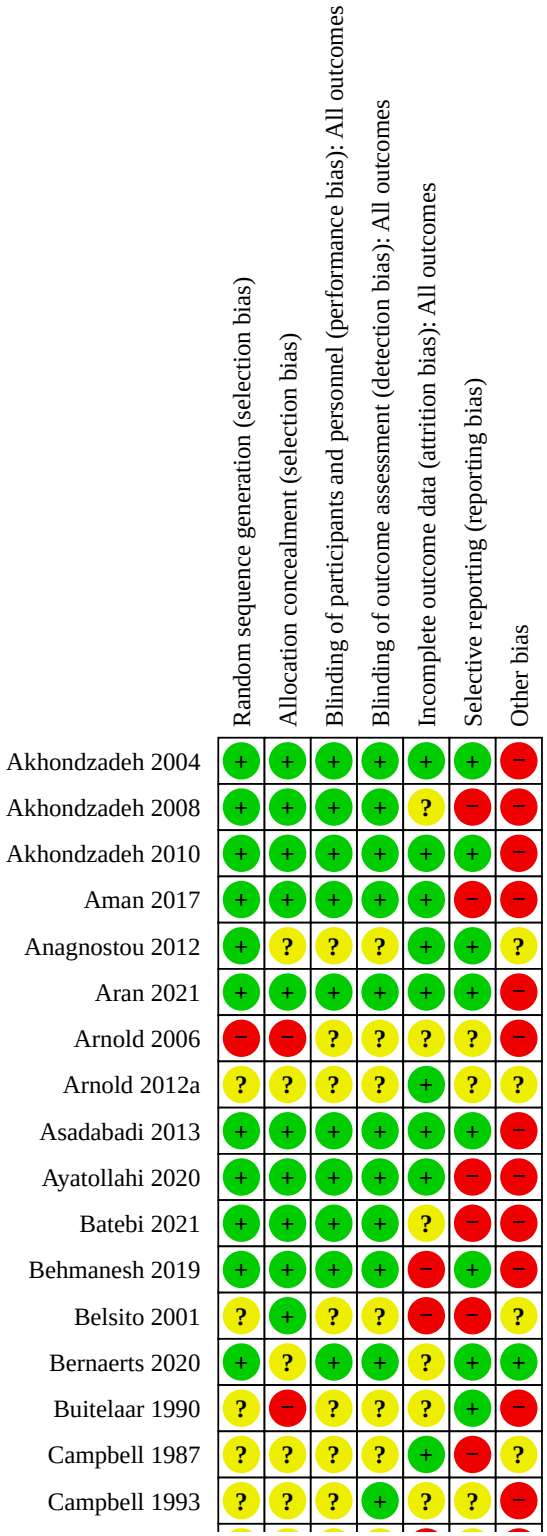


Figure 3. (Continued)

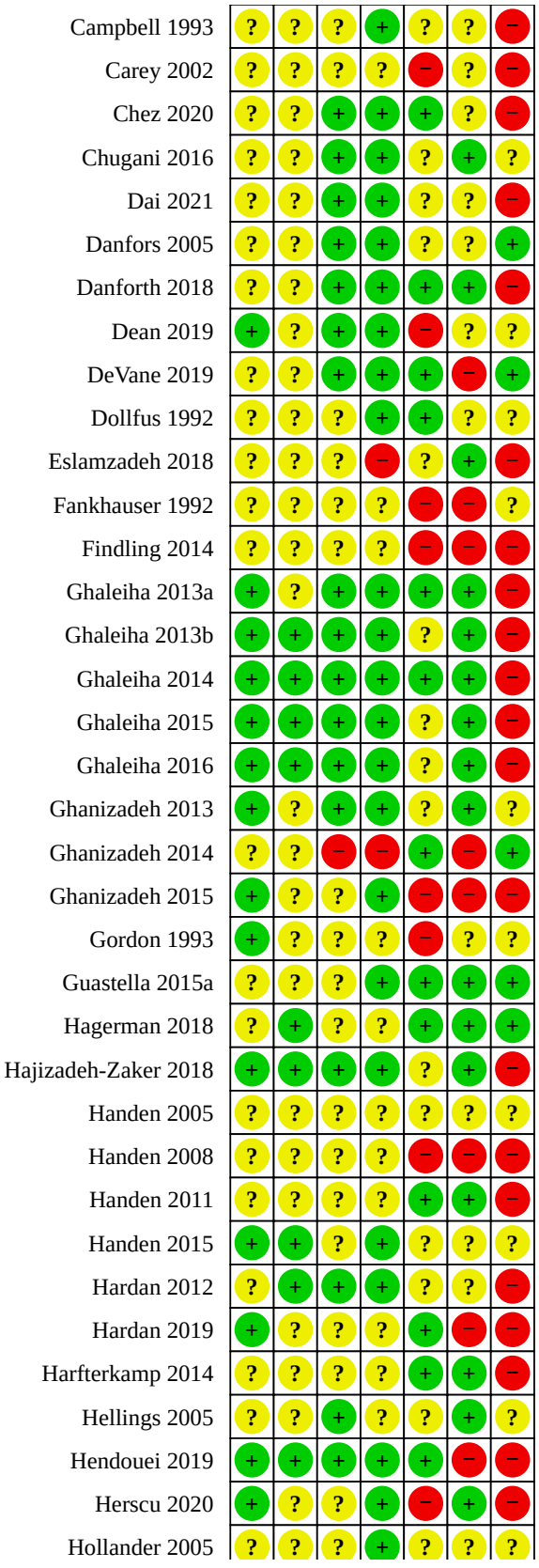
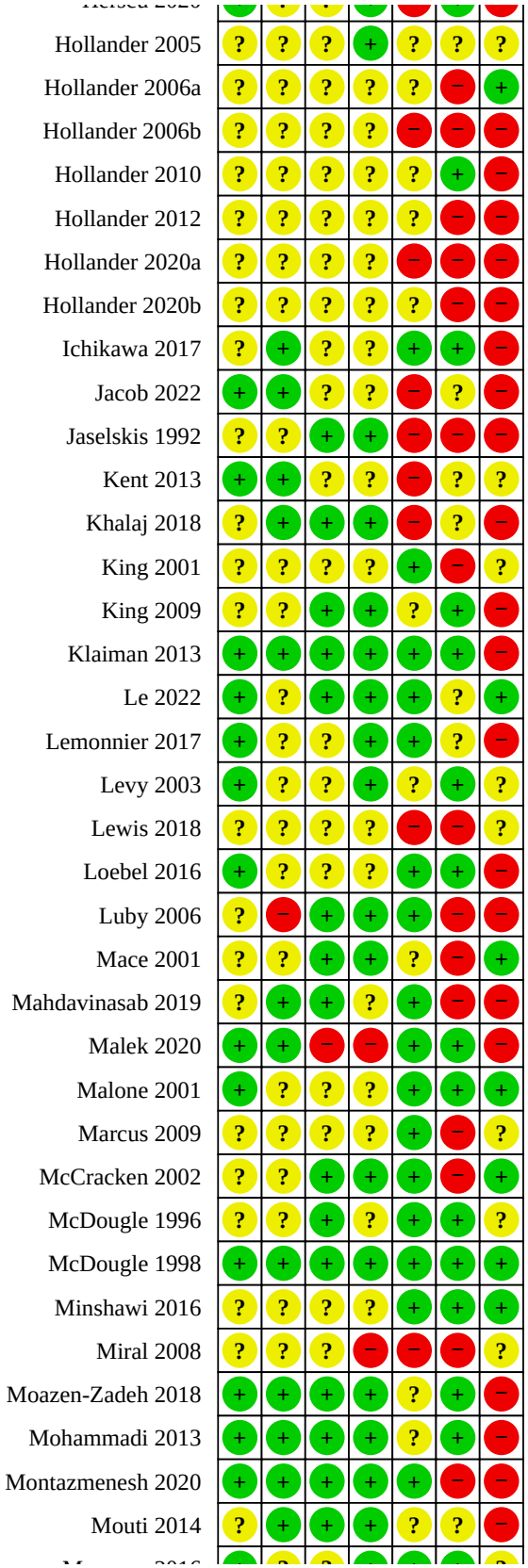


Figure 3. (Continued)



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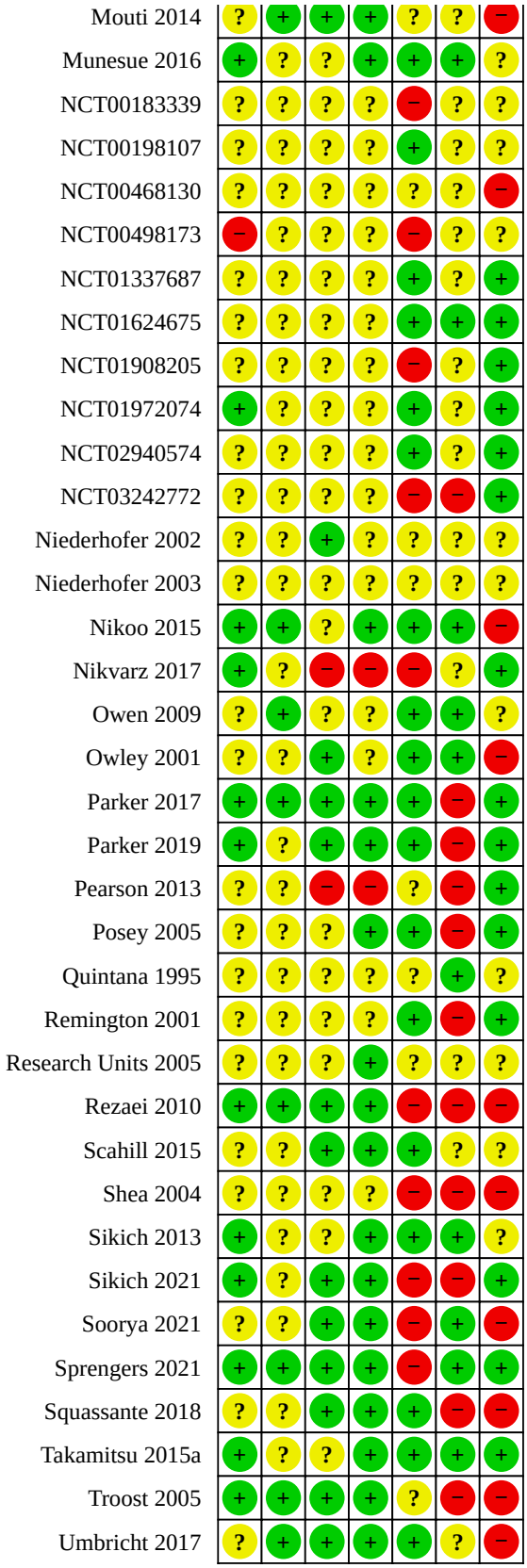


Figure 3. (Continued)

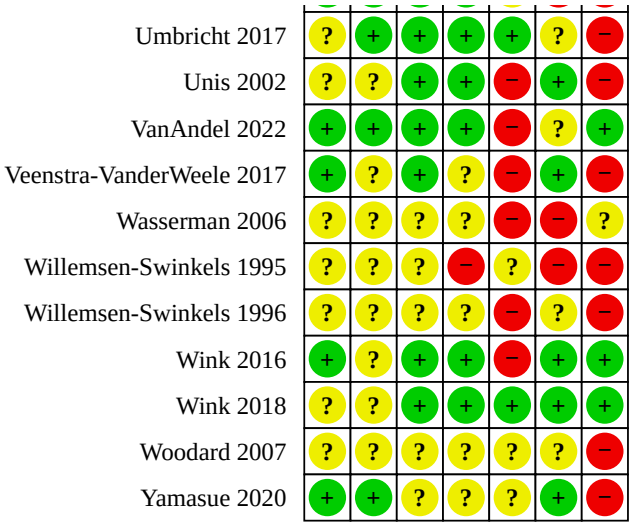
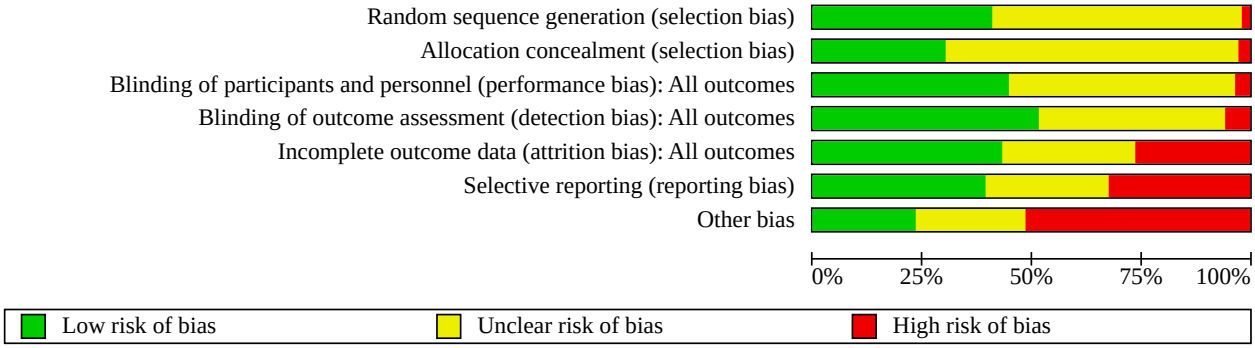


Figure 4. Visual representation of risk of bias across all included studies



See below for more detailed information on risk of bias.

Allocation

- **Atypical or typical antipsychotics versus placebo or other treatment:** we rated 16 studies as unclear risk of bias for randomisation and allocation concealment, mostly due to a lack of details regarding methods of randomisation and allocation concealment. We rated three studies (20%) as low because they conducted randomisation using a computer-generated code, and one study as high due to a clear lack of randomisation and allocation concealment.
- **Neurohormones versus placebo or other treatment:** we rated 12 studies as unclear and 12 studies as having a low risk of bias. Studies rated as unclear either did not provide details or provided very vague details regarding the randomisation and allocation of participants. We rated studies as low risk of bias because randomisation was conducted using a computer-generated code.
- **ADHD-related medications versus placebo or other treatment:** we rated 10 studies as unclear risk of bias due to a lack of details regarding methods of randomisation and allocation concealment. We rated one study as low and two studies as high. The reason for the high ratings was because the investigators used 'sequential assignment'. The study rated as low randomised using a computer-generated method.
- **Antidepressants versus placebo or other treatment:** we rated eight studies as unclear due to a lack of details regarding methods of randomisation and allocation concealment. We rated the other two studies as low risk of bias as randomisation was conducted externally to the trial.
- **Atypical antipsychotic versus another atypical antipsychotic:** we rated allocation concealment as unclear for both of the studies due to a lack of information.
- **Atypical antipsychotic versus an anti-dementia drug:** we rated allocation concealment as unclear for Nikvarz 2017 because although referred to as "simple balanced blocked randomisation", the study authors did not provide information on how allocation was concealed.
- **Atypical antipsychotic versus an antiparkinsonian drug (bromocriptine):** we rated allocation concealment as unclear for Dollfus 1992 due to a lack of information.
- **Anticonvulsants versus placebo or other treatment:** we rated five studies as having an unclear risk of bias due to a

lack of details and one study as low because it conducted randomisation using a computer-generated code.

- **Antidementia interventions versus placebo or other treatments:** we rated six studies as low risk of bias because they conducted randomisation using a computer-generated code, and the other two studies as unclear due to a lack of detail regarding the allocation process.
- **Antiparkinsonian interventions versus placebo or other treatments:** we rated one study as low because it conducted randomisation using a computer-generated code and the other study as having an unclear risk of bias due to insufficient details regarding allocation concealment.
- **Anxiolytic interventions versus placebo or other treatment:** we rated one study as unclear due to a lack of details and the other study as low risk of bias because it conducted randomisation using a computer-generated code.
- **Experimental interventions versus placebo or other treatment:** we rated 24 studies as low risk of bias because they conducted randomisation using a computer-generated code. We rated the remaining 18 studies as unclear, mainly due to a lack of details regarding randomisation methods and allocation concealment.

Blinding

- **Atypical or typical antipsychotics versus placebo or other treatment:** we rated 14 studies as unclear risk of bias due to a lack of details regarding blinding and who was blinded, and the remaining six studies as low risk of bias.
- **Neurohormones versus placebo or other treatment:** we rated 13 studies as unclear and the remaining 11 studies as having low risk of bias. Studies with an unclear risk of bias usually did not provide further details apart from stating that they used double-blinding.
- **ADHD-related medications versus placebo or other treatment:** we rated eight studies as unclear risk of bias, three as low risk of bias and the remaining two studies as high risk of bias. This was due to investigators being unblinded.
- **Antidepressants versus placebo or other treatment:** we rated seven studies as unclear risk of bias, with the remaining three studies at low risk of bias.
- **Atypical antipsychotic versus another atypical antipsychotic:** we rated one study as a low risk of bias and the other as high due to some participants being unblinded and an unblinded clinician.
- **Atypical antipsychotic versus an anti-dementia drug:** we rated this study as having a high risk of bias due to being an open-label (randomised) study and therefore lacking blinding.
- **Atypical antipsychotic versus an antiparkinsonian (bromocriptine):** we rated this study as having an unclear risk of bias because it did not provide details regarding blinding.
- **Anticonvulsants versus placebo or other treatment:** we rated three studies as being of low risk of bias and three studies as unclear, mainly due to lack of details.
- **Antidementia interventions versus placebo or other treatments:** we rated six studies as having low risk of bias because they clearly stated the blinding methods that they used, and the other two studies as unclear risk of bias due to lack of further details apart from stating the study was double-blinded.
- **Antiparkinsonian interventions versus placebo or other treatments:** we rated one study as low risk of bias because different people were involved in the allocation of participants and the measurement of outcomes. We rated the other study as unclear risk of bias due to insufficient details regarding blinding.
- **Anxiolytic interventions versus placebo or other treatment:** we rated one study as low risk of bias because an external person, who was not involved in enrolment or allocation, monitored outcomes. We rated the other study as unclear risk of bias because although the study stated that they used double-blinding, the person who allocated participants to groups was unblinded.
- **Experimental interventions versus placebo or other treatment:** we rated 30 studies as low risk of bias, 11 as unclear, and one as high risk of bias due to the use of single-blinding only. The studies rated as unclear were due to a lack of details regarding blinding and who was blinded, and the high risk of bias was because the assessors were unblinded.

Incomplete outcome data

- **Atypical or typical antipsychotics versus placebo or other treatment:** we rated 12 studies at low risk of bias, with a further four studies being rated as unclear and four studies as high risk of bias due to high rates of attrition, not including some participants in the analysis due to lack of efficacy, or lack of details regarding participants lost to follow-up. We rated studies as unclear due to vague details regarding imputation of missing data, or an intention-to-treat analysis that did not include all participants.
- **Neurohormones versus placebo or other treatment:** we rated 13 studies as low, six studies as unclear and five as high risk of bias. Studies rated as high had up to 50% missing data or did not provide reasons for loss to follow-up. Studies rated as unclear did not provide reasons for participants lost to follow-up, or some participants were not accounted for in analysis or numbers of participants lost to follow-up. Studies rated as low had included all participants in the analysis and used an intention-to-treat analysis for any participants who did not complete the trial.
- **ADHD-related medications versus placebo or other treatment:** we rated five studies as unclear, two as low and six as high. We judged studies as high risk due to unexplained loss to follow-up, incomplete data or lack of post-baseline ratings. Ratings of unclear were because the study authors did not clearly report numbers of participants who completed the study and any who were lost to follow-up throughout the study. Studies with ratings of low had included all participants in the final analysis or used an intention-to-treat analysis, or both.
- **Antidepressants versus placebo or other treatment:** we rated four studies as having an unclear risk of bias, three studies as high and three studies as low risk of bias. 'Unclear' ratings were because it was not clear how many participants were included in the analysis, or loss to follow-up was not reported by group. Reasons for a judgement of high risk of bias included high attrition of 20% to 25%, and not providing reasons for participant loss to follow-up. The studies rated as low risk of bias used an intention-to-treat analysis and included all participants in the final analysis.

- **Atypical antipsychotic versus another atypical antipsychotic:** we rated both studies as having a low risk of bias as all participants were included in the analysis.
- **Atypical antipsychotic versus an anti-dementia drug:** we rated the study as high risk of bias because data were not imputed for participants who discontinued.
- **Atypical antipsychotic versus an antiparkinsonian (bromocriptine):** we rated the study as having a low risk of bias because only one participant did not complete the study, and it used a last observation carried forward.
- **Anticonvulsants versus placebo or other treatment:** we rated three studies as unclear risk of bias and three studies as high risk of bias. The ratings of unclear were mainly due to unaccounted for participants, not imputing data where participants were lost to follow-up, or lack of clarity regarding the number included in the analysis. The studies rated as high risk of bias were because of incomplete data.
- **Anti-dementia interventions versus placebo or other treatments:** we rated six studies as having low risk of bias, one study as high and one study as unclear risk of bias. The study with a high risk of bias had almost 50% attrition and the study rated as unclear provided vague details regarding loss to follow-up and number analysed. Studies rated as low risk of bias included all participants in the analysis and used an intention-to-treat analysis for any participants who did not complete the trial.
- **Antiparkinsonian interventions versus placebo or other treatments:** we rated one study as low risk of bias because all participants were included in the analysis, while we rated the other study as unclear due to imputation using last observation carried forward for all participants with at least one measurement post-baseline.
- **Anxiolytic interventions versus placebo or other treatment:** we rated one study as unclear and the other study as high risk of bias. The high risk of bias was due to not reporting outcome data at one of the prespecified time points and the study rated as unclear was due to "unavailable data" for almost half of the discontinued participants.
- **Experimental interventions versus placebo or other treatment:** we rated 17 studies as low risk of bias, 14 as unclear and 11 studies as high risk of bias. The studies rated at high risk of bias were mainly due to significant attrition or not reporting reasons for loss to follow-up. The ratings of unclear were because it was unclear how many were included in the analysis, or no further statistical measures such as intention-to-treat were used for those lost to follow-up.

Selective reporting

- **Atypical or typical antipsychotics versus placebo or other treatment:** we rated nine studies as high risk of bias, seven studies as low and four studies as unclear risk of bias. We rated the nine studies as high because of incomplete or absent reporting of outcomes, and not reporting AEs when it is highly likely they would have occurred. The studies rated as low were because all outcomes listed in the protocol or on the trial registry were reported in the published paper. The unclear ratings were due to lack of a protocol.
- **Neurohormones versus placebo or other treatment:** we rated 11 studies as low risk of bias because outcomes reported matched those listed in the protocol, seven studies as unclear due to an absence of a published protocol or trial registration, and six as high risk of bias. Studies rated as high risk of bias did not report outcomes that were mentioned or listed on the clinical trials registry.
- **ADHD-related medications versus placebo or other treatment:** we rated seven studies as high risk of bias, three studies as low and two were unclear. The reasons for the high ratings were either incomplete or absent outcome data. The ratings of unclear were because of the absence of a published paper and details only provided on the trial registry. The ratings of low were because all outcomes listed in the protocol or on the trial registry were reported in the published paper.
- **Antidepressants versus placebo or other treatment:** we rated four studies as low risk of bias, four studies as unclear and two studies as high risk of bias. Reasons for a rating of high were incomplete or absent outcome data. We rated studies as low because all outcomes listed in the protocol or on the trials registry were reported in the published paper. The unclear ratings were because of an absence of a published paper and details only provided on the trial registry.
- **Atypical antipsychotic versus another atypical antipsychotic:** we rated one study as having a high risk of bias, due to conflicting statements that disagree with the statistics that they provided, and the other study as low risk of bias.
- **Atypical antipsychotic versus an antidementia drug:** we rated this study as having an unclear risk of bias due to lack of a protocol.
- **Atypical antipsychotic versus an antiparkinsonian (bromocriptine):** we rated this study as having an unclear risk of bias due to lack of a protocol.
- **Anticonvulsants versus placebo or other treatment:** we rated five studies as high risk of bias and one as low risk. The ratings of high risk of bias were due to lack of outcome data, the use of P values or t-values to report data, or differences between information in published papers and the clinical trials registry. The rating of low was because outcomes reported matched those listed in the protocol or on the trials registry.
- **Antidementia interventions versus placebo or other treatments:** we rated three studies as having a high risk of bias, four studies as low and one study as having an unclear risk of bias. The unclear rating was because of an absence of a published protocol, and the low ratings were because all outcomes listed in a protocol or trial registry were reported by the study authors in the published paper. The ratings of high were because outcome data were not reported.
- **Antiparkinsonian interventions versus placebo or other treatments:** we rated one study as low risk of bias and the other as unclear because it used last observation carried forward for any participant with at least one post-baseline measure.
- **Anxiolytic interventions versus placebo or other treatment:** we rated one study as low risk of bias because all outcomes listed in a protocol or trial registry were reported by the study authors in the published paper, and the study rated as high risk of bias was due to outcome measures not reported at the time points mentioned.
- **Experimental interventions versus placebo or other treatment:** we rated 21 studies as low risk of bias because outcomes reported matched those listed in the protocol, 12 as unclear due to an absence of a published protocol or trial registry, and nine studies as high. The reasons for high risk of

bias were failure to report outcomes mentioned in protocols or on trial registries, or reporting data at different time points to that mentioned in the protocol or trial registry.

Other potential sources of bias

- **Atypical or typical antipsychotics versus placebo or other treatment:** we rated six studies as low risk of bias, eight as high risk of bias, and six as unclear. Most of the studies rated as high risk of bias were because of funding or other support by pharmaceutical companies, agreements between study authors and sponsors regarding the publishing of results, a small proportion of the sample with a diagnosis of autism despite the title mentioning autism spectrum disorder, or study authors' direct involvement in the ethics committee or funding process. The studies rated as unclear were because of some financial or other support from pharmaceutical companies. The six studies rated as low were because we identified no other sources of bias.
- **Neurohormones versus placebo or other treatment:** we rated nine studies as high risk of bias, 10 as low and five studies as unclear risk of bias. All studies rated as high risk of bias were either funded by pharmaceutical companies, the pharmaceutical companies were involved in the analysis, or participants were responders to the intervention in a previous trial. Studies rated as low were because we did not identify any other sources of bias, and the studies rated as unclear were due to some involvement by pharmaceutical companies in the study.
- **ADHD-related medications versus placebo or other treatment:** we rated five studies as high risk of bias due to a lack of standardised measures, having received funding by pharmaceutical companies, or study authors' direct involvement in the ethics committee or funding process. We rated five studies as unclear due to highly divergent samples in addition to small sample sizes or lack of details regarding sponsorship or funding, and three studies as low because we did not identify any other sources of bias.
- **Antidepressants versus placebo or other treatment:** we rated five studies as unclear risk of bias because of lack of details regarding funding, a published paper not being available, or a lack of baseline comparisons reported by group. We rated one study as low and four as high risk of bias. We rated studies as high risk of bias due to involvement or employment of study authors by pharmaceutical companies, study authors' direct involvement in the ethics committee or funding process, or an imbalance in baseline characteristics between the two groups. The one study rated as low was because we did not identify any other sources of bias.
- **Atypical antipsychotic versus another atypical antipsychotic:** we rated both studies as having a low risk of bias because we did not identify any other sources of bias.
- **Atypical antipsychotic versus an antidementia drug:** we rated this study as having a low risk of bias because we did not identify any other sources of bias.
- **Atypical antipsychotic versus an antiparkinsonian (bromocriptine):** we rated this study as having an unclear risk of bias because we did not identify any other sources of bias. However, without a protocol or trial registry entry, it is difficult to know.
- **Anticonvulsants versus placebo or other treatment:** we rated three studies as unclear risk of bias, two as high and one as low risk of bias. The studies rated as unclear were due to funding or other support from pharmaceutical companies, and the studies rated as high were due to a change in study duration without explanation or study authors' direct involvement in the ethics committee or funding process. The study rated as low was because we did not identify any other sources of bias.
- **Antidementia interventions versus placebo or other treatments:** we rated one study as a low risk of bias because we did not identify any other sources of bias. We rated seven studies as high risk of bias due to funding and other involvement by pharmaceutical companies or study authors' direct involvement in the ethics committee or funding process.
- **Antiparkinsonian interventions versus placebo or other treatments:** we rated one study as unclear risk of bias due to pharmaceutical companies providing funding and the unknown role they may have had in the study. We rated the other study as high risk of bias due to study authors' direct involvement in the ethics committee or funding process.
- **Anxiolytic interventions versus placebo or other treatment:** we rated one study as unclear and the other as a high risk of bias because the study was retrospectively registered on the clinical trials website.
- **Experimental interventions versus placebo or other treatment:** we rated six studies as low risk of bias because we did not identify any other sources of bias, six studies as unclear and 30 studies as high risk of bias. The reasons for high risk of bias were funding or other involvement by pharmaceutical companies in the studies, study authors being employed by the pharmaceutical companies funding the study, or study authors' direct involvement in the ethics committee or funding process. The reasons for an unclear rating were because of some involvement of pharmaceutical companies, or study authors did not provide baseline details regarding group differences.

Effects of interventions

See: **Summary of findings 1** Atypical antipsychotics compared to placebo for irritability, aggression, and self-injury in autism spectrum disorder (ASD); **Summary of findings 2** Neurohormones compared to placebo for irritability, aggression, and self-injury in autism spectrum disorder (ASD); **Summary of findings 3** Attention deficit hyperactivity disorder (ADHD)-related drugs compared to placebo for irritability, aggression, and self-injury in autism spectrum disorder (ASD); **Summary of findings 4** Antidepressants compared to placebo for irritability, aggression, and self-injury in autism spectrum disorder (ASD)

Atypical antipsychotics versus placebo

Primary outcomes

Behaviours of concern

Irritability

Atypical antipsychotics probably reduce irritability in the short term when compared to participants taking placebo (SMD −0.90, 95% CI −1.25 to −0.55; I^2 = 83%; 12 studies, 973 participants; moderate-certainty evidence; Analysis 1.1). The high level of heterogeneity across these 12 studies was reduced to 42% when we removed Ichikawa 2017 and Troost 2005 from the analysis (SMD −0.67, 95% CI −0.87 to −0.48; I^2 = 42%; 10 studies; 857 participants). Please refer to Summary of findings 1 for more information.

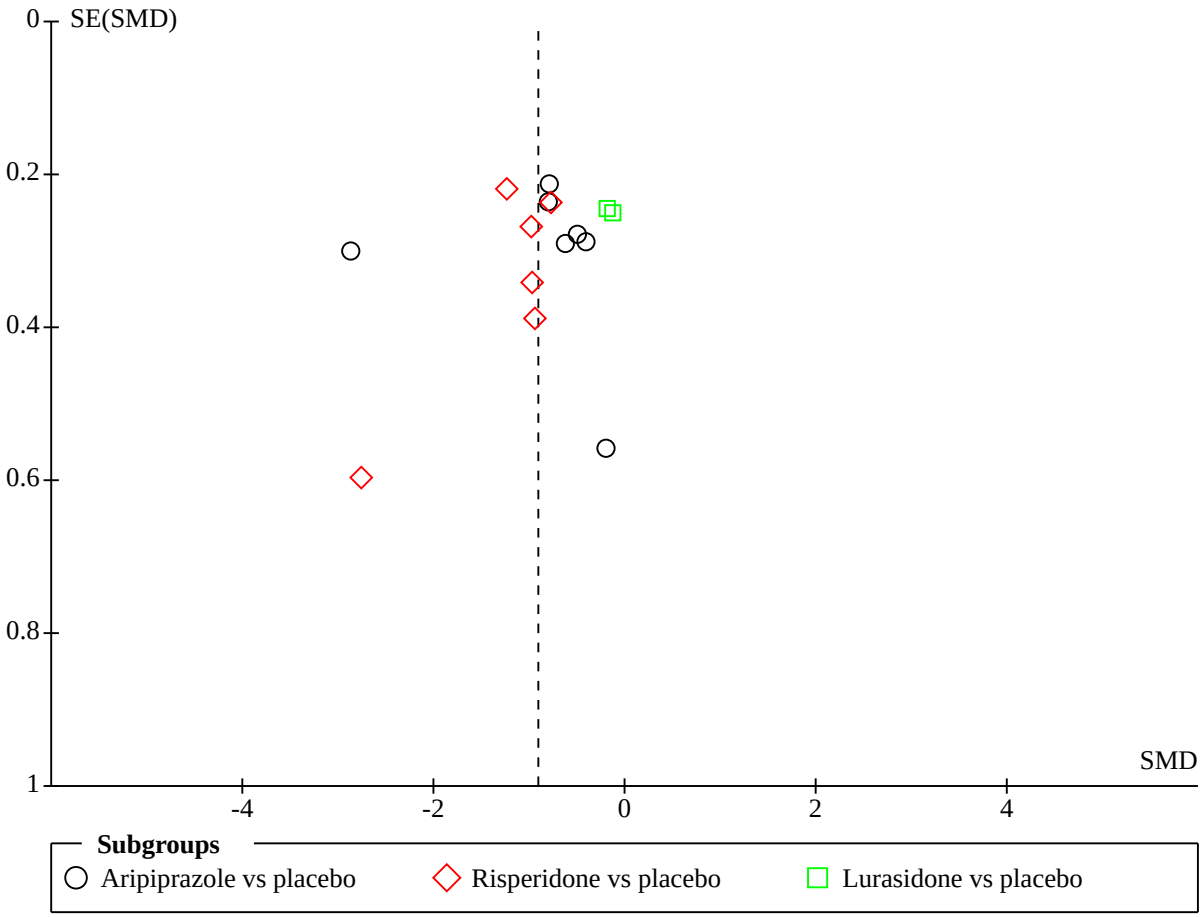
There were differences between types of atypical antipsychotics (P = 0.0005), however, there were no clear differences between atypical antipsychotics (P = 0.76) when we removed Loebel 2016 (lurasidone) from the analysis.

There were no clear differences between groups when we compared children only, and adults only (P = 0.87). There was insufficient information to conduct a subgroup analysis of irritability by cognitive or communication ability.

We were unable to include irritability data from one study in the meta-analyses because the data were skewed (Findling 2014). Details can be found in Table 4.

As there were more than 10 studies in this analysis, we created a funnel plot for this outcome but found no evidence of asymmetry (Figure 5).

Figure 5. SE: standard error; SMD: standardised mean difference Atypical antipsychotics versus placebo (12 studies, 973 participants; Analysis 1.1)



Improvement

Participants were twice as likely to improve, defined as a minimum 25% decrease in the ABC-I scores (RR 2.08, 95% CI 1.39 to 3.12; I^2 = 53%; 4 studies, 470 participants; Analysis 1.3). There were no clear differences between groups when risperidone and aripiprazole were compared (P = 0.17).

Relapse

Participants were less likely to relapse, defined as a minimum 25% increase in ABC-I scores, if they received risperidone compared to the placebo group (RR 0.30, 95% CI 0.13 to 0.68; I^2 = 0%; 2 studies, 56 participants; Analysis 1.2).

Because both studies involved children, we could not conduct a subgroup analysis. There was insufficient information to conduct a subgroup analysis by communication or cognitive ability.

Aggression

There was no clear evidence of an effect of atypical antipsychotics (risperidone) on aggression in the short term (SMD −0.44; 95% CI −0.89 to 0.01; I^2 = not applicable (NA); 1 study, 77 participants; very low-certainty evidence; Analysis 1.4). Please refer to Summary of findings 1 for more information.

Only one study provided data for this outcome, so we were unable to conduct subgroup analyses.

We could not include data from one study in the meta-analyses because the paper did not report endpoint data (Hollander 2006b). Details can be found in Table 5.

Self-injury

The evidence is very uncertain about the effect of atypical antipsychotics compared with placebo on self-injurious behaviour in the short term (SMD −1.43 95% CI −2.24 to −0.61; P < 0.0001; I^2 = NA; 1 study, 30 participants; very low-certainty evidence; Analysis 1.5). Please refer to Summary of findings 1 for more information.

We could not include data from one study in the meta-analyses because the data were skewed. Please refer to Table 6 for more information.

Only one study provided data for this outcome, so we could not conduct subgroup analyses.

Adverse effects

Cardiovascular

Participants were more likely to have tachycardia than those receiving placebo (RR 7.53, 95% CI 1.40 to 40.52; I^2 = 0%; 2 studies, 179 participants; Analysis 1.6).

Gastrointestinal

There was no clear evidence of a difference between participants receiving atypical antipsychotics and those receiving placebo (Analysis 1.7), in the reported rates of:

- diarrhoea (RR 0.93, 95% CI 0.46 to 1.88; I^2 = 0%; 5 studies, 318 participants; low-certainty evidence);
- dry mouth (RR 1.97, 95% CI 0.75 to 5.20; I^2 = 0%; 2 studies, 131 participants; low-certainty evidence);
- dyspepsia (RR 3.19, 95% CI 0.14 to 72.69; I^2 = NA; 1 study, 31 participants; low-certainty evidence);
- nausea (RR 1.47, 95% CI 0.61 to 3.56; I^2 = 0%; 4 studies, 531 participants; low-certainty evidence); or
- stomach ache (RR 0.50, 95% CI 0.19 to 1.32; I^2 = 0%; 2 studies, 166 participants; low-certainty evidence)

However, participants receiving atypical antipsychotics were more likely to report:

- abdominal pain (RR 2.70, 95% CI 1.04 to 7.07; I^2 = 0%; 4 studies, 400 participants; low-certainty evidence);
- constipation (RR 2.36, 95% CI 1.28 to 4.34; 7 studies, 596 participants; I^2 = 0%, low-certainty evidence);
- drooling (RR 9.64, 95% CI 1.29 to 72.10; 2 studies, 313 participants; I^2 = 0%, low-certainty evidence);
- hypersalivation (RR 4.15, 95% CI 1.77 to 9.71; 5 studies, 449 participants; I^2 = 0%, low-certainty evidence); and
- vomiting/nausea (RR 1.79, 95% CI 1.16 to 2.74; 9 studies, 920 participants; I^2 = 0%, low-certainty evidence).

Immune system

There was no clear evidence of a difference between atypical antipsychotics and placebo groups (Analysis 1.8), in:

- pyrexia (RR 1.81, 95% CI 0.85 to 3.86; I^2 = 0%; 5 studies, 540 participants);
- cough (RR 1.50, 95% CI 0.67 to 3.34; I^2 = 0%; 3 studies, 444 participants);
- flu-like symptoms (RR 1.95, 95% CI 0.38 to 10.04; I^2 = NA; 1 study, 79 participants);
- sore throat (RR 5.20, 95% CI 0.63 to 42.96; I^2 = NA; 1 study, 100 participants); and
- earache (RR 0.52, 95% CI 0.10 to 2.71; I^2 = NA; 1 study, 100 participants)

Metabolic

The antipsychotic group may be more likely to have an increase in appetite than the placebo group (RR 2.38, 95% CI 1.69 to 3.34; I^2 = 0%; 8 studies, 702 participants; low-certainty evidence; Analysis 1.9).

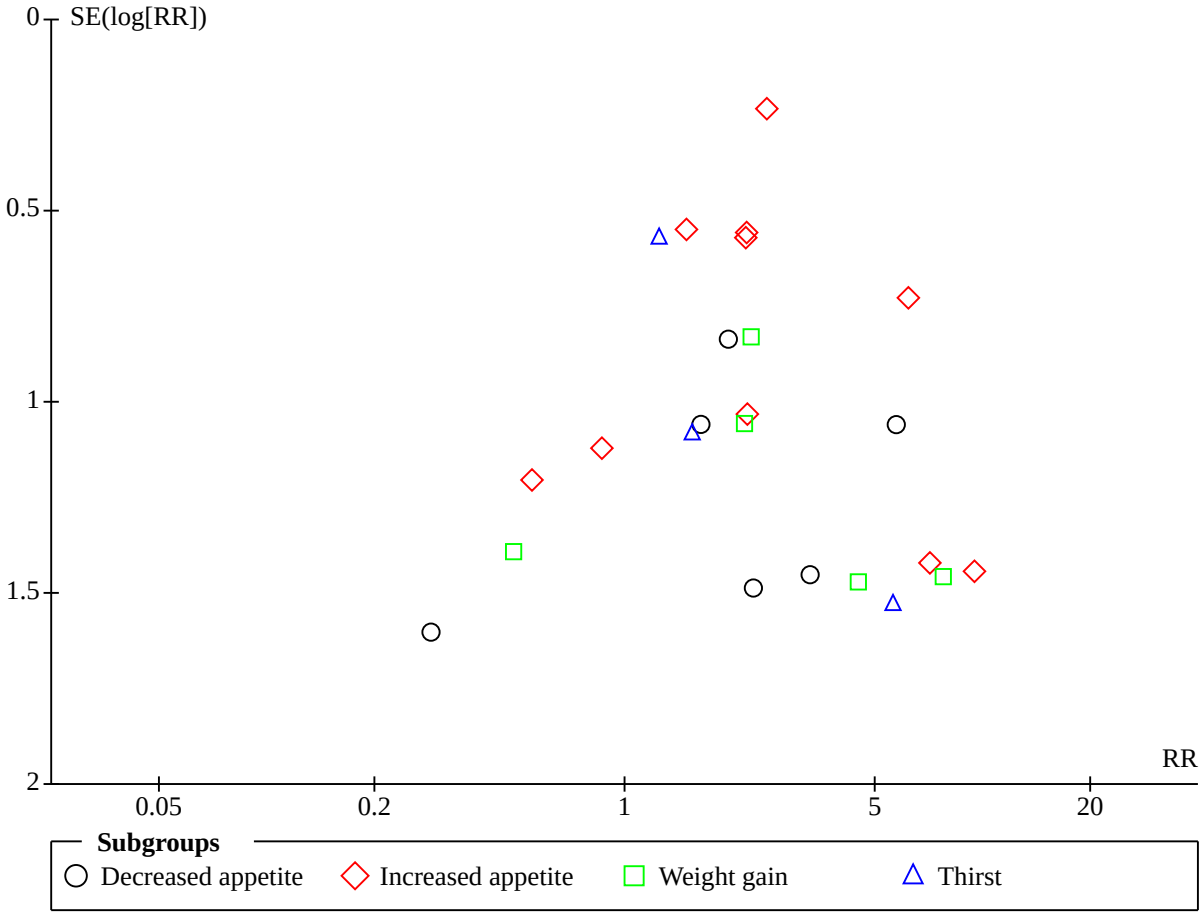
There was no difference between groups in:

- decreased appetite (RR 2.12, 95% CI 0.84 to 5.33; I^2 = 0%; 4 studies, 426 participants; moderate-certainty evidence; Analysis 1.9);
- thirst (RR 1.51, 95% CI 0.59 to 3.87; I^2 = 0%; 3 studies, 382 participants; Analysis 1.9);
- weight gain (RR 2.30, 95% CI 0.84 to 6.30; I^2 = 0%; 4 studies, 470 participants; Analysis 1.9); or
- weight gain in kilograms (MD 2.35, 95% CI 0.73 to 3.97; I^2 = NA; 1 study, 23 participants; Analysis 1.10).

We could not include data from one study in the analysis because it did not report data for both groups, and described weight gain by change in BMI (Malone 2010). In addition, we could not include data from Owen 2009 and the three datasets from Marcus 2009 because the data were skewed. Further details can be found in Table 7.

As there were more than 10 studies in this analysis, we created a funnel plot for this outcome but found no evidence of asymmetry (Figure 6).

Figure 6. log: logarithm; SE: standard error; RR: risk ratio Atypical antipsychotics versus placebo (8 studies, 702 participants; Analysis 1.9)



Musculoskeletal

In the one study with 100 participants that compared atypical antipsychotics and placebo (Analysis 1.11), there was no difference in:

- rigidity (RR 5.20, 95% CI 0.63 to 42.96; low-certainty evidence);
- movement disorder (RR 5.50, 95% CI 0.27 to 111.14; low-certainty evidence); or
- dyskinesia (RR 2.08, 95% CI 0.55 to 7.87; low-certainty evidence).

Neurological

A number of neurological AEs may be more likely to be reported in participants receiving atypical antipsychotics compared with placebo (Analysis 1.12). These were:

- dizziness (RR 4.19, 95% CI 1.10 to 16.00; I^2 = 0%; 2 studies, 139 participants, low-certainty evidence);
- fatigue (RR 2.58, 95% CI 1.68 to 3.97; I^2 = 0%; 8 studies, 881 participants; low-certainty evidence);
- sedation (RR 2.98, 95% CI 1.15 to 7.73; I^2 = 21%; 5 studies, 366 participants; low-certainty evidence);
- somnolence (RR 4.84, 95% CI 3.18 to 7.36; I^2 = 0%; 9 studies, 869 participants, low-certainty evidence); and
- tremor (RR 5.99, 95% CI 1.87 to 19.19; I^2 = 0%; 5 studies, 574 participants; low-certainty evidence).

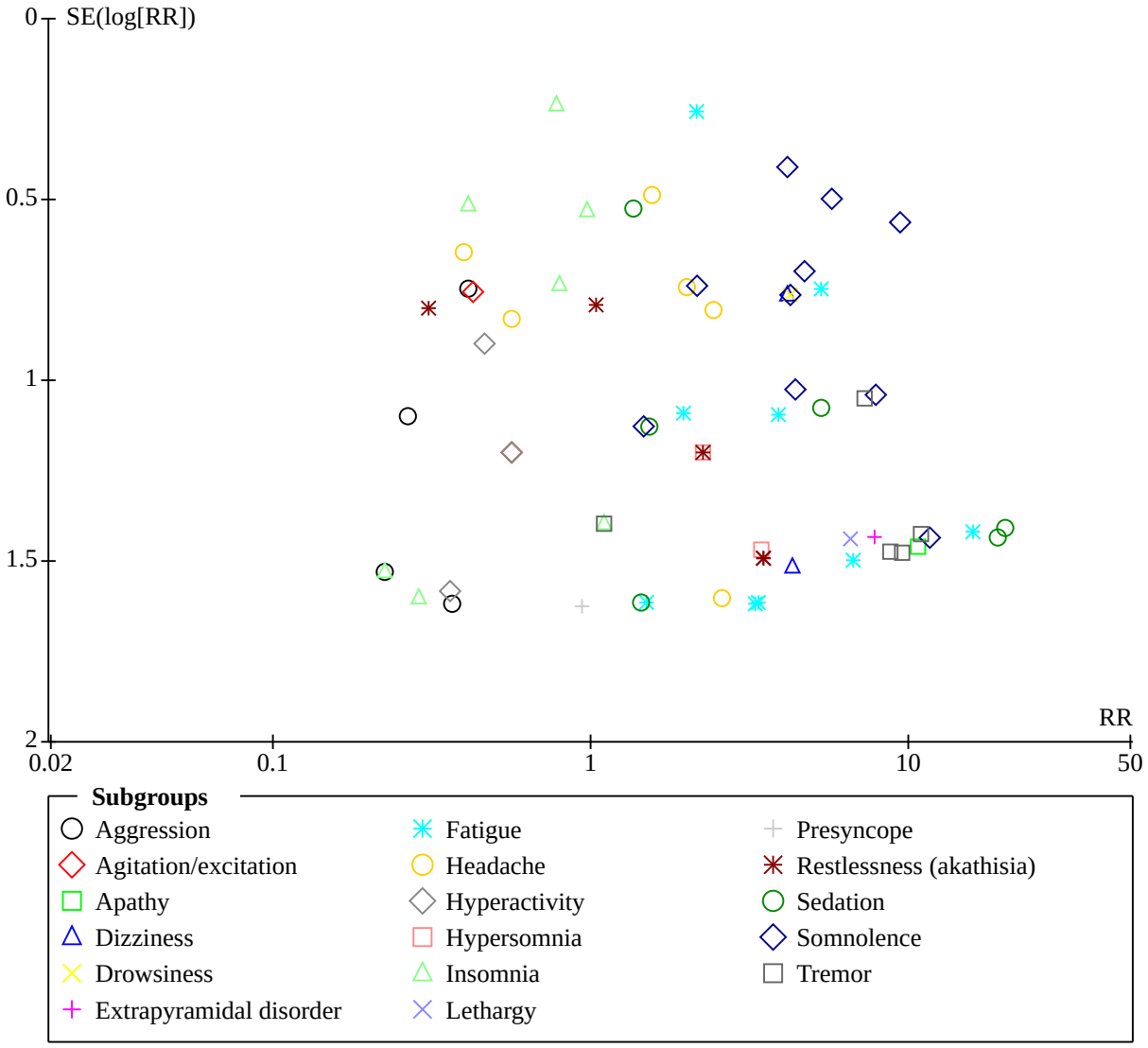
There was no clear evidence of a difference between atypical antipsychotics and placebo groups in:

- agitation/excitation (RR 0.46, 95% CI 0.13 to 1.62; I^2 = 0%; 2 studies, 97 participants);
- aggression (dichotomous) (RR 0.34, 95% CI 0.12 to 0.98; I^2 = 0%; 4 studies, 461 participants);
- apathy (RR 10.73, 95% CI 0.61 to 187.79; P = 0.10; I^2 = NA; 1 study, 79 participants);
- drowsiness (RR 4.26, 95% CI 0.95 to 19.02; P = 0.06; I^2 = NA; 1 study, 97 participants);
- extrapyramidal disorder (RR 7.83, 95% CI 0.47 to 130.01; P = 0.15; I^2 = NA; 1 study, 216 participants);
- hypersomnia (RR 2.67, 95% CI 0.43 to 16.52; I^2 = 0%; 2 studies, 282 participants);
- insomnia (RR 0.72, 95% CI 0.50 to 1.04; I^2 = 0%; 7 studies, 679 participants);
- presyncope (RR 0.94, 95% CI 0.04 to 22.72; I^2 = NA; 1 study, 216 participants);

- headache (RR 1.17, 95% CI 0.63 to 2.15; I^2 = 9%; 6 studies, 597 participants);
- lethargy (RR 6.58, 95% CI 0.39 to 110.35; I^2 = NA; 1 study, 216 participants);
- hyperactivity (RR 0.47, 95% CI 0.13 to 1.70; I^2 = 0%; 3 studies, 305 participants); and
- restlessness (akathisia) (RR 0.99, 95% CI 0.40 to 2.43; I^2 = 1%; 4 studies, 531 participants).

As there were more than 10 studies in this analysis, we created a funnel plot for this outcome but found no evidence of asymmetry (Figure 7).

Figure 7. log: logarithm; RR: risk ratio; SE: standard error; SMD: standardised mean difference Atypical antipsychotics versus placebo (11 studies, 974 participants; Analysis 1.12)



Psychological

There was no clear evidence of a difference between atypical antipsychotic and placebo groups in

- anxiety (RR 1.34, 95% CI 0.65 to 2.76; I^2 = 0%; 2 studies, 139 participants; very low-certainty evidence); or
- depression (RR 3.86, 95% CI 0.46 to 32.60; I^2 = 0%; 2 studies, 79 participants; very low-certainty evidence; Analysis 1.13).

Respiratory

There was no clear evidence of a difference between the atypical antipsychotic and placebo groups in the respiratory symptoms of:

- ear infection (RR 5.63, 95% CI 0.28 to 112.84; I^2 = NA; 1 study, 66 participants);
- epistaxis (RR 5.63, 95% CI 0.28 to 112.84; I^2 = NA; 1 study, 66 participants);

- nasal congestion (RR 2.39, 95% CI 0.52 to 11.00; I^2 = 0%; 2 studies, 313 participants);
- nasopharyngitis (RR 1.26, 95% CI 0.73 to 2.17; I^2 = 0%; 6 studies, 702 participants);
- pharyngolaryngeal pain (RR 0.31, 95% CI 0.06 to 1.48; I^2 = NA; 1 study, 216 participants); or
- rhinitis (RR 2.68, 95% CI 0.93 to 7.71; I^2 = NA; 1 study, 79 participants).

However, there was a higher rate of upper respiratory tract infection in the antipsychotic group (RR 2.15, 95% CI 1.08 to 4.27; I^2 = 8%; 6 studies, 640 participants; Analysis 1.14).

Skin

There was no clear evidence of a difference between groups in the likelihood of:

- bruise (RR 0.32, 95% CI 0.03 to 2.96; I^2 = NA; 1 study, 92 participants); or
- rash (RR 0.79, 95% CI 0.14 to 4.62; I^2 = 0%; 2 studies, 228 participants; Analysis 1.15).

Urinary

Enuresis was not different between the atypical antipsychotic and placebo groups (RR 1.12, 95% CI 0.67 to 1.86; I^2 = 0%; 6 studies, 552 participants; Analysis 1.16).

Other adverse effects

No other AEs were reported.

Secondary outcomes

Quality of life

Child, adolescent or adult with autism

Quality of life was not different at endpoint in participants receiving aripiprazole compared to those receiving placebo (SMD 0.95, 95% CI 0.14 to 1.76; I^2 = 75%; 2 studies, 135 participants; Analysis 1.17).

We could not include two of the quality-of-life datasets (5 mg/day and 10 mg/day) from Marcus 2009 in the meta-analysis because the data were skewed. Details can be found in Table 8.

Tolerability/acceptability

Participants were less likely to be lost to follow-up in the antipsychotic group than the placebo group (RR 0.54, 95% CI 0.41 to 0.71; I^2 = 12%; 13 studies, 1004 participants; Analysis 1.18).

Apart from one study, all studies involved children and adolescents, and therefore, we could not conduct a subgroup analysis of differences in tolerability based on age.

Neurohormones versus placebo

Primary outcomes

Challenging behaviours

Irritability

At short-term follow-up, there was some evidence that neurohormones may have a minimal to no effect on irritability (SMD −0.18, 95% CI −0.37 to −0.00; I^2 = 0%; 8 studies, 466 participants; low-certainty evidence; Analysis 2.1).

There were no differences between types of neurohormones (P = 0.54) or when male participants were compared to a mixed population of male and female participants (P = 0.94). There was insufficient information to conduct subgroup analyses of irritability by communication ability or cognitive ability.

We could not include data from three studies in the analysis because the data were skewed (Levy 2003; Squassante 2018; Unis 2002). Details can be found in Table 9.

Please refer to Summary of findings 2 for further information.

Self-injury

There was no clear evidence of a difference in self-injury between participants receiving neurohormones compared to those receiving placebo at endpoint (SMD −0.37, 95% CI −0.93 to 0.19; I^2 = NA; 1 study, 50 participants; Analysis 2.2) and at three-month follow-up (SMD −0.32, 95% CI −0.88 to 0.23; I^2 = NA; 1 study, 50 participants; Analysis 2.2).

We could not include data from one study in the analysis because the data were skewed (Guastella 2015a). Details can be found in Table 10.

Adverse effects

Cardiovascular

There was no clear evidence of a difference between participants receiving neurohormones compared to those receiving placebo in the likelihood of:

- cardiac disorders (RR 1.45, 95% CI 0.23 to 9.05; I^2 = 0%; 3 studies, 456 participants);
- palpitations (RR 2.96, 95% CI 0.12 to 72.04; I^2 = NA; 1 study, 290 participants); or
- vascular disorders (RR 1.00, 95% CI 0.06 to 15.57; I^2 = NA; 1 study, 106 participants Analysis 2.3).

Gastrointestinal

Only vomiting showed a difference between groups when oxytocin was compared to a placebo (RR 0.45, 95% CI 0.21 to 0.97; I^2 = 0%; 4 studies, 409 participants, low-certainty evidence; Analysis 2.4).

There was no clear evidence of differences between the neurohormone and placebo groups in any of the other gastrointestinal AEs:

- abdominal pain or discomfort (RR 0.42, 95% CI 0.17 to 1.07; I^2 = NA; 1 study, 290 participants);
- constipation (RR 0.89, 95% CI 0.46 to 1.73; 3 studies, 361 participants);
- diarrhoea (RR 0.71, 95% CI 0.39 to 1.28; I^2 = 0%; 5 studies, 450 participants);
- dry mouth (RR 0.43, 95% CI 0.06 to 2.88; I^2 = 0%; 2 studies, 350 participants);
- encopresis (RR 0.74, 95% CI 0.17 to 3.25, I^2 = NA; 1 study, 290 participants);

- gastrointestinal disorders (RR 1.25, 95% CI 0.35 to 4.49; I^2 = 0%; 2 studies, 166 participants);
- nausea (RR 0.14, 95% CI 0.01 to 2.65; I^2 = NA; 1 study, 60 participants);
- salivary hypersecretion (RR 0.32, 95% CI 0.03 to 2.99; I^2 = 0%; 2 studies 319 participants); and
- stomatitis (RR 0.13, 95% CI 0.02 to 1.11; I^2 = 0%; 2 studies, 321 participants, low-certainty evidence Analysis 2.4).

Immune system

Infections and infestations were not different between groups (RR 2.00, 95% CI 0.81 to 4.93; I^2 = NA; 1 study, 106 participants; Analysis 2.5).

Metabolic

There was no clear evidence of a difference between neurohormone and placebo groups in any of the metabolic AEs. These included:

- decreased appetite (RR 0.67, 95% CI 0.37 to 1.22; I^2 = 0%; 4 studies, 409 participants; very low-certainty evidence);
- increased appetite (RR 1.74, 95% CI 0.96 to 3.16; I^2 = 0%; 2 studies, 350 participants);
- metabolism and nutrition disorders (RR 0.50, 95% CI 0.05 to 5.35; I^2 = NA; 1 study, 106 participants; very low-certainty evidence);
- thirst (RR 1.42, 95% CI 0.35 to 5.67; I^2 = 15%; 2 studies, 319 participants);
- weight gain (RR 1.21, 95% CI 0.52 to 2.82; I^2 = NA; 1 study, 290 participants);
- weight change (RR -0.45, 95% CI -1.76 to 0.86; I^2 = NA; 1 study, 24 participants) or
- weight loss (RR 1.97, 95% CI 0.69 to 5.63; I^2 = NA; 1 study, 290 participants; Analysis 2.6).

We could not include one study in the analysis because the data were skewed (Sikich 2013). Details can be found in Table 10.

There was no clear evidence of a difference between neurohormones and placebo groups in mean change in weight in kilograms (SMD −0.45; 95% CI −1.76 to 0.86; 1 study, 24 participants; Analysis 2.7).

Musculoskeletal

There was no difference between participants receiving neurohormones and those receiving placebo in:

- muscle spasms (RR 2.81, 95% CI 0.12 to 63.83; I^2 = NA; 1 study, 29 participants; very low-certainty evidence);
- musculoskeletal and connective tissue disorders (RR 3.00, 95% CI 0.12 to 72.02; I^2 = NA; 1 study, 106 participants); and
- rhabdomyolysis (RR 1.47, 95% CI 0.06 to 35.64; I^2 = NA; 1 study, 220 participants); Analysis 2.8.

Neurological

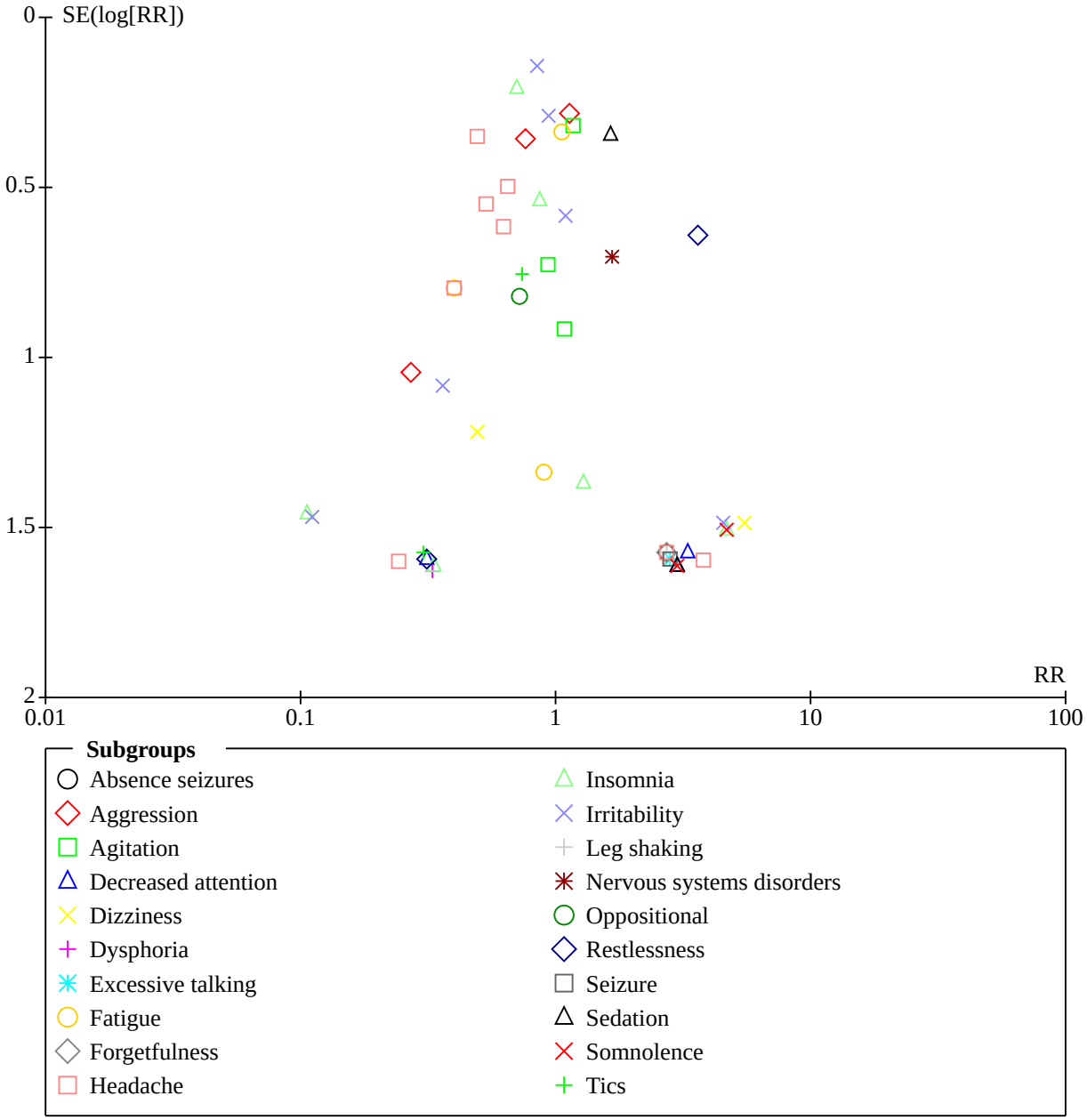
Numerous neurological AEs were reported in studies comparing neurohormones to placebo. We found low-certainty evidence that neurohormones may decrease the risk of headaches (RR 0.58, 95% CI 0.38 to 0.89; I^2 = 0%; 7 studies, 689 participants; Analysis 2.9).

The other neurological AEs showed no differences between the groups and included:

- absence seizures (RR 2.73, 95% CI 0.12 to 59.57; 1 study, 19 participants);
- agitation (RR 1.12, 95% CI 0.65 to 1.94; I^2 = 0%; 3 studies, 344 participants; low-certainty evidence);
- aggression (dichotomous) (RR 0.91, 95% CI 0.57 to 1.44; I^2 = 9%; 3 studies, 356 participants; low-certainty evidence);
- decreased attention (RR 1.46, 95% CI 0.24 to 8.84; 3 studies, 108 participants);
- dizziness (RR 0.65, 95% CI 0.08 to 5.27; I^2 = 44%; 3 studies, 369 participants; low-certainty evidence);
- excessive talking (RR 2.81, 95% CI 0.12 to 63.83; 1 study, 29 participants, low-certainty evidence);
- fatigue (RR 0.91, 95% CI 0.50 to 1.65; I^2 = 0%; 3 studies, 120 participants; low-certainty evidence);
- insomnia (RR 0.72, 95% CI 0.50 to 1.04; I^2 = 0%; 6 studies, 477 participants; low-certainty evidence);
- irritability (dichotomous) (RR 0.86, 95% CI 0.68 to 1.10; I^2 = 0%; 6 studies, 655 participants);
- leg shaking (RR 2.73, 95% CI 0.12 to 59.57; I^2 = NA; 1 study, 19 participants; low-certainty evidence);
- nervous system disorders (RR 1.67, 95% CI 0.42 to 6.62; I^2 = NA; 1 study, 106 participants);
- oppositional behaviour (RR 0.72, 95% CI 0.14 to 3.61; I^2 = NA; 1 study, 25 participants; low-certainty evidence);
- restlessness (RR 1.64, 95% CI 0.17 to 15.47; I^2 = 51%; 2 studies, 319 participants; low-certainty evidence);
- seizure (RR 2.81, 95% CI 0.12 to 63.83; I^2 = NA; 1 study 29 participants; low-certainty evidence);
- sedation (RR 1.69, 95% CI 0.87 to 3.27; I^2 = 0%; 2 studies, 350 participants; low-certainty evidence);
- somnolence (RR 3.81, 95% CI 0.44 to 32.96; I^2 = 0%; 2 studies, 89 participants; low-certainty evidence); or
- tics (RR 0.63, 95% CI 0.16 to 2.38; I^2 = 0%; 2 studies, 309 participants; low-certainty evidence; Analysis 2.9).

As there were more than 10 studies in this analysis, we created a funnel plot for this outcome but found no evidence of asymmetry (Figure 8).

Figure 8. log: logarithm; RR: risk ratio; SE: standard error; SMD: standardised mean difference Neurohormone versus placebo (10 studies, 863 participants; Analysis 2.9)



Psychological

The psychological outcomes were not different between those receiving neurohormones and those receiving placebo. These included:

- anxiety (RR 3.05, 95% CI 0.50 to 18.55; I^2 = 0%; 2 studies, 97 participants);
- depression (RR 0.89, 95% CI 0.29 to 2.68; I^2 = 0%; 4 studies, 427 participants);
- panic attack (RR 0.30, 95% CI 0.01 to 6.62; I^2 = NA; 1 study, 19 participants);
- psychiatric (RR 4.00, 95% CI 0.46 to 34.61; I^2 = NA; 1 study, 106 participants); and
- self-injury (dichotomous) (RR 1.00, 95% CI 0.11 to 9.35; 2 studies, 118 participants; I^2 = 0%; Analysis 2.10).

Respiratory

There was no clear evidence of a difference between neurohormone and placebo groups in respiratory symptoms. These included:

- cold symptoms (RR 0.65, 95% CI 0.26 to 1.65; ^{2} = 0%; 2 studies, 73 participants);

- cough (RR 1.35, 95% CI 0.81 to 2.25; I^2 = 0%; 5 studies, 430 participants;);
- croup (RR 3.23, 95% CI 0.14 to 72.46; I^2 = NA; 1 study, 25 participants);
- epistaxis (RR 1.21, 95% CI 0.63 to 2.31; I^2 = 0%; 3 studies, 379 participants);
- nasal congestion (RR 0.79, 95% CI 0.59 to 1.05; I^2 = 0%; 5 studies, 468 participants);
- nasal irritation/runny nose (RR 0.55, 95% CI 0.10 to 2.92; I^2 = NA; 1 study, 40 participants);
- nasopharyngitis (RR 0.93, 95% CI 0.15 to 5.76; I^2 = NA; 1 study, 29 participants);
- respiratory, thoracic and mediastinal disorders (RR 0.49, 95% CI 0.09 to 2.56; I^2 = 0%; 2 studies, 147 participants);
- sinusitis (RR 0.47, 95% CI 0.05 to 4.60; I^2 = NA; 1 study, 29 participants);
- upper respiratory tract infection (RR 1.10, 95% CI 0.35 to 3.47; I^2 = 0%; 2 studies, 273 participants; Analysis 2.11).

Skin

There was no clear evidence of a difference in the neurohormone group compared to placebo in:

- general/systemic disorders and administration site conditions (RR 4.00, 95% CI 0.46 to 34.61; I^2 = NA; 1 study, 106 participants); or
- rash (RR 1.12, 95% CI 0.63 to 1.97; I^2 = 0%; 4 studies, 416 participants; Analysis 2.12).

Urinary

There was no difference between the neurohormone group and the placebo group in renal and urinary disorders (RR 3.00, 95% CI 0.12 to 72.02; I^2 = NA; 1 study, 106 participants). However, neurohormones (oxytocin) showed a reduced risk of enuresis when compared to placebo (RR 0.18, 95% CI 0.06 to 0.62; I^2 = NA; 1 study, 290 participants; Analysis 2.13).

Other adverse effects

There was no clear evidence of a difference in the neurohormone group compared to placebo in:

- injury, poisoning, and procedural complications (RR 3.00, 95% CI 0.12 to 72.02; I^2 = NA; 1 study, 106 participants);
- investigations (RR 0.50, 95% CI 0.05 to 5.35; I^2 = NA; 1 study, 106 participants);
- lymphadenopathy (RR 0.33, 95% CI 0.01 to 7.87; I^2 = NA; 1 study, 60 participants);
- neoplasms benign, malignant, and unspecified (RR 3.00, 95% CI 0.12 to 72.02; I^2 = NA; 1 study, 106 participants); or
- increased troponin 1 (RR 1.47, 95% CI 0.06 to 35.64; I^2 = NA; 1 study, 220 participants, Analysis 2.14).

Please refer to Summary of findings 2 for further information.

Secondary outcomes

Quality of life

There was no clear evidence of a difference in quality of life between neurohormone and placebo groups in the short term (SMD 0.70, 95% CI −0.12 to 1.53; P = 0.001, I^2 = 81%; 4 studies, 191 participants; Analysis 2.15).

We were unable to include data from five studies because the data were skewed (Bernaerts 2020; Jacob 2022; NCT01908205; NCT02940574; Squassante 2018). Details can be found in Table 11

Tolerability/acceptability

There was no clear evidence of a difference in loss to follow-up between neurohormone and placebo groups (RR 1.10, 95% CI 0.87 to 1.40; I^2 = 0%; 14 studies, 1312 participants; Analysis 2.16).

Outcomes not reported

No data were available for the outcome of aggression.

Comparison 3: ADHD-related medications versus placebo

Primary outcomes

Challenging behaviours

Irritability

ADHD-related medications may reduce irritability in the short term when compared to placebo (SMD −0.20, 95% CI −0.40 to −0.01; 10 studies, 400 participants; P = 0.86, I^2 = 0%; low-certainty evidence; Analysis 3.1). Please refer to Summary of findings 3 for further information.

There was no difference between groups when we compared stimulant to non-stimulant ADHD-related medication (P = 0.33), when we compared children only to children and adults (P = 0.74) and when we compared male participants to a mixed male and female sample (P = 0.58). There was insufficient information to conduct subgroup analyses of irritability by communication ability or cognitive ability.

Self-injury

At short-term follow-up, there was no clear evidence that ADHD-related medications have an effect on self-injurious behaviour (SMD −0.62; 95% CI −1.63 to 0.39, I^2 = NA; 1 study, 16 participants, very low-certainty evidence; Analysis 3.2). Please refer to Summary of findings 3 for further information.

There was only one study, so we could not conduct a subgroup analysis.

Adverse effects

Cardiovascular

There was no clear evidence of a difference between groups in ADHD-related medications AEs (bradycardia and tachycardia) (RR 0.64, 95% CI 0.16 to 2.54; 2 studies, 114 participants). There was no difference between the ADHD-related medication and placebo groups in the likelihood of:

- bradycardia (RR 0.36, 95% CI 0.09 to 1.37; I^2 = NA; 1 study, 66 participants), or

- tachycardia (RR 3.52, 95% CI 0.44 to 27.85; I^2 = 0%; 2 studies, 48 participants; Analysis 3.3).

Gastrointestinal

When ADHD-related medications were compared to placebo (Analysis 3.4) there was no clear evidence of a difference in the gastrointestinal side effects of:

- diarrhoea (RR 0.81, 95% CI 0.46 to 1.40; I^2 = 0%; 6 studies, 426 participants);
- stomach ache (RR 2.58, 95% CI 1.10 to 6.06; I^2 = 0%; 2 studies, 86 participants; Analysis 3.4); or
- vomiting (RR 1.35, 95% CI 0.81 to 2.25; I^2 = 0%; 4 studies, 347 participants).

However, ADHD-related medications may increase the risk of:

- constipation (RR 2.68, 95% CI 1.61 to 4.45; I^2 = 0%; 5 studies, 220 participants);
- dry mouth (RR 5.92, 95% CI 1.86 to 18.81; I^2 = 0%; 3 studies, 102 participants);
- nausea (RR 3.08, 95% CI 1.51 to 6.29; I^2 = 0%; 5 studies, 239 participants), and
- stomach or abdominal discomfort (RR 2.26, 95% CI 1.41 to 3.63; I^2 = 0%; 6 studies, 504 participants).

Immune system

There was no clear evidence of differences between groups on the immune effects of:

- fever (RR 0.27, 95% CI 0.06 to 1.27; I^2 = 0%; 3 studies, 183 participants);
- influenza (RR 7.14, 95% CI 0.38 to 134.69; I^2 = NA; 1 study, 97 participants);
- myalgia (RR 4.72, 95% CI 0.56 to 39.55; I^2 = 0%; 2 studies, 115 participants); or
- weakness (RR 3.20, 95% CI 0.35 to 29.10; I^2 = NA; 1 study, 62 participants; Analysis 3.5).

Metabolic

ADHD-related medications may increase the risk of decreased appetite when compared to placebo (RR 2.15, 95% CI 1.55 to 2.99; I^2 = 0%; 9 studies, 511 participants; low-certainty evidence; Analysis 3.6).

There were no clear differences between groups in:

- increased appetite (RR 0.67, 95% CI 0.14 to 3.34; I^2 = 0%; 2 studies, 121 participants; low-certainty evidence); and
- increased energy (RR 1.60, 95% CI 0.65 to 3.95; I^2 = NA; 1 study, 62 participants; Analysis 3.6).

We were unable to include one study in the analysis because the data were skewed (Jaselskis 1992). Details can be found in Table 12.

Neurological

Very uncertain evidence shows that ADHD-related medications compared to placebo may increase:

- drowsiness (RR 3.42, 95% CI 1.54 to 7.59; I^2 = 20%; 4 studies, 186 participants; very low-certainty evidence);
- emotion/tearfulness (RR 6.32, 95% CI 2.47 to 16.18; I^2 = 0%; 2 studies, 128 participants; very low-certainty evidence);
- fatigue (RR 3.73, 95% CI 1.98 to 7.03; I^2 = 0%; 4 studies, 235 participants; very low-certainty evidence);
- headache (RR 1.63, 95% CI 1.09 to 2.44; I^2 = 0%; 8 studies, 383 participants; very low-certainty evidence);
- insomnia (RR 1.58, 95% CI 1.01 to 2.47; I^2 = 5%; 7 studies, 411 participants; very low-certainty evidence);
- irritability (dichotomous) (RR 1.61, 95% CI 1.25 to 2.07; I^2 = 0%; 6 studies, 336 participants; very low-certainty evidence; Analysis 3.7).

There was no clear evidence (all very low-certainty evidence) of differences between groups in:

- agitation (RR 0.95, 95% CI 0.56 to 1.60; I^2 = NA; 1 study, 128 participants);
- aggression (dichotomous) (RR 0.95, 95% CI 0.58 to 1.53; I^2 = 0%; 5 studies, 365 participants);
- dizziness (RR 2.17, 95% CI 0.63 to 7.53; I^2 = 0%; 3 studies, 175 participants);
- hyperactivity (RR 0.68, 95% CI 0.06 to 7.20; I^2 = 39%; 2 studies, 115 participants);
- increased motor activity (RR 1.89, 95% CI 0.48 to 7.47; I^2 = NA; 1 study, 66 participants);
- motor tics (RR 2.33, 95% CI 0.51 to 10.69; I^2 = 20%; 3 studies, 118 participants);
- nightmares (RR 1.48, 95% CI 0.38 to 5.75; I^2 = 0%; 2 studies, 122 participants);
- repetitive behaviour (RR 1.59, 95% CI 0.74 to 3.39; I^2 = 0%; 2 studies, 128 participants);
- restlessness (RR 1.52, 95% CI 0.06 to 40.44; I^2 = 71%; 2 studies, 76 participants);
- sleep disturbance (RR 1.12, 95% CI 0.54 to 2.31; I^2 = 0%; 2 studies, 84 participants);
- talking excessively (RR 0.24, 95% CI 0.06 to 1.01, I^2 = NA; 1 study, 62 participants);
- waking (RR 1.60, 95% CI 0.29 to 8.92, I^2 = NA; 1 study, 62 participants); and
- tremor (RR 3.00, 95% CI 0.14 to 64.26; I^2 = NA; 1 study, 16 participants; Analysis 3.7).

There was also no clear evidence of a difference in the continuous neurological AEs of:

- drowsiness (SMD 4.80, 95% CI 0.55 to 9.05; I^2 = NA; 1 study, 8 participants); and
- decreased activity (SMD 2.00, 95% CI −2.66 to 6.66; I^2 = NA; 1 study, 8 participants; Analysis 3.8).

Psychological

ADHD-related medications may increase the risk of depression in the ADHD-related medication group when compared to placebo although the evidence is very uncertain (RR 2.45, 95% CI 1.12

to 5.36; I^2 = 0%; 3 studies, 152 participants, very low-certainty evidence).

There was no clear evidence of differences between groups in:

- anxiety (RR 1.39, 95% CI 0.74 to 2.62; I^2 = 10%; 5 studies, 252 participants);
- mood change (RR 13.00, 95% CI 0.78 to 216.39; I^2 = NA; 1 study, 40 participants);
- self-injury (dichotomous) (RR 1.67, 95% CI 0.78 to 3.58; I^2 = 0%; 3 studies, 188 participants; moderate-certainty evidence);
- 'silly' behaviour (RR 0.64, 95% CI 0.17 to 2.45; I^2 = NA; 1 study, 62 participants); or
- social withdrawal (RR 2.28, 95% CI 0.39 to 13.37; 2 studies, 126 participants; I^2 = 43%) Analysis 3.9.

Respiratory

There was no clear evidence of a difference between groups in cough (RR 0.81, 95% CI 0.26 to 2.46; I^2 = 0%; 2 studies, 122 participants; Analysis 3.10).

Skin

There was no clear evidence of a difference in the likelihood of:

- rash (RR 2.21, 95% CI 0.79 to 6.16; I^2 = 14%; 3 studies, 102 participants); or
- skin picking (RR 0.36, 95% CI 0.04 to 3.23; I^2 = NA; 1 study, 62 participants; Analysis 3.11).

Urinary

Enuresis was not different between groups (RR 0.81, 95% CI 0.19 to 3.55; P = 0.65, I^2 = 0%; 2 studies, 122 participants; Analysis 3.12).

Secondary outcomes

Quality of life

There was no clear evidence of a difference between groups in quality of life (SMD 0.21. 95% CI −0.33 to 0.75; I^2 = NA; 1 study, 54 participants; Analysis 3.13).

Tolerability/acceptability

Follow-up was not different in the ADHD-related and placebo groups (RR 0.91, 95% CI 0.50 to 1.69; I^2 = 7%; 9 studies, 380 participants; Analysis 3.14).

Outcomes not reported

No data were available for the outcomes of aggression, musculoskeletal AEs, or other AEs.

Antidepressants versus placebo

Primary outcomes

Challenging behaviours

Irritability

There was no clear evidence of a difference in irritability in the short term when antidepressants were compared to placebo (SMD −0.06, 95% CI −0.30 to 0.18; I^2 = 0%, 3 studies, 267 participants; low-certainty evidence; Analysis 4.1). There were no clear differences between groups when we compared types of antidepressants (P = 0.76), or when we compared male participants to a mixed population of male and female participants (P = 0.67).

We were unable to include data from five studies in the analysis because data were either not reported, reported without standard deviation, reported as median and range, or were skewed (Carminati 2016; Gordon 1993; Hollander 2012; NCT00183339; Remington 2001). Details of these studies can be found in Table 13.

Aggression

We were unable to pool data from two studies because the data were reported as a median and range or not reported fully (Carminati 2016; McDougle 1996). Details of the studies can be found in Table 14.

Self-injury

We were unable to include data from three studies in the analysis because the data were reported as median and range or the data were skewed (Carminati 2016; Mouti 2014; King 2009). Details can be found in Table 1.

Adverse effects

Cardiovascular

There was no clear evidence of a difference between antidepressants and placebo in the cardiovascular AEs of:

- flushing (RR 2.00, 95% CI 0.24 to 16.61; I^2 = NA; 1 study 12 participants); or
- tachycardia (RR 2.67, 95% CI 0.31 to 23.25; I^2 = 0%; 2 studies, 35 participants; Analysis 4.2).

Gastrointestinal

Antidepressants were no more likely to be associated with gastrointestinal AEs than placebo. These included:

- constipation (RR 0.95, 95% CI 0.09 to 10.03; I^2 = 61%; 2 studies, 70 participants);
- diarrhoea (RR 0.94, 95% CI 0.33 to 2.64; I^2 = 81%; 4 studies, 409 participants);
- dry mouth (RR 2.00, 95% CI 0.24 to 16.61; I^2 = NA; 1 study, 12 participants);
- gastrointestinal disturbance (RR 1.41, 95% CI 0.97 to 2.05; I^2 = 0%; 3 studies, 341 participants);
- nausea/abdominal pain (RR 1.67, 95% CI 0.85 to 3.27; I^2 = 0%; 5 studies, 251 participants); and
- vomiting (RR 1.49, 95% CI 0.76 to 2.92; I^2 = 17%; 5 studies, 400 participants; Analysis 4.3).

Immune system

There were no differences between participants receiving antidepressants and those receiving placebo in:

- allergies (RR 1.42, 95% CI 0.70 to 2.88; I^2 = NA; 1 study, 149 participants);
- cold, flu or other systemic infection (RR 1.24, 95% CI 0.82 to 1.87; I^2 = NA; 1 study, 149 participants); and
- infections (RR 1.15, 95% CI 0.85 to 1.56; I^2 = 0%; 3 studies, 472 participants; Analysis 4.4).

Metabolic

There was no clear evidence of a difference between antidepressant and placebo groups for:

- appetite disturbance (RR 0.55, 95% CI 0.14 to 2.23; I^2 = NA; 1 study, 165 participants; very low-certainty evidence);
- decreased appetite (RR 1.35, 95% CI 0.68 to 2.69; I^2 = 0%; 4 studies, 242 participants; very low-certainty evidence);
- increased appetite (RR 0.91, 95% CI 0.35 to 2.38; I^2 = NA; 1 study, 149 participants; very low-certainty evidence); or
- weight gain (RR 1.47, 95% CI 0.08 to 27.39; I^2 = 46%; 2 studies, 93 participants; very low-certainty evidence; Analysis 4.5).

There may be higher levels of decreased energy (RR 1.94, 95% CI 1.13 to 3.33; P = 0.02; I^2 = NA; 1 study, 149 participants, very low-certainty evidence) in the antidepressant group although the evidence is very uncertain.

Musculoskeletal

There was no clear evidence of a difference between antidepressants and placebo in the musculoskeletal AEs of:

- motor disturbance (RR 0.31, 95% CI 0.03 to 2.88; I^2 = NA; 1 study, 165 participants; very low-certainty evidence); or
- neck pain (RR 2.09, 95% CI 0.09 to 48.04; I^2 = NA; 1 study, 37 participants; Analysis 4.6).

Neurological

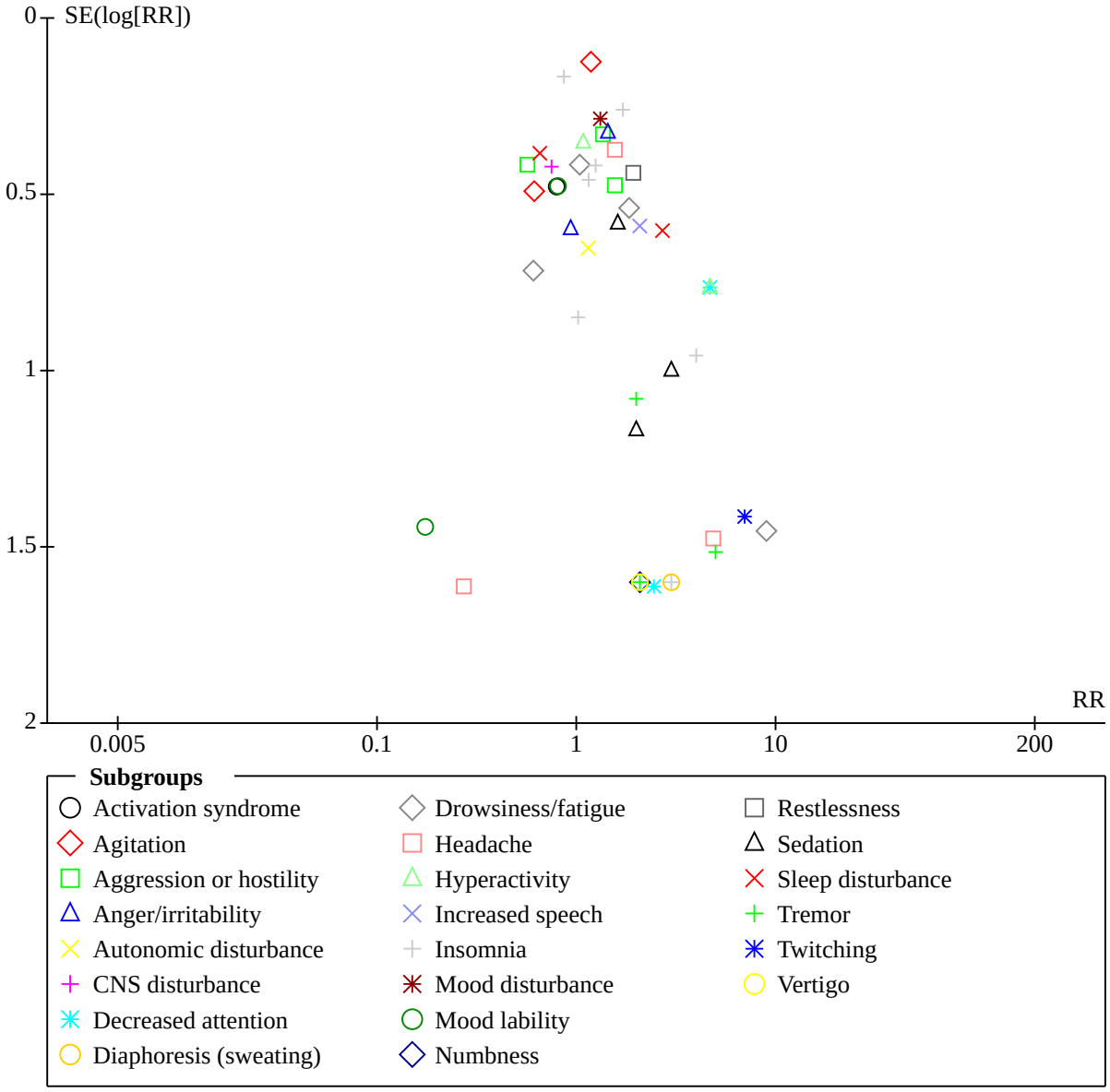
There was no clear evidence of a difference between antidepressant and placebo groups in most of the reported neurological AEs (Analysis 4.7). These included:

- activation syndrome (RR 0.80, 95% CI 0.31 to 2.04; I^2 = NA; 1 study, 159 participants);
- agitation (RR 1.01, 95% CI 0.59 to 1.75; I^2 = 40%; 2 studies, 197 participants; low-certainty evidence);
- aggression or hostility (dichotomous) (RR 1.07, 95% CI 0.59 to 1.95; I^2 = 42%; 3 studies, 225 participants; low-certainty evidence);
- anger/irritability (dichotomous) (RR 1.31, 95% CI 0.75 to 2.29; I^2 = 0%; 2 studies, 167 participants; low-certainty evidence);
- autonomic disturbance (RR 1.15, 95% CI 0.32 to 4.12; I^2 = NA; 1 study, 165 participants; low-certainty evidence);
- central nervous system disturbance (RR 0.75, 95% CI 0.33 to 1.72; I^2 = NA; 1 study, 165 participants; low-certainty evidence);
- diaphoresis (sweating) (RR 3.00, 95% CI 0.13 to 69.09; I^2 = NA; 1 study, 36 participants; low-certainty evidence);
- drowsiness/fatigue (RR 1.25, 95% CI 0.65 to 2.41; I^2 = 16%; 4 studies, 282 participants; low-certainty evidence);
- headache (RR 1.53, 95% CI 0.77 to 3.07; I^2 = 0%; 3 studies, 244 participants; low-certainty evidence);
- hyperactivity (RR 1.93, 95% CI 0.47 to 7.82; I^2 = 67%; 2 studies, 207 participants; low-certainty evidence);
- increased speech (RR 2.08, 95% CI 0.66 to 6.62; I^2 = NA; 1 study, 149 participants; low-certainty evidence);
- insomnia (RR 1.19, 95% CI 0.87 to 1.63; I^2 = 18%; 7 studies, 449 participants; low-certainty evidence);
- mood disturbance (RR 1.32, 95% CI 0.75 to 2.31; I^2 = NA; 1 study, 165 participants; low-certainty evidence);
- mood lability (RR 0.69, 95% CI 0.27 to 1.74; I^2 = 2%; 2 studies, 167 participants; low-certainty evidence);
- numbness (RR 2.09, 95% CI 0.09 to 48.04; I^2 = NA; 1 study, 37 participants; low-certainty evidence);
- restlessness (RR 1.93, 95% CI 0.82 to 4.57; I^2 = NA; 1 study, 149 participants; low-certainty evidence);
- sedation (RR 1.91, 95% CI 0.77 to 4.72; I^2 = 0%; 3 studies, 117 participants; low-certainty evidence);
- sleep disturbance (RR 1.24, 95% CI 0.31 to 4.92; I^2 = 75%; 2 studies, 223 participants; low-certainty evidence);
- tremor (RR 2.56, 95% CI 0.57 to 11.60; I^2 = 0%; 3 studies, 85 participants; low-certainty evidence);
- twitching (RR 7.00, 95% CI 0.44 to 111.91; I^2 = NA; 1 study, 12 participants; low-certainty evidence); or
- vertigo (RR 2.09, 95% CI 0.09 to 48.04; I^2 = NA; 1 study, 37 participants; low-certainty evidence).

There may be evidence of higher levels of decreased attention in the antidepressant group (RR 4.16, 95% CI 1.07 to 16.11; I^2 = 0%; 2 studies, 207 participants; low-certainty evidence; Analysis 4.7).

As there were more than 10 studies in this analysis, we created a funnel plot for this outcome (Figure 9) but found no evidence of asymmetry.

Figure 9. log: logarithm; RR: risk ratio; SE: standard error; SMD: standardised mean difference Antidepressant versus placebo (4 studies, 243 participants; Analysis 4.7)



Psychological

There was no clear evidence of a difference between antidepressant and placebo groups in the likelihood of:

- anorexia (RR 1.58, 95% CI 0.53 to 4.74; I^2 = NA; 1 study, 39 participants; very low-certainty evidence);
- anxiety/nervousness (RR 0.66, 95% CI 0.37 to 1.18; I^2 = 0%; 2 studies, 188 participants; very low-certainty evidence);
- depression (RR 1.36, 95% CI 0.14 to 13.72; I^2 = NA; 1 study, 37 participants; very low-certainty evidence);
- self-injury (dichotomous) (RR 1.25, 95% CI 0.09 to 17.02; I^2 = NA; 1 study, 18 participants, very low-certainty evidence),
- silliness (RR 0.94, 95% CI 0.40 to 2.17; I^2 = NA; 1 study, 149 participants); very low-certainty evidence;
- suicidal ideation (RR 2.09, 95% CI 0.09 to 48.04; I^2 = NA; 1 study, 37 participants; very low-certainty evidence);
- unstable mood (RR 0.81, 95% CI 0.32 to 2.06; I^2 = NA; 1 study, 149 participants; very low-certainty evidence);
- verbal aggression (RR 0.23, 95% CI 0.01 to 5.34; I^2 = NA; 1 study, 37 participants; very low-certainty evidence); or
- vivid or bad dreams (RR 4.87, 95% CI 0.27 to 87.94; I^2 = NA; 1 study, 37 participants; very low-certainty evidence).

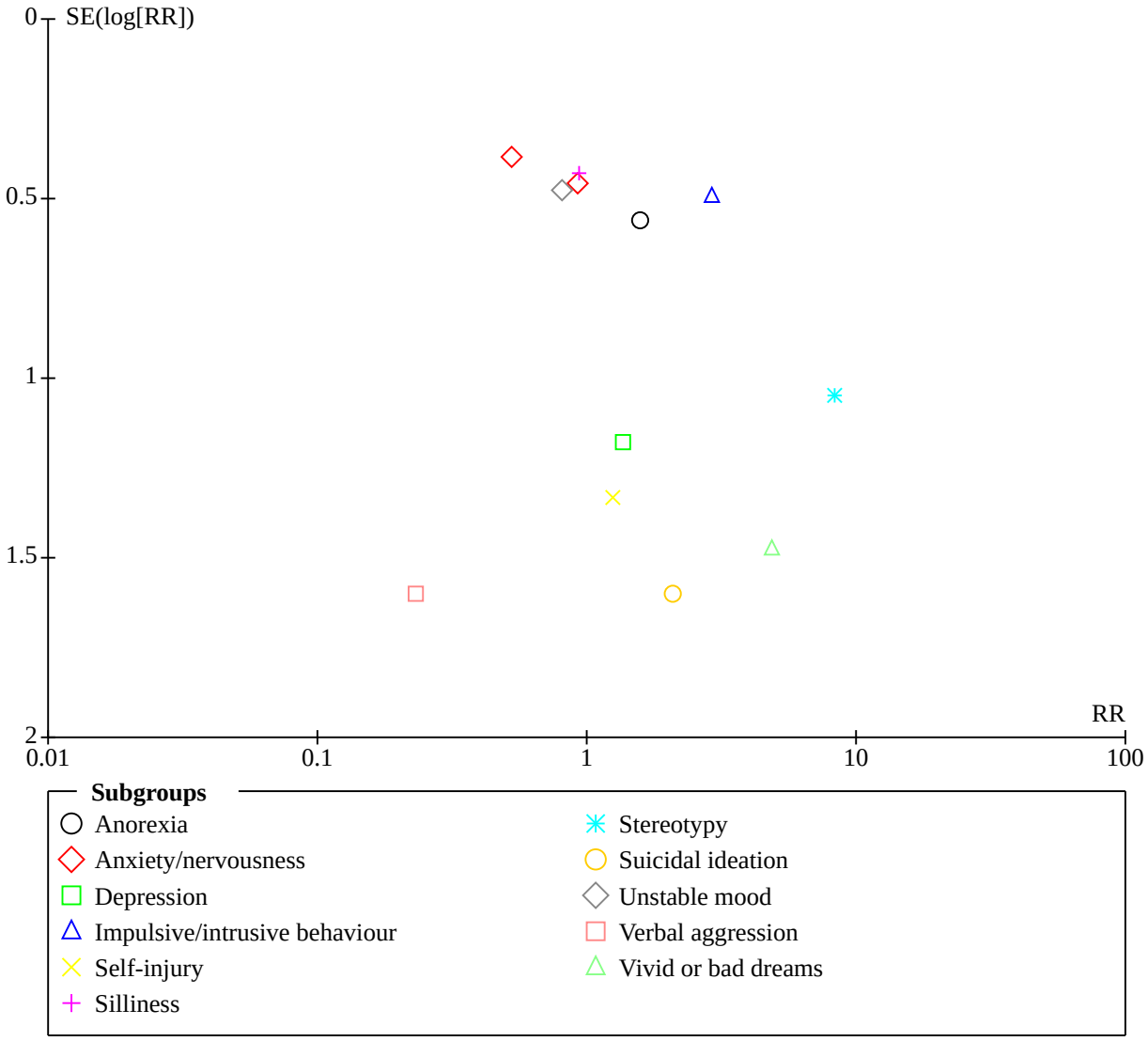
There may be evidence in the antidepressant group of increased rates of:

- impulsive/intrusive behaviour (RR 2.92, 95% CI 1.11 to 7.68; I^2 = NA; 1 study, 149 participants; very low-certainty evidence); and
- stereotypy (RR 8.33, 95% CI 1.07 to 64.95; I^2 = NA; 1 study, 149 participants; very low-certainty evidence; Analysis 4.8)

although the evidence is very uncertain.

As there were more than 10 studies in this analysis, we created a funnel plot for this outcome but found no evidence of asymmetry (Figure 10).

Figure 10. log: logarithm; RR: risk ratio; SE: standard error; SMD: standardised mean difference Antidepressant versus placebo (4 studies, 243 participants; Analysis 4.8)



Respiratory

There was no clear evidence of a difference between antidepressant and placebo groups in:

- overall respiratory effects (RR 2.19, 95% CI 0.86 to 5.55; I^2 = 0%; 2 studies, 314 participants);
- upper respiratory infection (RR 0.98, 95% CI 0.73 to 1.31; I^2 = 0%; 2 studies, 216 participants; or
- cough (RR 1.67, 95% CI 0.52 to 5.39; 1 study, 18 participants; Analysis 4.9).

Skin

There was no clear evidence of a difference between antidepressant and placebo groups in the likelihood of rash or skin irritation (RR 1.00, 95% CI 0.36 to 2.78; I^2 = 74%; 3 studies, 332 participants; Analysis 4.10).

Urinary

There was no clear evidence of a difference in:

- enuresis (RR 3.13, 95% CI 0.81 to 12.06; I^2 = NA; 1 study, 18 participants);

- polyuria (RR 2.09, 95% CI 0.09 to 48.04; I^2 = NA; 1 study, 37 participants); or
- urinary tract infection (RR 0.60, 95% CI 0.21 to 1.73; I^2 = NA; 1 study, 39 participants; Analysis 4.11).

Other adverse effects

There was no clear evidence of a difference in:

- salty taste (RR 2.09, 95% CI 0.09 to 48.04; I^2 = NA; 1 study, 37 participants); or
- mild trembling (RR 2.09, 95% CI 0.09 to 48.04; I^2 = NA; 1 study, 37 participants; Analysis 4.12).

Secondary outcomes

Tolerability/acceptability

Loss to follow-up was not different in the antidepressant group compared to the placebo group (RR 1.22, 95% CI 0.93 to 1.59; I^2 = 0%; 7 studies, 564 participants; Analysis 4.13).

Outcomes not reported

No data were available for the outcome of quality of life.

Atypical versus typical antipsychotics

Challenging behaviours

Irritability

There was no clear evidence of differences in irritability at endpoint when atypical antipsychotics were compared to typical antipsychotics (SMD −0.23, 95% CI −0.95 to 0.48; I^2 = NA; 1 study, 30 participants; Analysis 5.1).

There were insufficient studies (1 study) to conduct subgroup analyses.

Adverse effects

Cardiovascular

There was no clear evidence of a difference between groups in tachycardia when atypical antipsychotics (olanzapine) were compared to typical antipsychotics (haloperidol) (RR 0.33, 95% CI 0.02 to 6.86; I^2 = NA; 1 study 12 participants; Analysis 5.2).

Gastrointestinal

There was no clear evidence of differences in:

- constipation (RR 1.00, 95% CI 0.24 to 4.18; I^2 = NA; 1 study, 30 participants);
- dry mouth (RR 1.00, 95% CI 0.08 to 12.56; I^2 = NA; 1 study, 12 participants); or
- nausea/vomiting (RR 5.00, 95% CI 0.29 to 86.43; I^2 = NA; 1 study, 12 participants; Analysis 5.3).

Metabolic

There was no difference between atypical antipsychotics (olanzapine) compared to typical antipsychotics (haloperidol) in:

- weight gain (RR 1.18, 95% CI 0.76 to 1.83; I^2 = NA; 1 study, 12 participants); and
- weight loss (RR 0.33, 95% CI 0.02 to 6.86; I^2 = NA; 1 study, 12 participants; Analysis 5.4).

There was also no change in weight (SMD 0.26 kg, 95% CI −1.54 to 2.06; I^2 = 83%; 2 studies, 42 participants; Analysis 5.5).

Neurological

There was no clear evidence of a difference between those receiving typical and atypical antipsychotics in the neurological AEs:

- ataxia (RR 0.33, 95% CI 0.02 to 6.86; I^2 = NA; 1 study, 12 participants);
- blunted effect (RR 0.11, 95% CI 0.01 to 1.90; I^2 = NA; 1 study, 30 participants);
- insomnia (RR 3.00, 95% CI 0.15 to 61.74; I^2 = NA; 1 study, 12 participants);
- rigidity (RR 0.33, 95% CI 0.02 to 6.86; I^2 = NA; 1 study, 12 participants); or
- sedation (RR 2.50, 95% CI 0.76 to 8.19; I^2 = NA; 1 study, 12 participants; Analysis 5.6).

Respiratory

There was no clear evidence of a difference between participants receiving typical (haloperidol) and atypical antipsychotics (risperidone) in the likelihood of respiratory tract infection (RR 0.88, 95% CI 0.43 to 1.80; 1 study, 30 participants; Analysis 5.7).

Skin

There was no clear difference in rash between typical and atypical antipsychotic groups (RR 0.33, 95% CI 0.02 to 6.86; I^2 = NA; 1 study, 12 participants; Analysis 5.8).

Urinary

Enuresis was not different between groups (RR 1.00, 95% CI 0.29 to 3.48; I^2 = 0%; 2 studies, 42 participants; Analysis 5.9).

Secondary outcomes

Tolerability/acceptability

There was no clear evidence of a difference between groups in follow-up (RR 5.00, 95% CI 0.26 to 96.13; P = 0.29, I^2 = 0%; 2 studies, 42 participants; Analysis 5.10).

Outcomes not reported

No data were available for the outcomes of aggression, self-injury and quality of life, or immune, musculoskeletal, psychological, or other AEs.

Atypical antipsychotics versus atypical antipsychotics

Primary outcomes

Challenging behaviours

Irritability

Compared to risperidone, there was evidence of an increased risk of irritability in the aripiprazole group at endpoint (SMD 0.40, 95% CI 0.02 to 0.78; P = 0.92, I^2 = 0%; 2 studies, 110 participants; Analysis 6.1).

There was insufficient information to conduct subgroup analyses of irritability by age, gender, communication ability, or cognitive ability.

Adverse effects

Cardiovascular

There was no clear evidence of a difference between different types of atypical antipsychotics in the likelihood of tachycardia (RR 1.07, 95% CI 0.16 to 7.04; I^2 = 0%; 2 studies, 120 participants; Analysis 6.2).

Gastrointestinal

There was no clear evidence of differences between atypical antipsychotics in any of the gastrointestinal side effects:

- abdominal pain (RR 3.10, 95% CI 0.34 to 28.15; 1 study, 59 participants);
- constipation (RR 1.30, 95% CI 0.34 to 4.91; I^2 = 0%; 2 studies, 120 participants);
- diarrhoea (RR 3.10, 95% CI 0.13 to 73.14; 1 study, 59 participants);
- drooling (RR 0.72, 95% CI 0.38 to 1.37; I^2 = 0%; 2 studies, 120 participants);
- dry mouth (RR 5.17, 95% CI 0.26 to 103.21; 1 study, 59 participants);
- nausea (RR 0.52, 95% CI 0.05 to 5.40; 1 study, 59 participants); and
- vomiting (RR 1.61, 95% CI 0.20 to 12.65; I^2 = 0%; 2 studies, 120 participants; Analysis 6.3).

Metabolic

There was no clear evidence of a difference between groups in:

- decreased appetite (RR 1.67, 95% CI 0.56 to 4.96; I^2 = 0%; 2 studies, 120 participants); and
- increased appetite (RR 0.61, 95% CI 0.15 to 2.47; I^2 = 30%; 2 studies, 120 participants).

However, there was a reduced risk of weight gain in the aripiprazole group when compared to risperidone (RR 0.37, 95% CI 0.19 to 0.70; 1 study, 61 participants; Analysis 6.4).

Musculoskeletal

There was no clear evidence of a difference between groups in muscle rigidity (RR 2.91, 95% CI 0.12 to 68.66; 1 study, 61 participants; Analysis 6.5).

Neurological

There was no clear evidence of differences in neurological side effects including:

- agitation (RR 4.84, 95% CI 0.24 to 96.89; 1 study, 61 participants);
- difficulty sleeping (RR 6.78, 95% CI 0.37 to 125.95; 1 study, 61 participants);
- dizziness (RR 0.73, 95% CI 0.10 to 5.39; I^2 = 15%; 2 studies, 120 participants);
- fatigue (RR 1.03, 95% CI 0.29 to 3.75; 1 study, 59 participants);
- headache (RR 0.97, 95% CI 0.06 to 14.78; 1 study, 61 participants);
- nausea (RR 2.91, 95% CI 0.12 to 68.66; 1 study, 61 participants);
- nervousness (RR 2.07, 95% CI 0.20 to 21.60; 1 study, 59 participants);
- restlessness (RR 0.44, 95% CI 0.07 to 2.88; I^2 = 0%; 2 studies, 120 participants);
- sedation (RR 3.39, 95% CI 0.76 to 15.02; 1 study, 61 participants);
- somnolence (RR 8.72, 95% CI 0.49 to 155.27; 1 study, 61 participants); or
- tremor (RR 1.55, 95% CI 0.28 to 8.62; 1 study, 59 participants; Analysis 6.6).

Psychological

There was no clear evidence of a difference in depression when different atypical antipsychotics were compared (RR 0.34, 95% CI 0.01 to 8.13; 1 study, 59 participants; Analysis 6.7).

Skin

The likelihood of rash was not different when different atypical antipsychotics were compared (RR 1.03, 95% CI 0.07 to 15.77; 1 study, 59 participants; Analysis 6.8).

Urinary

Enuresis did not differ between atypical antipsychotic groups (RR 1.37, 95% CI 0.04 to 53.78; I^2 = 68%; 2 studies, 120 participants; Analysis 6.9).

Secondary outcomes

Tolerability/acceptability

There was no clear evidence of a difference in loss to follow-up between typical and atypical antipsychotic groups (MD 0.71, 95% CI 0.36 to 1.37; 2 studies, 120 participants; P = 0.31, I^2 = 0%; Analysis 6.10).

Outcomes not reported

No data were available for the outcomes of aggression, self-injury, and quality of life, or immune, respiratory, and other AEs.

Atypical antipsychotics versus antidementia medications

Primary outcomes

Challenging behaviours

Irritability

There was no clear evidence of a difference in irritability at endpoint when atypical antipsychotics (risperidone) were compared to antidementia medications (memantine) (SMD 0.46, 95% CI −0.27 to 1.19; 1 study, 30 participants; Analysis 7.1).

There were insufficient studies (1) to conduct subgroup analyses.

Adverse effects

Neurological

There was no clear evidence of a difference in somnolence when we compared atypical antipsychotics to antidementia medications (RR 1.30, 95% CI 0.86 to 1.96; 1 study, 30 participants; Analysis 7.2)

Secondary outcomes

Tolerability/acceptability

There was no clear evidence of a difference in loss to follow-up between atypical antipsychotic and antidementia groups (RR 0.38, 95% CI 0.04 to 3.25; 1 study, 34 participants; Analysis 7.3).

Outcomes not reported

No data were available for the outcomes of aggression, self-injury, and quality of life, or cardiovascular, gastrointestinal, immune, metabolic, musculoskeletal, psychological, respiratory, skin, urinary, or other AEs.

Atypical antipsychotics versus antiparkinsonians

Primary outcomes

Challenging behaviours

None of the studies reported these outcomes.

Adverse effects

Gastrointestinal

There was no clear evidence of a difference in any of the gastrointestinal side effects when atypical antipsychotics (amulsipride) were compared to antiparkinsonians (bromocriptine):

- diarrhoea (RR 3.00, 95% CI 0.14 to 65.16; 1 study, 9 participants);
- increased salivation (RR 3.00, 95% CI 0.14 to 65.16; 1 study, 9 participants); or
- vomiting (RR 0.20, 95% CI 0.01 to 3.66; 1 study, 9 participants; Analysis 8.1).

Metabolic

There was no clear evidence of a difference between those receiving atypical antipsychotics and antiparkinsonian medications in decreased appetite (RR 0.09, 95% CI 0.01 to 1.44; 1 study, 9 participants; Analysis 8.2).

Neurological

There was no clear evidence of a difference between those receiving atypical antipsychotics and antiparkinsonian medications in any of the neurological side effects: agitation/ excitement (RR 1.50, 95% CI 0.32 to 6.94; 1 study, 9 participants); increased hyperactivity (RR 7.00, 95% CI 0.41 to 118.69; 1 study, 9 participants); insomnia (RR 2.00, 95% CI 0.48 to 8.31; 1 study, 9 participants); or sedation (RR 0.14, 95% CI 0.01 to 2.42; 1 study, 9 participants) Analysis 8.3.

Secondary outcomes

None of the studies reported these outcomes.

Outcomes not reported

No data were available for the outcomes of irritability, aggression, self-injury, quality of life, or tolerability/acceptability, and cardiovascular, immune, musculoskeletal, psychological, respiratory, skin, urinary, and other AEs.

Anticonvulsants versus placebo

Primary outcomes

Challenging behaviours

Irritability

There was no clear evidence of a difference in measures of irritability at endpoint between participants receiving anticonvulsants and those receiving placebo (SMD −0.67, 95% CI −1.93 to 0.59; P = 0.30, I^2 = 88%; 3 studies, 97 participants; Analysis 9.1).

There was insufficient information to conduct subgroup analyses of irritability by age, gender, communication ability, or cognitive ability.

Aggression

There was no clear evidence of a difference in measures of aggression at endpoint between participants receiving anticonvulsants and those receiving placebo (SMD −0.18, 95% CI −0.71 to 0.35; I^2 = 0%; 2 studies, 57 participants; Analysis 9.2).

There was insufficient information to conduct subgroup analyses of aggression by age, gender, communication ability, or cognitive ability.

Adverse effects

Gastrointestinal

There was no clear evidence of a difference between anticonvulsants and placebo groups in:

- abdominal pain (RR 1.75, 95% CI 0.38 to 8.15; 1 study 30 participants);
- constipation (RR 0.58, 95% CI 0.11 to 3.00; 1 study, 30 participants);
- diarrhoea (RR 3.50, 95% CI 0.44 to 27.75; 1 study, 30 participants);
- nausea (RR 2.32, 95% CI 0.80 to 6.72; I^2 = 0%; 2 studies, 70 participants); or
- vomiting (RR 3.50, 95% CI 0.44 to 27.75; 1 study, 30 participants; Analysis 9.3).

Immune system

There was no difference between anticonvulsant and placebo groups in:

- chills (RR 2.63, 95% CI 0.31 to 22.46; 1 study, 30 participants); or
- fever (RR 3.50, 95% CI 0.44 to 27.75; 1 study, 30 participants; Analysis 9.4).

Metabolic

There were higher rates of decreased appetite in anticonvulsant groups when compared to placebo groups (RR 5.45, 95% CI 1.02 to 29.23; I^2 = 0%; 2 studies, 60 participants).

There was no clear evidence of a difference between anticonvulsant and placebo groups in:

- increased appetite (RR 0.99, 95% CI 0.05 to 18.14; I^2 = 82%; 2 studies, 70 participants);

- weight gain (RR 1.48, 95% CI 0.61 to 3.62; I^2 = 0%; 3 studies, 77 participants);
- weight loss (RR 3.00, 95% CI 0.14 to 65.90; 1 study, 20 participants; Analysis 9.5); or
- weight gain in kilograms (SMD 0.48 kg, 95% CI −0.77 to 1.74; 1 study, 11 participants; Analysis 9.6).

Neurological

There was no clear evidence of a difference between anticonvulsant and placebo groups in any of the neurological AEs:

- aggression (dichotomous) (RR 2.29, 95% CI 0.37 to 14.12; 2 studies, 48 participants);
- agitation (RR 1.20, 95% CI 0.21 to 6.70; I^2 = 0%; 2 studies, 47 participants);
- dizziness (RR 4.00, 95% CI 0.49 to 32.72; 1 study, 40 participants);
- drowsiness (RR 0.88, 95% CI 0.21 to 3.66; 1 study, 30 participants);
- echolalia (RR 1.00, 95% CI 0.07 to 14.45; 1 study, 28 participants);
- headache (RR 2.12, 95% CI 0.09 to 47.68; 1 study, 27 participants);
- hyperactivity (RR 3.00, 95% CI 0.14 to 65.90; 1 study, 20 participants);
- hypersomnolence (RR 0.10, 95% CI 0.01 to 1.78; 1 study, 27 participants);
- insomnia (RR 1.69, 95% CI 0.44 to 6.56; I^2 = 25%; 4 studies, 115 participants);
- lethargy (RR 6.18, 95% CI 0.35 to 110.11; 1 study, 30 participants);
- paresthesia (RR 5.00, 95% CI 0.64 to 39.06; 1 study 40 participants);
- sedation (RR 0.25, 95% CI 0.03 to 2.05, 1 study, 40 participants);
- self-injurious behaviour (dichotomous) (RR 3.00, 95% CI 0.14 to 65.90; 1 study, 20 participants); or
- somnolence (RR 7.00, 95% CI 0.95 to 51.80; 1 study, 20 participants; Analysis 9.7).

Psychological

There was no clear evidence of a difference in impulsivity when anticonvulsants were compared to placebo (RR 3.00, 95% CI 0.14 to 65.90; 1 study, 20 participants; Analysis 9.8).

Skin

There was no difference in the risk of rash between anticonvulsant and placebo groups (RR 4.63, 95% CI 0.89 to 24.13; I^2 = 0%; 2 studies, 57 participants; Analysis 9.9).

Urinary

Enuresis was not different between groups (RR 0.33, 95% CI 0.02 to 7.32; 1 study, 20 participants; Analysis 9.10).

Secondary outcomes

Tolerability/acceptability

There was no clear evidence of a difference in loss to follow-up between anticonvulsants and placebo groups (RR 1.98, 95% CI 0.84 to 4.66; I^2 = 0%; 6 studies, 167 participants; Analysis 9.11).

Outcomes not reported

No data were available for the outcomes of self-injury or quality of life, or cardiovascular, respiratory, musculoskeletal, and other AEs.

Antidepressants versus antidepressants

Primary outcomes

Challenging behaviours

Irritability

One study with 36 participants compared two antidepressants, clomipramine and desipramine, but did not report any data on irritability.

Aggression

One study with 36 participants compared two antidepressants, clomipramine and desipramine, but did not report any data on aggression.

Self-injury

One study with 36 participants compared two antidepressants, clomipramine and desipramine, but did not report any data on self-injury.

Adverse effects

Cardiovascular

There was no clear evidence of a difference in tachycardia in the one study with 36 participants that compared clomipramine with desipramine (RR 2.60, 95% CI 0.13 to 50.25; 1 study, 24 participants; Analysis 10.1).

Gastrointestinal

There was no clear evidence of a difference in any gastrointestinal AEs when clomipramine was compared to desipramine. The effects that were reported were:

- constipation (RR 1.50, 95% CI 0.35 to 6.35; 1 study, 36 participants);
- dry mouth (RR 0.50, 95% CI 0.12 to 2.12; 1 study, 36 participants);
- nausea/abdominal pain (RR 1.00, 95% CI 0.10 to 9.96; 1 study, 36 participants); and
- vomiting (RR 1.56, 95% CI 0.07 to 35.67; 1 study, 36 participants; Analysis 10.2).

Secondary outcomes

Quality of life

One study with 36 participants compared two antidepressants, clomipramine and desipramine, but did not report any data on quality of life.

Tolerability/acceptability

One study with 36 participants compared two antidepressants, clomipramine and desipramine, but did not report any data on loss to follow-up.

Outcomes not reported

No data were available for the outcomes of irritability, aggression, or self-injury, or immune, metabolic, musculoskeletal,

neurological, psychological, respiratory, skin, urinary, and other AEs, or quality of life, and tolerability/acceptability.

Antidementia interventions versus placebo or other treatment

Primary outcomes

Challenging behaviours

Irritability

There was no clear evidence of a difference in continuous irritability scores at endpoint when antidementia medications were compared to placebo (SMD −0.40, 95% CI −1.31 to 0.52; I^2 = 83%; 3 studies, 140 participants; Analysis 11.1).

There was also no clear evidence of a difference in partial response (≥ 25% reduction in irritability score; RR 1.38, 95% CI 0.97 to 1.97; 1 study, 40 participants); or complete response (≥ 50% reduction in irritability score; RR 1.60, 95% CI 0.98 to 2.61; 1 study, 40 participants); or dichotomous irritability (RR 0.51, 95% CI 0.16 to 1.66; 1 study, 317 participants; Analysis 11.2).

There was no clear evidence of a difference between groups when children were compared to adults (P = 0.40). There was insufficient information to conduct subgroup analyses of irritability by gender, communication ability, or cognitive ability.

Aggression

There was no clear evidence of a difference in aggression at endpoint when antidementia medications were compared to placebo (SMD 0.54, 95% CI -0.05 to 1.13; 1 study, 50 participants; Analysis 11.3).

There were insufficient studies (1 study) to conduct a subgroup analysis.

Adverse effects

Gastrointestinal

Gastrointestinal AEs were not increased in the group receiving antidementia medications. The reported gastrointestinal effects were:

- abdominal pain (RR 0.97, 95% CI 0.21 to 4.50; I^2 = 0%; 2 studies, 83 participants);
- constipation (RR 0.33, 95% CI 0.04 to 3.01; I^2 = 0%; 2 studies, 83 participants);
- diarrhoea (RR 2.87, 95% CI 0.12 to 66.75; 1 study, 43 participants);
- dry mouth (RR 0.14, 95% CI 0.01 to 2.60; 1 study, 40 participants);
- gastroenteritis (RR 7.13, 95% CI 0.37 to 136.97; 1 study, 317 participants);
- nausea (RR 2.00, 95% CI 0.41 to 9.71; 1 study, 40 participants);
- vomiting (RR 0.54, 95% CI 0.18 to 1.67; I^2 = 0%; 2 studies, 438 participants; Analysis 11.4).

Metabolic

There was no clear evidence of a difference in the effects of antidementia medications on:

- decreased appetite (RR 0.99, 95% CI 0.24 to 4.07; I^2 = 0%; 4 studies, 163 participants); or
- increased appetite (RR 1.14, 95% CI 0.54 to 2.43; I^2 = 0%; 4 studies, 163 participants; Analysis 11.5).

Musculoskeletal

There was no clear evidence of a difference in effects of antidementia medications compared to placebo on musculoskeletal pain (RR 0.32, 95% CI 0.01 to 7.42; 1 study, 43 participants; Analysis 11.6).

Neurological

Neurological AEs were not different between participants receiving antidementia medications and those receiving placebo. The neurological AEs that were reported included:

- daytime drowsiness (RR 0.85, 95% CI 0.41 to 1.77; I^2 = 0%; 2 studies, 80 participants);
- decreased energy (RR 0.37, 95% CI 0.09 to 1.52, 1 study, 23 participants);
- dizziness (RR 0.99, 95% CI 0.27 to 3.61; I^2 = 0%; 2 studies, 83 participants);
- fatigue (RR 1.39, 95% CI 0.48 to 4.02; I^2 = 0%; 2 studies, 83 participants);
- headache (RR 0.85, 95% CI 0.26 to 2.75; I^2 = 0%; 2 studies, 438 participants);
- hyperactivity (RR 0.35, 95% CI 0.07 to 1.73; I^2 = 0%; 2 studies, 438 participants);
- insomnia (RR 0.98, 95% CI 0.37 to 2.59; I^2 = 2%; 4 studies, 227 participants);
- morning drowsiness (RR 1.38, 95% CI 0.71 to 2.68; 1 study, 40 participants);
- sedation (RR 1.34, 95% CI 0.30 to 5.98; I^2 = 5%; 2 studies, 83 participants);
- tremor (RR 3.00, 95% CI 0.13 to 69.52; 1 study, 40 participants; Analysis 11.7).

Psychological

Psychological AEs were not different between participants receiving antidementia medications and those receiving placebo. The psychological AEs that were reported included:

- agitation (RR 1.89, 95% CI 0.45 to 8.05; I^2 = 0%; 2 studies, 438 participants);
- aggression (dichotomous) (RR 1.69, 95% CI 0.42 to 6.78; 1 study, 121 participants);
- anger (RR 0.31, 95% CI 0.01 to 6.85; 1 study, 23 participants);
- anxiety (RR 0.41, 95% CI 0.03 to 5.61; I^2 = 67%; 3 studies, 478 participants);
- emotional lability (RR 1.83, 95% CI 0.19 to 17.51, 1 study, 23 participants);
- irritability (dichotomous) (RR 0.87, 95% CI 0.43 to 1.76; I^2 = 0%; 3 studies, 461 participants);
- mood changes (RR 1.68, 95% CI 0.95 to 2.96; 1 study, 23 participants);
- self-injurious behaviour (dichotomous) (RR 2.77, 95% CI 0.12 to 61.65, 1 study, 23 participants; Analysis 11.9).

Respiratory

Respiratory AEs were not different between participants receiving antidementia medications and those receiving placebo. The respiratory AEs that were reported included:

- cough (RR 1.83, 95% CI 0.63 to 5.34; I^2 = 0%; 2 studies, 438 participants); and
- nasopharyngitis (RR 0.61, 95% CI 0.08 to 4.35; I^2 = 51%; 2 studies, 438 participants; Analysis 11.10).

Skin

There was no difference between participants receiving antidementia medications and those receiving placebo in:

- rash (RR 2.00, 95% CI 0.20 to 20.33; 1 study, 40 participants); and
- skin irritation (RR 0.46, 95% CI 0.15 to 1.40, 1 study, 23 participants; Analysis 11.11).

Other adverse effects

Other AEs were not different between participants receiving antidementia medications and those receiving placebo. The other AEs reported were:

- pyrexia (RR 0.68, 95% CI 0.19 to 2.41; I^2 = 0%; 2 studies, 438 participants); and
- increased infections (RR 0.69, 95% CI 0.35 to 1.35; 1 study, 23 participants).

Secondary outcomes

Tolerability/acceptability

There was no clear evidence of a difference in loss to follow-up between antidementia and placebo groups (RR 0.95, 95% CI 0.83 to 1.09; P = 0.56, I^2 = 0%; 5 studies, 553 participants; Analysis 11.13).

Outcomes not reported

No data were available for the outcomes of self-injury, or cardiovascular, immune, and urinary AEs, or quality of life.

Antiparkinsonian medications versus placebo or other treatment

Primary outcomes

Challenging behaviours

Irritability

There was a reduction in irritability at endpoint in the one study with 40 participants that compared antiparkinsonians (amantadine) with placebo and reported this outcome (SMD −0.75, 95% CI −1.39 to −0.11; 1 study, 40 participants; Analysis 12.1).

There were insufficient studies (1 study) to conduct a subgroup analysis.

Adverse effects

Gastrointestinal

One study with 40 participants reported gastrointestinal AEs. There was no difference between the antiparkinsonian and placebo groups. Gastrointestinal effects reported included:

- abdominal pain (RR 0.33, 95% CI 0.01 to 7.72; 1 study, 40 participants);
- constipation (RR 0.20, 95% CI 0.01 to 3.92; 1 study, 40 participants); and
- drooling (RR 0.33, 95% CI 0.01 to 7.72; 1 study, 40 participants; Analysis 12.2).

Metabolic

There was no clear evidence of an effect of antiparkinsonians compared with placebo on:

- increased appetite (RR 3.00, 95% CI 0.69 to 13.12; 1 study, 40 participants); or
- decreased appetite (RR 0.11, 95% CI 0.01 to 1.94; 1 study, 40 participants; Analysis 12.3).

Neurological

Across two studies that compared antiparkinsonians (amantadine) to placebo, there was no difference in neurological AEs including:

- daytime drowsiness (RR 3.00, 95% CI 0.13 to 69.52; 1 study, 40 participants);
- insomnia (RR 2.26, 95% CI 0.55 to 9.26; I^2 = 0%; 2 studies, 79 participants);
- nervousness (RR 0.33, 95% CI 0.04 to 2.94; 1 study, 40 participants);
- somnolence (RR 5.25, 95% CI 0.27 to 102.74; 1 study 39 participants); and
- tremor (RR 3.00, 95% CI 0.13 to 69.52; 1 study, 40 participants; Analysis 12.4).

Psychological

There was no evidence of a change in adverse behaviour (dichotomous) (RR 0.53, 95% CI 0.11 to 2.55; 1 study, 39 participants) when antiparkinsonians were compared to placebo (Analysis 12.5).

Secondary outcomes

Tolerability/acceptability

There was no clear evidence of a difference in loss to follow-up between antiparkinsonian and placebo groups (RR 0.33, 95% CI 0.01 to 7.72, 1 study, 40 participants; Analysis 12.6).

Outcomes not reported

No data were available for the outcomes of aggression, self-injury, quality of life, and cardiovascular, immune, musculoskeletal, respiratory, skin, urinary, and other AEs.

Anxiolytic interventions versus placebo or other treatment

Primary outcomes

Challenging behaviours

Irritability

There was no clear evidence of a difference in continuous measures of irritability at endpoint (SMD −0.20, 95% CI −0.88 to 0.47; 1 study, 34 participants; Analysis 13.1), although dichotomous measures of irritability (> 25% decrease in irritability score) showed a reduction in irritability (RR 1.83, 95% CI 1.04 to 3.22; 1 study, 34 participants; Analysis 13.2) when anxiolytics were compared to placebo.

There were insufficient studies (1 study) to conduct a subgroup analysis.

Adverse effects

Gastrointestinal

There was no clear evidence of differences between anxiolytics and placebo in any of the gastrointestinal AEs:

- constipation (RR 0.97, 95% CI 0.35 to 2.67; 1 study, 166 participants);
- diarrhoea (RR 1.04, 95% CI 0.68 to 1.61; 1 study, 166 participants); or
- vomiting (RR 1.02, 95% CI 0.68 to 1.53; 1 study, 166 participants; Analysis 13.3).

Immune system

There was no difference between anxiolytic and placebo groups in the likelihood of:

- nasopharyngitis (RR 0.87, 95% CI 0.33 to 2.28; 1 study, 166 participants); and
- pyrexia (RR 1.00, 95% CI 0.73 to 1.37; 1 study, 166 participants).

However, upper respiratory tract infection was reduced in the anxiolytic group (RR 0.40, 95% CI 0.18 to 0.91; 1 study, 166 participants; Analysis 13.4).

Metabolic

There was no difference between anxiolytic and placebo groups in:

- decreased appetite (RR 1.11, 95% CI 0.62 to 1.99; 1 study, 166 participants); and
- increased appetite (RR 1.50, 95% CI 0.93 to 2.42; I^2 = 0%; 2 studies, 200 participants; Analysis 13.5).

Neurological

Neurological AEs were not different between anxiolytics and placebo groups in one study with 166 participants. These included:

- hyperactivity (RR 0.79, 95% CI 0.47 to 1.30);
- increased aggression (RR 0.91, 95% CI 0.60 to 1.38);
- insomnia (RR 1.26, 95% CI 0.90 to 1.78); irritability (RR 0.84, 95% CI 0.48 to 1.47);
- irritability (dichotomous) (RR 0.84, 95% CI 0.48 to 1.47); and
- somnolence (RR 1.70, 95% CI 0.58 to 4.97; Analysis 13.6).

Psychological

Anxiety was not decreased in the anxiolytic group in one study with 166 participants (RR 2.76, 95% CI 0.48 to 15.83; Analysis 13.7).

Respiratory

There was no difference between anxiolytic and placebo groups in one study with 166 participants in:

- cough (RR 0.90, 95% CI 0.64 to 1.26);
- epistaxis (RR 0.52, 95% CI 0.19 to 1.43);
- nasal congestion (RR 0.80, 95% CI 0.36 to 1.77);
- rhinorrhea (RR 1.12, 95% CI 0.66 to 1.88); and
- sinus congestion (RR 0.90, 95% CI 0.55 to 1.47; Analysis 13.8).

Skin

There was no difference in rash between anxiolytic and placebo groups in one study with 166 participants (RR 1.19, 95% CI 0.52 to 2.73; Analysis 13.9).

Secondary outcomes

Tolerability/acceptability

There was no clear evidence of a difference in loss to follow-up between anxiolytic and placebo groups (RR 0.88, 95% CI 0.45 to 1.73; I^2 = 0%; 2 studies, 206 participants; Analysis 13.11).

Outcomes not reported

No data were available for the outcomes of aggression, self-injury, or quality of life, and cardiovascular, musculoskeletal, urinary, and other AEs.

Experimental interventions versus placebo or other treatment

Primary outcomes

Challenging behaviours

Irritability

Studies compared a variety of interventions to placebo. As they covered a range of different pharmacological classes, we categorised them as experimental drugs. These interventions included: celecoxib (NSAID); d-cycloserine; dextromethorphan; mecamylamine; riluzole; pioglitazone; n-acetylcysteine; *Trichuris suis* ova; tetrahydrobiopterin; lofexedine; naltrexone; minocycline; propentofylline; sulforaphane; folinic acid; carnosine; prednisolone (corticosteroid); dextromethorphan/quinidine; pregnenolone; baclofen; palmitoylethanolamide; bumetanide; resveratrol; arbaclofen; simvastatin; and nicotine.

There was some evidence that irritability was reduced at endpoint in participants in the experimental intervention groups compared to placebo (SMD −0.30, 95% CI −0.53 to −0.07; I^2 = 72%, 28 studies, 1205 participants; Analysis 14.1). There were no differences between groups when we compared children to children and adults, and adults (P = 0.94), however, there was evidence of a difference between types of experimental interventions when we conducted a subgroup analysis of interventions by age group (children, children and adults, or adults; P < 0.00001). There was insufficient information to conduct subgroup analyses of irritability by gender, communication ability, or cognitive ability.

We were unable to include data from three studies because the data were skewed (Arnold 2012a; Hollander 2020a; Minshawi 2016). Details can be found in Table 15.

Self-injury

There was no clear evidence of a difference in self-injurious behaviour at endpoint between participants receiving any of the experimental interventions compared to participants receiving placebo:

- bumetanide (SMD 0.20, 95% CI −0.21 to 0.60, P = 0.34; I^2 = 22%, 2 studies, 148 participants;
- N-acetyl cysteine (SMD 0.08, 95% CI −0.29 to 0.44; P = 0.69; I^2 = 5%, 2 studies, 127 participants);
- *Trichuris suis* ova (SMD −0.30, 95% CI −1.55 to 0.95; P = 0.64; 1 study, 10 participants; Analysis 14.2).

We were unable to include data from three studies in the analysis because the data were skewed (Dean 2019; Hardan 2012; Hollander 2020a). Details can be found in Table 16.

There was no clear evidence of a difference in self-injury between groups when we compared interventions by age (children only versus adults; P = 0.65). There was insufficient information to conduct subgroup analyses of self-injury by gender, communication ability, or cognitive ability.

Adverse effects

The AEs from one study (Ghanizadeh 2013), could not be included in the analysis because AEs were reported as a percentage of all participants who experienced an AE, rather than percentage by group. See Table 17.

Gastrointestinal

There was some evidence of a difference between experimental interventions compared to placebo for thirst (RR 3.32, 95% CI 1.10 to 10.01; I^2 = 0%; 4 studies, 224 participants; Analysis 14.3).

There was no clear evidence of a difference in any of the other gastrointestinal AEs including:

- abdominal pain (RR 1.38, 95% CI 0.95 to 2.01; I^2 = 0%; 14 studies, 734 participants);
- change in bowel habits (RR 0.39, 95% CI 0.05 to 3.26; I^2 = 25%; 2 studies, 54 participants);
- constipation (RR 1.29, 95% CI 0.77 to 2.16; I^2 = 0%; 13 studies, 665 participants);
- diarrhoea (RR 0.83, 95% CI 0.55 to 1.25; I^2 = 0%; 18 studies, 982 participants);
- drooling (RR 0.29, 95% CI 0.01 to 5.79; 1 study, 11 participants);
- dry mouth (RR 0.87, 95% CI 0.37 to 2.09; I^2 = 0%; 5 studies, 173 participants);
- dyspepsia (RR 0.31, 95% CI 0.01 to 7.15; 1 study, 31 participants);
- encopresis (RR 0.31, 95% CI 0.01 to 7.15; 1 study, 31 participants);
- flatulence (RR 3.00, 95% CI 0.15 to 59.89; 1 study, 10 participants);
- increased salivation (RR 1.00, 95% CI 0.39 to 2.58; 1 study, 40 participants);
- nausea (RR 1.36, 95% CI 0.90 to 2.06; I^2 = 0%; 15 studies, 768 participants); or
- vomiting (RR 1.34, 95% CI 0.91 to 1.98; I^2 = 0%; 13 studies, 793 participants; Analysis 14.3).

Immune system

There was no clear evidence of a difference between experimental and placebo groups in:

- fever (RR 2.94, 95% CI 0.46 to 18.53; I^2 = 0%; 2 studies, 102 participants); or
- influenza (RR 0.31, 95% CI 0.01 to 7.15; 1 study, 31 participants; Analysis 14.4).

Metabolic

Participants receiving experimental interventions (bumetanide) compared to placebo were more likely to experience:

- hypokalemia (RR 12.48, 95% CI 4.04 to 38.62, I^2 = 0%; 4 studies, 331 participants); and
- increased appetite (RR 1.42, 95% CI 1.02 to 1.98, I^2 = 0%; 14 studies, 676 participants; Analysis 14.5).

The other metabolic effects were no different to placebo:

- decreased appetite (RR 1.62, 95% CI 0.95 to 2.75; I^2 = 0%; 15 studies, 806 participants);
- hypoglycaemia (RR 0.71, 95% CI 0.09 to 5.68; I^2 = 21%; 2 studies, 120 participants);
- hyponatremia (RR 3.00, 95% CI 0.13 to 69.31; 1 study, 38 participants);
- weight gain (RR 0.32, 95% CI 0.04 to 2.77; I^2 = 0%; 2 studies, 39 participants);
- weight loss (RR 1.49, 95% CI 0.50 to 4.39; I^2 = 0%; 4 studies, 306 participants);
- weight loss (0.12 kg to 0.67 kg) (RR 9.43, 95% CI 0.65 to 137.77; 1 study, 11 participants); or
- weight loss (0.45 kg to 2.19 kg) (RR 0.17, 95% CI 0.01 to 2.92; 1 study, 11 participants; Analysis 14.5);
- weight change in kilograms (MD 0.13, 95% CI −0.24 to 0.50; 1 study, 23 participants; Analysis 14.6).

Musculoskeletal

There was no clear evidence of a difference between any of the experimental medications compared to placebo for any musculoskeletal AEs including:

- arthralgia (RR 0.33, 95% CI 0.02 to 6.65; 1 study, 10 participants);
- difficulty walking (RR 0.20, 95% CI 0.01 to 3.92; 1 study, 40 participants);
- impaired balance (RR 1.67, 95% CI 0.08 to 33.75; 1 study, 12 participants);
- myalgia (RR 1.54, 95% CI 0.79 to 3.04; I^2 = 0%; 2 studies, 155 participants);
- slow movement (RR 4.17, 95% CI 0.22 to 80.25; 1 study, 31 participants);
- stiffness (RR 2.03, 95% CI 0.41 to 10.15; I^2 = 0%; 2 studies, 43 participants); or
- weakness (RR 0.63, 95% CI 0.21 to 1.89; I^2 = 0%; 3 studies, 90 participants; Analysis 14.7).

Neurological

There was some evidence of an increased risk of drowsiness in participants receiving an experimental intervention compared to placebo (RR 3.45, 95% CI 1.21 to 9.81, 5 studies, 298 participants).

There was no clear evidence of a difference between any of the experimental medications compared to placebo for any of the other neurological AEs including:

- agitation/excitement (RR 0.76, 95% CI 0.39 to 1.48; I^2 = 0%; 5 studies, 220 participants);
- anxiety (RR 1.06, 95% CI 0.44 to 2.57; I^2 = 0%; 3 studies, 250 participants);
- daytime drowsiness (RR 1.57, 95% CI 0.75 to 3.28; I^2 = 0%; 6 studies, 172 participants);
- dazed (RR 2.57, 95% CI 0.13 to 52.12; 1 study, 11 participants);

- difficulty concentrating (RR 2.50, 95% CI 0.42 to 14.83; 1 study, 12 participants);
- difficulty sleeping (RR 0.81, 95% CI 0.44 to 1.50; I^2 = 0%; 6 studies, 326 participants);
- dizziness (RR 1.21, 95% CI 0.67 to 2.18; I^2 = 0%; 9 studies, 441 participants);
- fatigue (RR 1.23, 95% CI 0.70 to 2.17; I^2 = 0%; 7 studies, 338 participants);
- headache (RR 0.91, 95% CI 0.66 to 1.26; I^2 = 0%; 18 studies, 943 participants);
- hypoactivity (RR 0.44, 95% CI 0.07 to 2.95; I^2 = 23%; 3 studies, 28 participants);
- increased aggression (dichotomous) (RR 0.78, 95% CI 0.36 to 1.70; I^2 = 0%; 4 studies, 149 participants);
- increased hyperactivity (RR 0.75, 95% CI 0.35 to 1.58; I^2 = 0%; 6 studies, 321 participants);
- increased irritability (dichotomous) (RR 1.11, 95% CI 0.71 to 1.72; I^2 = 0%; 5 studies, 177 participants);
- increased stereotypies (RR 0.52, 95% CI 0.10 to 2.80; 1 study, 41 participants);
- insomnia (RR 1.04, 95% CI 0.66 to 1.65; I^2 = 0%; 8 studies, 488 participants);
- migraine (RR 3.00, 95% CI 0.15 to 59.89; 1 study, 10 participants);
- nervousness (RR 1.86, 95% CI 0.47 to 7.37; I^2 = 51%; 4 studies, 159 participants);
- new onset seizures (RR 0.33, 95% CI 0.01 to 7.78; 1 study, 46 participants);
- restlessness (RR 1.22, 95% CI 0.53 to 2.82; I^2 = 0%; 5 studies, 158 participants);
- rocking (RR 0.29, 95% CI 0.01 to 5.79; 1 study, 11 participants);
- sedation (RR 0.93, 95% CI 0.61 to 1.42; I^2 = 0%; 13 studies, 624 participants);
- syncope (RR 2.80, 95% CI 0.30 to 25.94; 1 study, 89 participants);
- tremor (RR1.80, 95% CI 0.44 to 7.37; I^2 = 0%; 4 studies, 140 participants); or
- twitching (RR 3.60, 95% CI 0.42 to 31.04; I^2 = 0%; 2 studies, 71 participants; Analysis 14.8).

Psychological

There was no clear evidence of a difference between any of the experimental medications compared to placebo for any psychological AEs including:

- anorexia (RR 0.53, 95% CI 0.20 to 1.40; 1 study, 20 participants);
- aggression (dichotomous) (RR 1.17, 95% CI 0.37 to 3.66; 1 study, 150 participants);
- depression (RR 1.93, 95% CI 0.62 to 6.00; I^2 = 0%; 3 studies, 108 participants);
- increased self-injurious behaviour (RR 0.46, 95% CI 0.11 to 1.84; I^2 = 0%; 3 studies, 105 participants);
- irritability (dichotomous) (RR 0.91, 95% CI 0.36 to 2.27; I^2 = 0%; 2 studies, 162 participants);
- worsening of temper tantrums (dichotomous) (RR 1.88, 95% CI 0.30 to 11.83; I^2 = 0%; 2 studies, 52 participants);
- mental symptoms (RR 1.00, 95% CI 0.41 to 2.45; 1 study, 20 participants); and
- repetitive behaviour (RR 0.50, 95% CI 0.05 to 5.14; 1 study, 46 participants; Analysis 14.9).

Respiratory

There was no clear evidence of a difference between any of the experimental medications when compared to placebo for any respiratory AEs including:

- aggravation of asthma (RR 3.26, 95% CI 0.14 to 77.35; 1 study, 71 participants);
- congestion/cold (RR 1.02, 95% CI 0.62 to 1.68; I^2 = 0%; 4 studies, 256 participants);
- cough (RR 1.16, 95% CI 0.55 to 2.49; I^2 = 0%; 3 studies, 248 participants);
- ear infection (RR 1.88, 95% CI 0.19 to 18.60; 1 study, 31 participants);
- lung congestion (RR 1.00, 95% CI 0.60 to 1.68; 1 study, 20 participants) ;
- nasopharyngitis (RR 0.78, 95% CI 0.22 to 2.79; 1 study, 150 participants); or
- respiratory AEs (RR 5.43, 95% CI 0.27 to 109.19; 1 study, 71 participants; Analysis 14.10).

Skin

There was no clear evidence of a difference between experimental and placebo groups in:

- hives (RR 0.31, 95% CI 0.01 to 7.15; 1 study, 31 participants);
- itches (RR 0.55, 95% CI 0.07 to 4.19; I^2 = 0%; 2 studies, 62 participants);
- rash (RR 0.76, 95% CI 0.30 to 1.92; I^2 = 0%; 7 studies, 440 participants);
- skin lesion (RR 1.66, 95% CI 0.74 to 3.70; I^2 = 0%; 2 studies, 98 participants); or
- overall skin AEs (RR 1.09, 95% CI 0.16 to 7.30; 1 study, 71 participants; Analysis 14.11).

Urinary

There was no clear evidence of a difference between experimental and placebo groups in:

- diuresis (RR 0.93, 95% CI 0.25 to 3.51; 1 study, 89 participants);
- enuresis (RR 2.70, 95% CI 0.82 to 8.87; I^2 = 0%; 3 studies, 205 participants);
- urinary retention (RR 0.74, 95% CI 0.05 to 10.49; I^2 = 33%; 2 studies, 88 participants);
- urinary tract infection (RR 0.31, 95% CI 0.01 to 7.15; 1 study, 31 participants; Analysis 14.12)

Other adverse effects

There was no clear evidence of a difference between any of the experimental medications compared to placebo for any other AEs including:

- blurred vision (RR 2.50, 95% CI 0.11 to 56.98; 1 study, 31 participants);
- dilated pupils (RR 0.67, 95% CI 0.05 to 9.19; 1 study, 20 participants);
- fever (RR 0.49, 95% CI 0.13 to 1.88; 1 study, 150 participants);

- sweating (RR 0.75, 95% CI 0.15 to 3.86; I^2 = 0%; 3 studies, 129 participants)
- conjunctivitis (RR 0.33, 95% CI 0.02 to 6.65; 1 study, 10 participants) Analysis 14.13.

Secondary outcomes

Tolerability/acceptability

There was no clear evidence of a difference in loss to follow-up between experimental and placebo groups (RR 1.07, 95% CI 0.89 to 1.28; 30 studies, 1913 participants; Analysis 14.14).

Outcomes not reported

No data were available for the outcomes of aggression, quality of life, and cardiovascular AEs.

Typical antipsychotics versus placebo

Primary outcomes

Challenging behaviours

Self-injury

There was no clear evidence of a difference between haloperidol and placebo on levels of self-injury in the short term (SMD −0.54, 95% CI −1.52 to 0.43; 1 study, 17 participants; Analysis 15.1).

There were insufficient studies (1 study) to conduct a subgroup analysis.

Adverse effects

Musculoskeletal

There was no clear evidence of a difference between haloperidol and placebo in risk of dystonia in the short term (RR 2.36, 95% CI 0.11 to 52.41; 1 study, 23 participants; Analysis 15.2).

Neurological

There was no clear evidence of a difference between haloperidol and placebo groups in risk of fatigue (RR 8.64, 95% CI 0.53 to 140.05; 1 study, 23 participants; Analysis 15.3).

Psychological

There was some evidence of a reduction in risk of behaviour problems in the haloperidol group compared to the placebo group (RR 0.34, 95% CI 0.16 to 0.73; 1 study, 23 participants; Analysis 15.4).

Secondary outcomes

Tolerability/acceptability

There was no difference in loss to follow-up when participants receiving haloperidol were compared to those receiving placebo (RR 0.46, 95% CI 0.14 to 1.49; I^2 = 0%; 2 studies, 40 participants; Analysis 15.5).

Outcomes not reported

No data were available for the outcomes of irritability, aggression, quality of life, and cardiovascular, gastrointestinal, immune, metabolic, respiratory, skin, urinary, and other AEs.

Sensitivity analyses

Where we had sufficient data, we carried out sensitivity analyses on irritability data excluding studies at:

- high risk of attrition bias;
- high risk of other bias; and
- with a sample size less than 50.

Atypical antipsychotics versus placebo

Aripiprazole

Ichikawa 2017 was at high risk of other bias. We found evidence of an effect of aripiprazole on irritability regardless of whether it was included in meta-analysis (SMD −0.90, 95% CI −1.52 to −0.29) or excluded (SMD −0.64, 95% CI −0.86 to −0.42).

There was also evidence of an effect on irritability whether we included NCT00468130 in the analysis (SMD −0.90, 95% CI −1.52 to −0.29) or excluded it because it was at high risk of bias and had fewer than 50 participants (SMD −0.99, 95% CI −1.65 to −0.33).

Risperidone

Kent 2013 and Troost 2005 were both at high risk of attrition bias and Troost 2005 had multiple domains at high risk of bias. We found evidence of an effect of risperidone when we included both studies in meta-analysis (SMD −1.11, 95% CI −1.47 to −0.76), when we excluded Kent 2013 from the meta-analysis (SMD −1.17, 95% CI −1.62 to 0.72) and when we excluded Troost 2005 from the meta-analysis SMD −1.00, 95% CI −1.23 to −0.76).

Shea 2004 had multiple domains at high risk of bias. We found evidence of an effect of risperidone on irritability whether it was excluded from the meta-analysis or not (SMD −1.21, 95% CI −1.63 to −0.79).

Neurohormone versus placebo

The effect of neurohormone (oxytocin) on irritability compared with placebo with all three included oxytocin studies in the meta-analysis was SMD −0.24 (95% CI −0.45 to −0.03). When we excluded Sikich 2021 (due to high risk of attrition bias) from the meta-analysis, the effect was SMD −0.41 (95% CI −0.91 to 0.09), when we excluded Munesue 2016 and Parker 2017 (both because they included fewer than 50 participants) from the meta-analysis, the effect was SMD −0.20 (95% CI −0.43 to 0.03), and when we excluded Munesue 2016 only (because it was a cross-over study), the effect was SMD −0.21 (95% CI −0.43 to 0.01). This shows that, after removing the relevant studies, there was no longer any evidence of an effect of oxytocin.

DISCUSSION

Summary of main results

This large review included 15 major comparisons with data from 131 studies. The major drug classes that the included studies compared to placebo were typical and atypical antipsychotics, ADHD-related drugs, anticonvulsants, antidementia drugs, antidepressants, antiparkinsonian drugs, anxiolytics, neurohormones, and a number of drugs that did not fall into any of these classes, which we grouped under an 'experimental' category. Studies also compared atypical antipsychotics to typical antipsychotics, antidementia drugs, and antiparkinsonian drugs. They also compared three different types of antidepressants.

Antipsychotics

At short-term follow-up (up to 6 months), atypical antipsychotics compared with placebo probably reduce irritability (moderate-certainty evidence) and may also reduce self-injury (low-certainty evidence). However, there was no clear evidence of a difference in aggression between groups (very low-certainty evidence) in participants with ASD. Some AEs may be higher in participants who receive atypical antipsychotics. These include the neurological AEs of dizziness, fatigue, sedation, somnolence, and tremor (low-certainty evidence), the metabolic AE of increased appetite (low-certainty evidence), and the gastrointestinal AEs of abdominal pain, constipation, drooling, hypersalivation, and vomiting or nausea, but there was no clear evidence of a difference between groups for any of the other AEs.

Studies that investigated typical antipsychotics reported only self-injury, with no clear evidence of a difference compared to placebo in the short term. Similarly, the two trials of typical antipsychotics versus placebo showed no clear differences in reported musculoskeletal, neurological or psychological AEs.

There was no clear evidence of a difference between typical and atypical antipsychotics on behaviours of concern or AEs.

Neurohormones

Eight studies reported irritability (466 participants). There was minimal to no clear evidence of a difference in irritability in the short term when neurohormones were compared to placebo (very low-certainty evidence). None of the neurohormone studies reported aggression or self-injury.

Neurohormones may reduce the risk of headaches (very low-certainty evidence) but there were no clear differences between groups for any of the other neurological AEs. Neurohormones may decrease the rates of vomiting (low-certainty evidence), but there were no clear differences between groups for any other gastrointestinal AEs. There were no clear differences between groups for any metabolic or psychological AEs (low-certainty evidence), or musculoskeletal AEs (very low-certainty evidence).

ADHD-related medications

At short term follow-up, ADHD-related medications may reduce irritability when compared to placebo (low-certainty evidence). There was no clear evidence of a difference in self-injury between those receiving ADHD-related medications compared to a placebo (very low-certainty evidence). No data were reported for aggression.

We found very uncertain evidence that participants who receive ADHD-related medications have higher rates of AEs compared to those who receive placebo. ADHD-related medications may increase rates of drowsiness, emotion/tearfulness, fatigue, headache, insomnia, and irritability (very low-certainty evidence) but there was no clear difference between groups for other neurological AEs: dizziness, motor tics, agitation, repetitive behaviour, or restlessness. ADHD-related medications may increase rates of depression (very low-certainty evidence) but there were no clear differences between groups for any of the other psychological AEs. ADHD-related medications may lead to higher rates of decreased appetite (very low-certainty evidence) but there were no clear differences between groups for the metabolic AEs of increased appetite or increased motor activity (very low-certainty evidence). ADHD-related medications may increase rates of constipation, dry mouth, and stomach or abdominal discomfort, but there were lower rates of diarrhoea in the ADHD-related medication group compared to placebo. None of the studies in this comparison reported musculoskeletal AEs.

Antidepressants

At short-term follow-up, there was no clear evidence of a difference in irritability between those receiving antidepressants and those receiving placebo (low-certainty evidence). Data for aggression and self-injury were either not reported or could not be included in the analysis.

Antidepressants may lead to higher rates of decreased attention (low-certainty evidence), but there was little to no difference between groups for the other neurological AEs. Antidepressants may increase rates of impulsive behaviour and stereotypy (very low-certainty evidence) but there were no clear differences between groups for any of the other psychological AEs (very low-certainty evidence). Antidepressants may increase the rates of decreased energy (very low-certainty evidence) but there were no clear differences between groups for any of the other metabolic AEs. There were no clear differences between groups for any musculoskeletal AEs (very low-certainty evidence).

Overall completeness and applicability of evidence

The included studies in this review were conducted over approximately a 30-year period. Most of the studies were short term (less than 3 months) and as such it is unclear if these AEs and improvements would be observed beyond three months. Several antipsychotic studies did not report sedation as an AE when it is very likely to have occurred. However, sedation is usually a short-term AE and the reporting and awareness of long-term effects of antipsychotic use is more important considering the lack of long-term studies and the risk of serious metabolic disorders such as diabetes mellitus and significant weight gain following antipsychotic use.

Prior to the DSM-5 2013, the DSM did not permit a diagnosis of ADHD with an existing diagnosis of ASD or PDD-NOS (Cortese 2012). The DSM-5 has removed this criterion for an ADHD diagnosis (Antshel 2013; Epstein 2013). As such, there is uncertainty whether improvements in behaviours of concern with ADHD-related medications in this review are due to improvements in concurrent ADHD symptoms that previously may not have been diagnosed in participants with ASD, rather than improvements in behaviours of concern associated with ASD.

Large studies have shown that people with ASD are at least two to three times more likely to have comorbid psychiatric conditions such as anxiety or depression (Brooks 2021; Schendel 2016; Vohra 2017). As such, there is uncertainty whether improvements in behaviours of concern observed with antipsychotics or other agents are due to improvements in undiagnosed or unreported psychiatric conditions rather than improvements in ASD-related behaviours of concern.

The vast majority of the studies did not provide details such as severity of ASD, other diagnoses apart from ASD, or the presence of comorbid psychiatric conditions. Furthermore, only some of the studies reported baseline scores of behaviours of concern.

Therefore, there are many varying factors and inconsistencies across both the population of interest and the included studies, and the heterogeneity creates a limitation in the synthesis of data.

There are also challenges associated with obtaining an accurate record of AEs in people with cognitive or communication limitations. Similarly, the outcome of quality of life is often reported by the family member or caregivers rather than self-rated by the person with the disability. Although the studies often did not report the severity of ASD, this may introduce bias.

A lack of studies involving adults emerged as a major theme in the included trials, with only 22 of 131 trials involving adults as the target population. This highlights the need for more studies involving adults to identify the effectiveness and AEs associated with pharmacological intervention use amongst adults with ASD and behaviours of concern.

Quality of the evidence

Of the comparisons in the summary of findings tables, we downgraded the majority of results by at least one level due to study limitations (refer to Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4 for further details). Approximately only 25% of included studies appropriately detailed their random sequence generation and allocation concealment processes. The remaining studies in the review either provided insufficient information to allow us to make a judgement, or we judged them to be at high risk of bias due to 'sequential assignment' methods. We judged approximately 50% of the studies to be at either unclear or high risk of performance and detection bias. In addition, 25% to 30% of the studies were at high risk of attrition or reporting bias.

Despite the large number of included studies in this review, we downgraded many of the outcomes by at least one level due to imprecision. This was because important outcomes were often only reported by a few studies, providing a small evidence base of fewer than 200 participants. In addition, the 95% CIs of many of the results were wide and included the possibility of both benefit and harm.

As the focus of this review was the effect of these interventions on the ASD population regardless of age, we decided to downgrade some outcomes for indirectness if the only available evidence related to children, as these results may not be directly applicable to the population as a whole.

We downgraded many of the outcomes in this review due to inconsistency, based on the high I^2 statistic values in many of the analyses. We explored reasons for this heterogeneity via subgroup analyses, but the subjective nature of these analyses means we cannot be confident about their results, and therefore cannot attribute the high I^2 statistic values to these potential effect modifiers.

For many of the outcomes included in this review, it was not possible to create a funnel plot to assess publication bias due to an insufficient number of studies. When it was possible to construct these forest plots, there was no evidence of asymmetry, and therefore no reason to downgrade for publication bias.

Potential biases in the review process

Although we made every attempt to adhere to the protocol (Livingstone 2015), there remains the possibility of bias in this review process. The search was extensive, but there is a chance that we did not identify important unpublished evidence. Many of the included studies were lacking important details, and although we contacted some study authors to ask for clarification on these issues, in most cases we did not receive confirmation prior to publication. We judged many of the studies to be at unclear or high risk of bias, but we made the decision to pool together all evidence regardless of the results of the risk of bias assessment. If we had chosen to restrict analyses to low risk of bias studies only, the evidence base would be substantially smaller, but perhaps more certain. One aspect that we had not prepared for in our protocol was our choice of relevant 'adverse events'. Although we attempted to account for this post-protocol, our ultimate choice of which AEs to prioritise may have been biased.

There are a number of included studies involving one research group that were conducted within a short period of time. We believe there are some conflicts of interests that have not been disclosed by the authors. It is also uncertain whether different participants are involved in each study due to the consistency of numbers reported and the same comparison used in all trials. We attempted to contact the study authors regarding some of these issues, but we did not receive any correspondence from the contact authors involved.

Agreements and disagreements with other studies or reviews

To our knowledge, this is the first systematic review that has assessed the effectiveness and AEs of multiple classes of drugs commonly prescribed for behaviours of concern in people with ASD. Two previous systematic reviews focused on the atypical antipsychotics aripiprazole (Ching 2012), and risperidone (Jesner 2007), and two systematic reviews focused on antidepressants, namely tricyclic antidepressants (Hurwitz 2012), and SSRIs (Williams 2013), for children and adults with ASDs.

Antipsychotics

Since the protocol for this review was published, seven systematic reviews of the effectiveness of antipsychotics in people with autism, predominantly children and adolescents, and reported behaviours of concern were published (D'Alò 2021; Fallah 2019; Fung 2016; Hirsch 2016; Maneeton 2018a; Maneeton 2018b; Mano-Sousa 2021), in addition to the review by Jesner 2007. These included network meta-analyses (Fallah 2019), meta-analyses and narrative syntheses. Five of these systematic reviews were on the effectiveness of atypical antipsychotics, one systematic review was on multiple drug classes (Fung 2016), and the other review was on both typical and atypical antipsychotics (D'Alò 2021). All of these reviews involved children and adolescents, and the outcomes included irritability using the ABC-I subscale (all reviews), aggression (Fung 2016), and AEs (all reviews). Across these reviews, as with our current review, there was evidence for the effectiveness of aripiprazole and risperidone in reducing irritability.

However, as with this current review, there was evidence for AEs across a range of systematic reviews. This included an overall increase (Alfageh 2019; D'Alò 2021), but also increased serious adverse events (D'Alò 2021), in children and adolescents with ASD.

Mean weight was also higher in trials of olanzapine, risperidone and aripiprazole (Fallah 2019; Fung 2016; Jesner 2007; Hirsch 2016; Maneeton 2018a; Mano-Sousa 2021). Systematic reviews also found that haloperidol, risperidone, and aripiprazole were associated with somnolence or sedation (Fung 2016; Hirsch 2016; Maneeton 2018a; Maneeton 2018b). Extrapyramidal symptoms were also increased in the review by Fung 2016; and hypersalivation in the review by Maneeton 2018b.

Neurohormones

We found that neurohormones may have a minimal to small effect on behaviours of concern (irritability). In the Cochrane Review of intravenous secretin compared to a placebo treatment in children or adults diagnosed with ASD, there was no effect of secretin in any of the three studies that reported irritability (Williams 2012).

ADHD-related medications

The current review found that there was low-certainty evidence that overall ADHD-related medications decreased irritability. Findings from two previous reviews did not find evidence that ADHD medications had an effect on irritability. A narrative synthesis by Ghanizadeh 2019 of clinical trials of stimulants in children and adolescents with both autism and ADHD, concluded inadequate evidence to support or refute their effect on irritability. While a Cochrane Review by Sturman 2017 found that methylphenidate did change reports of irritability that were reported as AEs in children and adolescents with ASD.

Antidepressants

We found no clear differences between antidepressants and placebo in behaviours of concern and this seems to be in line with previous evidence from trials of antidepressants.

In the Cochrane Review of SSRIs for ASD there was no evidence that fenfluramine and fluoxetine had an effect, and only limited evidence that citalopram reduced irritability (Williams 2013). In addition, citalopram and fenfluramine were associated with increased AEs.

A Cochrane Review of tricyclic antidepressants for ASD in children and adolescents also found no evidence that clomipramine or tianeptine improved irritability, although clomipramine was associated with cardiac and neurological AEs, and tianeptine with sedation (Hurwitz 2012).

A more recent systematic review by Deb 2021, found no evidence that citalopram, clomipramine, venlafaxine or the SSRI fluoxetine decreased behaviours of concern, though one of two trials of fluvoxamine reduced aggression.

Anticonvulsants

As with our findings, there is little evidence that anticonvulsants decrease behaviours of concern. In a systematic review of anticonvulsants in children and adolescents by Davico 2018, there was limited evidence of valproate having an effect on irritability and aggression in a single trial at 12 but not eight weeks, and no evidence that levetiracetam had any effect. In the narrative review by Brondino 2016 there were mixed findings with one of two trials finding no effect of valproate on aggression and irritability, while the other reported that valproate reduced irritability. Similarly, one of the two trials in the systematic review by Fung 2016 reported that valproate decreased irritability with no apparent effect in the other trial.

The review of valproate use in Brondino 2016 also reported mild side effects but no serious adverse events were reported. The review by Fung 2016 also reported that valproate was associated with weight gain.

Antiparkinsonians

As with the current review, there was no evidence that antiparkinsonians decreased behaviours of concern compared with placebo. The systematic review by Fung 2016 found no evidence that amantadine decreased irritability in the one small placebo-controlled trial, and amantadine was also associated with somnolence and sedation.

Anxiolytics

A recent review showed contradictory findings for the effectiveness of anxiolytics on behaviours of concern. In the systematic review by Deb 2021, only one of two trials of buspirone showed a decrease in irritability. No major adverse events were reported, with the most common adverse events being changes in appetite, drowsiness, and fatigue.

Experimental

Systematic reviews were identified for several individual drugs or drug classes that we categorised as experimental for the purposes of this review. They were reviews of the GABA modulators acamprosate, arbaclofen, bumetanide, carnosine, flumazenil, riluzole and valproate in autism reviewed by Brondino 2016 (the findings with valproate are discussed under anticonvulsants); a review of riluzole by De Boer 2019; and a review of n-acetylcysteine by Lee 2021.

As with our findings, in the systematic review by Brondino 2016, the authors concluded that there was insufficient evidence to suggest the use of the GABA modulators in autism. Though a later review of riluzole by De Boer 2019 found that riluzole decreased irritability in one trial with no apparent effect in the other trial.

In the meta-analysis of N-acetylcysteine by Lee 2021, there was no effect across all four identified studies in ASD, although mild AEs were reported. This was in line with our findings in this review.

AUTHORS' CONCLUSIONS

Implications for practice

Based on data from all identified trials, atypical antipsychotics (risperidone and aripiprazole) appear to reduce behaviours of concern in people with autism spectrum disorder (ASD) by approximately 34% and attention deficit hyperactivity disorder (ADHD)-related medications by approximately 32% in the short term. However, there was also evidence that certain adverse effects (e.g. sedation and weight gain) may be associated with their use. Consideration should be given to whether prescribing and administration is warranted given the risk of adverse events. There were inadequate data to draw conclusions about their effectiveness in the medium or long term.

There was little to no evidence of an effect of anticonvulsants, antidepressants, anxiolytics, antidementia

medications, antiparkinsonian medications, neurohormones, or 'experimental' interventions on behaviours of concern (irritability, aggression or self-injury) in the short term. In addition, there was little to no evidence of a difference in adverse effects between these intervention groups and placebo groups. There were inadequate data to draw conclusions about their effectiveness in the medium or long term.

Before considering medications to manage a person's behaviour of concern, a comprehensive assessment to gain a functional understanding of their behaviours should be undertaken and non-pharmacological interventions trialled, which supports the National Institute for Health and Care Excellence (NICE) guidance on interventions for people with intellectual disability and behaviours of concern (NICE 2015). In addition, clinicians should seek informed consent to use medications to manage behaviour from the person, or their substitute decision maker, and should discuss with them the risks and benefits associated with these medications to ensure that they are clearly understood.

Implications for research

Length of follow-up emerged as a major theme in the included studies, with only 12 studies following up participants for more than three months, one of which followed up participants for more than six months. This highlights the need for studies of longer than six months' duration to identify the long-term health effects of pharmacological interventions in people with ASD.

Another major theme to emerge is the lack of studies involving adults; only 23 of 131 trials included adults as the target population. This highlights the need for more studies with adults to identify the effectiveness and adverse effects associated with pharmacological intervention use amongst adults with ASD and behaviours of concern.

A total of 95 (72%) of the included studies across all comparisons reported irritability as an outcome, whereas only four studies reported aggression and only 13 studies reported self-injurious behaviour. This highlights the need for more studies to measure 'behaviour of concern' outcomes. Further, only 10 studies reported the outcome of quality of life. In addition, the consistent use of validated scales for each of these outcomes is important.

Adverse effects were reported by 110 (83%) of the studies, however, the inconsistency in reporting of adverse effects has highlighted the need for the use of consistent and validated scales particularly in relation to adverse effects associated with antipsychotic use. Consistent use of a validated adverse effect scale may lead to greater consistency in reporting and increase the relevance and usability of outcome data.

We downgraded certainty of evidence for most of the comparisons due to small sample sizes, as many of the studies included in this review involved fewer than 50 participants. Future studies should aim to involve at least 100 participants to increase the certainty of the evidence.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Akhondzadeh 2004

Study characteristics	
Methods	Parallel trial of haloperidol + cyproheptadine versus haloperidol + placebo
Participants	Inclusion criteria: • children and adolescents aged 3 -11 years • outpatients of children's clinic • DSM-4 clinical diagnosis of autism • presenting with a chief complaint of severely disruptive symptoms related to ASD Exclusion criteria: • previously received neuroleptics • any psychotropic drug treatment 6 months prior to recruitment • significant active medical problem Location/setting: speciality clinic for children at Roozbeh Psychiatric teaching hospital, Tehran, Iran Sample size: 40 Number of withdrawals/dropouts: none reported Gender: 24 boys, 16 girls Mean age: haloperidol + cyproheptadine = 6.4 years; haloperidol + placebo = 6.9 years IQ: not reported Baseline ABC-I scores or other behaviours of concern: not reported Concomitant medications: not reported History of previous medications: not reported
Interventions	Intervention (haloperidol + cyproheptadine) for 8 weeks (20 participants): cyproheptadine was titrated up to 0.2 mg/kg/day; haloperidol was titrated up to 0.05 mg/kg/day Comparator (haloperidol + placebo) for 8 weeks (20 participants): haloperidol was titrated up to 0.05 mg/kg/day; placebo was not described
Outcomes	Primary outcomes: AEs Secondary outcomes: not reported Timing of outcome assessment: baseline, 2, 4, 6 and 8 weeks
Notes	Study start date: January 2002 Study end date: January 2003 Funding source: Tehran University of Medical Sciences Conflicts of interest: none declared
Risk of bias	

Akhondzadeh 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised to receive cyproheptadine or placebo in a 1: 1 ratio using a computer-generated code.
Allocation concealment (selection bias)	Low risk	The assignments were kept in sealed, opaque envelopes until the point of allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Throughout the study, the person who administered the medications, the rater and the patients were blind to assignments."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Throughout the study, the person who administered the medications, the rater and the patients were blind to assignments."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 40 randomised patients completed the trial. No loss to follow up reported
Selective reporting (reporting bias)	Low risk	All primary outcomes appear to have been reported.
Other bias	High risk	• Main author is also on the ethics committee at the university funding the study • Main author is a peer-reviewer for one of the journals in which some of their studies are published

Akhondzadeh 2008

Study characteristics	
Methods	Parallel trial of piracetam + risperidone versus placebo + risperidone
Participants	Inclusion criteria: • children aged 3-11 years • DSM-4 clinical diagnosis of autism and severely disruptive symptoms relating to ASD • outpatients at a clinic for children at Roozbeh Psychiatric Teaching Hospital Exclusion criteria: • previously received neuroleptics or any other psychotropic drug treatment 6 months prior to recruitment • having significant active medical problems • severe or profound intellectual disability in whom a diagnosis of autism could not be made Location/setting: outpatient clinic of Roozbeh psychiatric hospital, Iran Sample size: 40 (20 each group) Number of withdrawals/dropouts: none reported Gender: 30 boys, 10 girls Mean age: piracetam = 6.9 years; placebo = 6.75 years

Akhondzadeh 2008 *(Continued)*

	IQ: not reported Baseline ABC-I scores or other behaviours of concern: not reported Concomitant medications: not reported History of previous medications: piracetam: 8/20 had taken risperidone, 4/20 had taken haloperidol; placebo: 10/20 had taken risperidone, 3/20 had taken haloperidol
Interventions	Intervention (piracetam + risperidone) for 10 weeks: piracetam dose was titrated up to 800 mg/day (200 mg/day starting dosage with 200 mg increments every 2 days). Risperidone was titrated up to 2 mg/day as fixed dose for children 10-40 kg or 3 mg/day for children ≥ 41 kg. Comparator (placebo + risperidone) for 10 weeks: risperidone was titrated up to 2 mg/day as fixed dose for children 10-40 kg or 3 mg/day for children ≥ 41 kg. Placebo was not described.
Outcomes	Primary outcomes: AEs Secondary outcomes: none reported Timing of outcome assessment: baseline, 2, 4, 6, 8 and 10 weeks
Notes	Study start date:January 2004 Study end date: January 2006 Funding source: grant from Tehran University of Medical Sciences Conflicts of interest: none reported Trial registry - none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised to receive piracetam or placebo in a 1:1 ratio using a computer-generated code."
Allocation concealment (selection bias)	Low risk	Quote: "The assignments were kept in sealed, opaque envelopes until the point of data analysis"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Throughout the study, the person who administered the medications, the rater and the patients were blind to assignments."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Throughout the study, the person who administered the medications, the rater and the patients were blind to assignments."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants were reported to have completed the entire study, however other details are vague such as "about 18 patients were excluded from the study". Some detail is provided about this exclusion, "they were receiving other psychotropic medications or had other significant active medical problems such as epilepsy". LTFU: no dropouts reported
Selective reporting (reporting bias)	High risk	Endpoint data were not reported despite the ABC being the primary outcome measure and apparently measured 6 times throughout the study.

Akhondzadeh 2008 *(Continued)*

Other bias	High risk	• Main author is also on the ethics committee at the university funding the study • Main author is a peer-reviewer for one of the journals in which some of their studies are published

Akhondzadeh 2010

Study characteristics	
Methods	Parallel trial of pentoxifylline + risperidone versus placebo + risperidone
Participants	Inclusion criteria: • diagnosis of autism confirmed by a child psychiatrist based on behavioural observation of the child and semi-structured interview with the parent • a score of ≥ 6 on the DSM-4-TR diagnosis criteria for autism and clinical judgement • chief complaint of severely disruptive symptoms related to autistic disorder Exclusion criteria: • concomitant schizophrenia or psychotic disorders • history of drug or alcohol abuse, tardive dyskinesia, previously received neuroleptics or any psychotropic drug treatment 6 months prior to recruitment or had significant active medical problem • severe or profound intellectual disabilities in whom a definitive diagnosis of autism could not be made. Location/setting: children's outpatient clinic of Roozbeh Psychiatric Hospital, Tehran, Iran Sample size: 40 Number of withdrawals/dropouts: none reported Gender: 29 boys, 11 girls Mean age: risperidone + pentoxifylline = 8.05 years; placebo = 7.37 years IQ: not reported Baseline ABC-I scores or other behaviours of concern: risperidone + pentoxifylline = 16.67; risperidone + placebo = 16.06 Concomitant medications: 0% History of previous medications: risperidone + pentoxifylline: 12/20 participants had previously received risperidone, 2/20 participants had previously received haloperidol; risperidone + placebo: 13/20 participants had previously received risperidone, 3/20 had previously received haloperidol
Interventions	Pentoxifylline + risperidone for 10 weeks (n = 20): pentoxifylline titrated up to 400 mg/day for children between 10 and 40 kg; or up to 600 mg for children weighing > 40 kg. The dose of risperidone was titrated up to 2 mg/day (0.5 mg starting dosage with 0.5 mg increments in weekly dosage for the first 3 weeks) for children between 10 and 40 kg and 3 mg/day for children weighting above 40 kg. Risperidone + placebo for 10 weeks (n = 20): risperidone was titrated up to 2 mg/day (0.5 mg starting dosage with 0.5 mg increments in weekly dosage for the first 3 weeks) for children between 10 and 40 kg and 3 mg/day for children weighing > 40 kg.
Outcomes	Primary outcomes - irritability, measured using the Abberant Behaviour Checklist and five subscales (Aman 1985); AEs

Akhondzadeh 2010 *(Continued)*

	Secondary outcomes: none reported Timing of outcome assessment: baseline, 2, 4, 6, 8 and 10 weeks
Notes	Study start date: April 2007 Study end date: 2009 Funding source: Tehran University of Medical Sciences Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised to receive pentoxifylline or placebo in a 1:1 ratio using a computer-generated code.
Allocation concealment (selection bias)	Low risk	The assignments were kept in sealed, opaque envelopes until the point of data analysis.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Throughout the study, the person who administered the medications, the rater and the patients were blind to assignments.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Throughout the study, the person who administered the medications, the rater and the patients were blind to assignments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	LTFU: none reported. All participants completed the trial and there were no missing data.
Selective reporting (reporting bias)	Low risk	Outcomes match protocol http://www.irct.ir/trial/857
Other bias	High risk	• Main author is also on the ethics committee at the university funding the study • Main author is a peer-reviewer for one of the journals in which some of their studies are published

Aman 2017

Study characteristics

Methods	12-week parallel trial of memantine versus placebo
Participants	Inclusion criteria: • 6-12 years with a diagnosis of ASD based on DSM-4 criteria • a parent or caregiver able to provide reliable information about the child's condition Exclusion criteria: • history of seizure disorders

Aman 2017 *(Continued)*

	• prohibited medications (antianginal, antiarrhythmic, anticoagulant, antihypertensive, antineoplastic, diuretic, hypoglycaemic or hypolipidaemic agents) insulin; muscle relaxants; systemic antifungal agents or steroids; hormone suppressants; or psychotropic drugs; • primary psychiatric diagnosis other than ASD Location/setting: USA Sample size: 121 randomised (61 memantine, 60 placebo) Reasons for withdrawals/ dropouts: memantine, 6 discontinued (3 AEs, 2 LTFU, 1 withdrew consent); placebo: 11 discontinued (4 AEs, 1 insufficient response, 1 protocol violation, 3 withdrew consent, 2 LTFU) Gender: 80% and 87% male participants in the memantine and placebo groups, respectively Mean age: not reported IQ: not reported Baseline ABC-I or other BoC scale: not reported Concomitant medications: not reported Previous medications: not reported
Interventions	Intervention (memantine): once daily oral administration of memantine extended release for 12 weeks. Memantine = 3 mg and 6 mg capsules, dose ranging 3-18 mg/day in 4 weight groups Comparator (placebo): once daily oral administration of placebo for 12 weeks Timing of outcome assessments: baseline, weeks 2, 4, 6, 8, 10 and 12
Outcomes	Primary outcomes: AEs Secondary outcomes: tolerability
Notes	Study start date: April 2009 Study end date: February 2013 Funding: "This study was supported by funding from Forest Laboratories, LLC, (Jersey City, New Jersey), Allergan. The study sponsor was involved in the study design, data collection (via contracted clinical investigator sites), analysis and interpretation of data, and the decision to present these results." Conflicts of interest: involvement with pharmaceutical companies either in advisory roles, research grants from pharmaceutical companies, or being employed by study sponsor.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization codes were generated and securely retained by the Statistical Programming and Drug Safety Surveillance Department at Forest Research Institute, Inc"
Allocation concealment (selection bias)	Low risk	Quote: "The randomization codes were generated and securely retained by the Statistical Programming and Drug Safety Surveillance Department at Forest Research Institute, Inc"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	• Allocation: randomised • Intervention model: parallel assignment

Aman 2017 *(Continued)*

		• Masking: quadruple (participant, care provider, investigator, outcomes assessor) • Primary purpose: treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	• Allocation: randomised • Intervention model: parallel assignment • Masking: quadruple (participant, care provider, investigator, outcomes assessor) • Primary purpose: treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for and an ITT analysis was used
Selective reporting (reporting bias)	High risk	ABC was listed as an outcome and measured at baseline, weeks 6 and 12. None were reported
Other bias	High risk	Pharma funded and involved in analysis etc

Anagnostou 2012

Study characteristics	
Methods	6-week parallel trial of oxytocin versus placebo
Participants	Inclusion criteria: • ASD diagnosis based on DSM-4 criteria; "male or female outpatients 18 to 60 years of age who had a Clinician Global Impression (CGI) – severity score ≥4 (moderately ill), were on stable pharmacologic and nonpharmacologic treatments for at least 3 months, had a normal physical examination, and with full-scale IQ >70." • "Sexually active women had to be on two barrier methods of contraception and no hormonal birth control" Exclusion criteria: • prematurity • primary axis 1 disorders such as bipolar disorder, psychosis, post-traumatic stress disorder, schizophrenia, or major depressive disorder/anxiety disorder • history of significant neurological disease including, but not limited to, unstable epilepsy disorder, known genetic syndromes, or known abnormal brain magnetic resonance imaging • history of malignancy or any significant haematological, endocrine, cardiovascular (including any rhythm disorder), respiratory, renal, hepatic, or gastrointestinal disease • unable to tolerate venipuncture procedures Location/setting: New York, USA Sample size: 19 adults Number of withdrawals/dropouts: oxytocin = 1 discontinued at week 4 because of staring spells; placebo = 2 discontinued, 1 at week 4 due to increased tics, and the other at baseline for not tolerating intranasal formulation Gender: 16 male participants, 3 female participants Mean age: 33.2 (SD 13.29) IQ: oxytocin = 99; placebo = 118

Anagnostou 2012 *(Continued)*

	Baseline ABC-I or other behaviours of concern: quality of life: oxytocin = 47.8; placebo = 65.2 Concomitant medications: not reported History of previous medications: not reported
Interventions	Intervention (oxytocin) for 6 weeks: oxytocin (Syntocinon; NOVARTIS) dosage was 24 IU (6 intranasal spray puffs) twice-daily for 6 weeks Comparator (placebo) for 6 weeks: placebo was saline solution in an identical bottle and label to oxytocin
Outcomes	Primary outcomes: AEs Secondary outcomes: QoL, measured using the WHOQOL emotional (WHO 1998); tolerability Timing of outcome assessment: AEs were recorded every 2 weeks. QoL was measured twice during the 6-week study: at baseline and at conclusion of the study.
Notes	Study start date: June 2006 Study end date: April 2012 Funding: a hospital and an autism centre funded the study Conflicts of interest: the primary author (EA) at the time of the study was receiving funding for other studies relating to the same pharmacological intervention, the other authors were also receiving funding for other clinical trials involving people with ASD. Trial registry - NCT00490802

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation table was created by the research pharmacist and used to randomise participants.
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were anlaysed using an ITT anlaysis and baseline and endpoint QoL scores were recorded.
Selective reporting (reporting bias)	Low risk	The primary and secondary outcomes of interest were recorded on clinicaltrials.gov and all results were provided.
Other bias	Unclear risk	No information

Aran 2021

Study characteristics	
Methods	12-week cross-over trial of cannabidiol versus placebo
Participants	Inclusion criteria: • male or female outpatients aged 5–21 years old • diagnosis of ASD according to DSM-5 • moderate or greater behavioral problems as measured by a CGI-S score of ≥ 4 at screening • involvement of a parent or caregiver able to consistently complete assessments throughout the study Exclusion criteria: • lifetime history of psychotic disorder • current or former treatment with cannabinoids • a medical condition (such as heart, liver, renal or haematological disorder) that impacts the participant's ability to participate in the study or makes them predisposed to severe adverse events • changes in pharmacological, educational, or behavioiral treatments for 4 weeks prior to randomisation or planned changes in existing interventions for the duration of the trial Location/setting: Shaare Zedek Medical Center, Jerusalem, Israel Sample size: pure cannabis (44), placebo (44) Reasons for withdrawals/dropouts: • pure cannabinoids: n = 6 (2 before treatment onset, 2 received license #, 1 had adverse events, 1 due to ineffectiveness) • placebo: n = 6 (1 died (treatment unrelated), 2 received license #, 2 sheltered living decision, 1 had adverse events) Gender: 80% male, 20% female Mean age: 11.8 (SD4.1) years IQ: not reported Baseline ABC-I or other BoC scale: Concomitant medications: any medication 72%; antipsychotics 54%; SSRIs 15%; antiepileptics 12%; stimulants 12%; benzodiazepines 7%; alpha-2 agonists 4% Previous medications: details not provided
Interventions	Intervention (pure cannabinoids): 99% pure cannabidiol (CBD) and 99% pure tetrahydrocannabinol in a 20:1 ratio at 1 mg/kg cannabidiol/d, up-titrated until intolerance or to a maximum dose of 10 mg/kg CBD/d, divided to 3 daily doses, for 3 months Comparator (placebo): oral olive oil and flavors that mimic in texture and flavour the cannabinoid solution.
Outcomes	Primary outcomes: AEs Secondary outcomes: none reported Timing of outcome assessments: 1 month, 2 months, and 3 months (endpoint)
Notes	Study start date: January 2017 Study end date: December 2018

Aran 2021 *(Continued)*

Funding: the study was funded by BOL Pharma, Revadim, Israel and the National Institute for Psychobiology in Israel (#203-17-18).

Conflicts of interest: details not provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation to treatment arm was based on a randomisation list. Randomisation scheme was generated by BioStats Statistical Consulting Ltd.
Allocation concealment (selection bias)	Low risk	Allocation to treatment arm was based on a randomisation list. Randomisation scheme was generated by BioStats Statistical Consulting Ltd.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The code key was kept by BioStats Statistical Consulting Ltd. until study end. Neither the principal investigator nor any other team member or individual had access to the codes until study end. No unblinding occurred during the study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The code key was kept by BioStats Statistical Consulting Ltd. until study end. Neither the principal investigator nor any other team member or individual had access to the codes until study end. No unblinding occurred during the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	12% overall attrition, doesn't appear to be bias in dropout reason
Selective reporting (reporting bias)	Low risk	it appears that all outcomes listed on trial registry have been reported
Other bias	High risk	The study was funded by BOL Pharma, Revadim, Israel.

Arnold 2006

Study characteristics

Methods	6-week cross-over trial of atomoxetine versus placebo
Participants	Inclusion criteria: • children/adolescents aged 5-15 years • with mental age Q18 months • ASD and symptoms of ADHD - met the first 4 of 5 DSM-4 criteria for ADHD: symptom count, impairment, chronicity, and pervasiveness across settings (the fifth criterion would technically rule out ADHD by the presence of PDD) • parent-rated symptom mean Q1.5 on either the 9 inattentive or the 9 hyperactive-impulsive ADHD symptoms, rated 0-3 Exclusion criteria: "cardiovascular disease, glaucoma, unstable seizure disorder, other significant physical illness, psychosis, severe mood disorder, substance abuse, or pregnancy." Location/setting: details not provided Sample size: 16

Arnold 2006 *(Continued)*

	Reasons for withdrawals/dropouts: 3 terminated early, 1 each after the 3rd, 4th, and 5th weeks of the second condition (1 on atomoxetine, 2 on placebo). The last observation was carried forward to endpoint for anyone who discontinued the trial. Gender: 12 male, 4 female Mean age: 9.26 years (SD2.93) IQ: details not provided Baseline ABC-I or other BoC scale: ABC-Irritability 16.00 (intervention group); 14.18 (placebo group) Concomitant medications: 6 participants were taking psychotropics during the trial (risperidone (3), aripiprazole (1), sertraline (1), divalproex (1), ziprasidone (1), and paroxetine (1). Previous medications: details not provided
Interventions	Intervention (atomoxetine) for 6 weeks: "Atomoxetine in six sizes from 2.5 to 40 mg were supplied by the manufacturer (Eli Lilly). They were administered in split doses, morning and afternoon, starting at 0.25 mg/kg/day and increased every 4 to 5 days by increments of 0.3 to 0.4 mg/kg/day, unless limiting side effects or satisfactory clinical results occurred first. The maximum daily dose was 1.4 mg/kg/day, not to exceed 100 mg/day total. For subjects also taking a significant CYP2D6 inhibitor (such as antidepressants or neuroleptics), the dose increments were 0.2 to 0.3 mg/kg/day and dose was capped at 1.2 mg/kg/day." Comparator (placebo) for 6 weeks: equivalent placebo
Outcomes	Primary outcomes: irritability (measured using the ABC-I subscale (Aman 1985), self-injurious behaviour (measured using the Repetitive Behaviour Checklist (self-injury subscale) (Bodfish 2000), AEs Secondary outcomes: none reported Timing of outcome assessments: baseline, week 6 (endpoint)
Notes	Study start date: details not provided Study end date: details not provided Funding: "The authors receive research funding from Lilly, Shire, Janssen, and PediaMed and are on speakers_ bureaus of and/or consult for Shire, Novartis, Janssen, Sigma Tau, and Forest Laboratories." Conflicts of interest: details not provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"randomization to order of conditions and stratification on autistic disorder versus other ASD diagnoses"
Allocation concealment (selection bias)	High risk	"randomization to order of conditions and stratification on autistic disorder versus other ASD diagnoses"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Apart from saying it was a double-blinded study, no further details were provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Apart from saying it was a double-blinded study, no further details were provided.

Arnold 2006 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No info on 2 out of 3 of the dropouts
Selective reporting (reporting bias)	Unclear risk	Without a protocol it is difficult to know if all outcomes were reported.
Other bias	High risk	Matched placebo and atomoxetine in 6 sizes from 2.5 to 40 mg were supplied by the manufacturer (Eli Lilly) and Eli Lilly supported the study.

Arnold 2012a

Study characteristics	
Methods	Parallel trial of mecamylamine versus placebo
Participants	Inclusion criteria: • met the DSM-4 criteria for ASD or PDD-NOS • IQ of > 36 or a mental age of > 18 months Exclusion criteria: • use of antipsychotic medications 3 months prior to baseline • psychoactive medications in the process of adjustment, systemic corticoids, or unstable seizure disorder • began a major behavioural intervention within 2 months prior to baseline or planned to during the trial Location/setting: not reported Sample size: 20 Number of withdrawals/dropouts: 2 in Intervention group dropped out after 4 weeks Gender*:* treatment = 11 male participants, 1 female participant; placebo = 6 male participants, 2 = female participants Mean age: mecamylamine = 6.76 (SD 2.24); placebo = 8.36 (SD 2.83) years IQ: an IQ of > 36 or mental age of > 18 months. Mean IQ mecamylamine group = 77.58, placebo mean IQ = 62.62 Baseline ABC-I scores or other BoC scale: mecamylamine = 12.75, placebo = 12.88 Concomitant medications: medications were allowed except for antipsychotic medications in the 3 months prior to the study and medications for unstable seizure disorders History of previous medications*:* not reported
Interventions	Mecamylamine for 14 weeks (n = 12): fixed dosages starting at 0.5 mg/day oral mecamylamine increasing in week 6 to 2.5 mg/day for 2 weeks, and increasing again to 5 mg/day for a further 6 weeks if tolerated Placebo for 14 weeks (n = 8): matched placebo starting at 0.5 mg/day, increasing in week 6 to 2.5 mg/day for 2 weeks, and increasing again to 5 mg/day for a further 6 weeks if tolerated
Outcomes	Primary outcomes:

Arnold 2012a *(Continued)*

	• irritability, measured every 2 weeks using the Abberant Behaviour Checklist - Irritability subscale (Aman 1985) • AEs Secondary outcomes: tolerability Timing of outcome assessments: baseline and weeks 2, 6, 8, 10, and 14
Notes	Study start date: not reported Study end date: not reported Source of funding: a grant from Autism Speaks Conflicts of interest: Dr Arnold receives or has recently received research support or consulting honoraria from Lilly, Shire, Curemark, Neuropharm,Noven, Organon, Seaside Therapeutics, Targacept, Biomarin, and Astra Zeneca. Dr Aman has received consulting honoraria or research support from Bristol-Myers Squibb, Johnson and Johnson,Forrest, Novartis, and Supernus. Dr Anand, Ms Bates, Ms Farmer, Ms Hollway, Dr Hurt, Dr Li, Dr Ramadan, MsThompson, and Dr Williams have no affiliations to report.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF was used for the 2 participants who did not complete the entire trial.
Selective reporting (reporting bias)	Unclear risk	ABC data collected each fortnight not reported - only change from baseline weeks 6, 8, 14
Other bias	Unclear risk	Quote: "Dr. Arnold receives or has received recently research support or consulting honoraria from Lilly, Shire, Curemark, Neuropharm, Noven, Organon, Seaside Therapeutics, Targacept, BioMarin, and AstraZeneca. Dr. Aman has received consulting honoraria or research support from Bristol-Myers Squibb, Johnson and Johnson, Forrest, Novartis and Supernus".

Asadabadi 2013

Study characteristics

Asadabadi 2013 *(Continued)*

Methods	Parallel, placebo-controlled trial of celecoxib + risperidone versus placebo + risperidone
Participants	Inclusion criteria: • children aged 4-12 years • met DSM-4-TR criteria for diagnosis of ASD • ABC-C-I score of ≥ 15 Exclusion criteria: • previously received neuroleptics or any psychotropic drug treatment 6 months prior to recruitment • significant active medical problem • severe or profound intellectual disabilities in whom a definitive diagnosis of autism could not be made • any diagnosis of psychiatric disorder in Axis I and II • any organic disorder Location/setting: children's outpatient clinic at Roozbeh hospital, Tehran, Iran Sample size: 40 Number of withdrawals/dropouts: none reported Gender: 25 boys, 15 girls Mean age: celcoxib = 7.6 (1.7) years; placebo = 7.5 (1.5) years IQ: not reported Baseline ABC-I scores or other BoC scale: celecoxib = 17.3; placebo = 17.6 Concomitant medications: not reported History of previous medications: celecoxib + risperidone: 19/20 had previously taken risperidone, 1/20 had taken haloperidol previously; placebo + risperidone: 18/20 had taken risperidone previously, 2/20 had taken haloperidol previously
Interventions	Intervention (celecoxib + risperidone) for 10 weeks: celecoxib (100 mg capsules) titrated up to 200 mg/day for children weighing < 30 kg and 300 mg/day for > 30 kg. Risperidone (0.5 mg tablets) was titrated up to 2 mg/day (starting dose of 0.5 mg with subsequent dose increase in 0.5 mg increments in the weekly dosage for the first 3 weeks) for children between 10 kg and 40 kg and 3 mg/day for children weighing above 40 kg Comparator (placebo + risperidone) for 10 weeks: placebo not described. Risperidone (0.5 mg tablets) was titrated up to 2 mg/day (starting dose of 0.5 mg with subsequent dose increase in 0.5 mg increments in the weekly dosage for the first 3 weeks) for children between 10 kg and 40 kg and 3 mg/day for children weighing above 40 kg
Outcomes	Primary outcomes • Irritability, measured using the ABC-I subscale (Aman 1985) at baseline and weeks 2, 4, 6 and 10 • AEs, recorded every 2 weeks Secondary outcome: none reported
Notes	Study start date: November 2009 Study end date: January 2012 Funding source: grant from Tehran University of Medical Sciences to Prof Shahin Akhondzadeh (grant No:. 8144) Conflict of interest: none reported

Asadabadi 2013 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomized in a 1:1 ratio using a computer-generated code"
Allocation concealment (selection bias)	Low risk	Quote: "The assignments were kept in sealed, opaque envelopes until data analysis". "Separate persons were responsible for random allocation and interviewing the patients."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Throughout the study, the person who administered the medications, the rater, and the patients and their parents were blind to assignments".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Throughout the study, the person who administered the medications, the rater, and the patients and their parents were blind to assignments".
Incomplete outcome data (attrition bias) All outcomes	Low risk	No LTFU reported. All children included in the analysis. Quote: "All patients completed the trial and there were no missing data."
Selective reporting (reporting bias)	Low risk	The ABC was reported at baseline and weeks 2, 4, 6, 8 and 10.
Other bias	High risk	Study was reduced from 10 weeks to 8 weeks and • the contact author is also on the ethics committee at the university funding the study • the contact author is a peer-reviewer for one of the journals in which some of their studies are published.

Ayatollahi 2020

Study characteristics

Methods	10-week parallel trial of pregnenolone + risperidone or placebo + risperidone
Participants	Inclusion criteria: "drug-naive 11- to 17-year-old adolescents who had met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition' (DSM-5 2013) who also display aggression, over-reactivity or repetitive behaviours, ABC-Irritability scores of at least 15 at screening" Exclusion criteria: • any medical condition or disorder apart from psychiatric diagnosis or mild to moderate intellectual disability • in receipt of any antipsychotic medications in the month prior to the trial • severe hepatic disease, allergy or intolerance to risperidone • history of seizures or taking anticonvulsant medications Location/setting: psychiatric hospital in Iran Sample size: 64 (32 to each group)

Ayatollahi 2020 *(Continued)*

	Reason for dropouts/withdrawals: 5; 2 withdrew from pregnenolone group due to withdrawing consent (prior to week 5), 3 from placebo group withdrew consent prior to week 5 Gender: placebo = 10/19 male participants, pregnenolone = 13/17 male participants Mean age: 13.5 years IQ: not reported Baseline ABC-I or other BoC scores: pregnenolone = 23.23 (4.88), placebo = 23.24 (6.0) Concomitant medications - not reported Previous medications: not reported
Interventions	Intervention: pregnenolone 100 mg twice daily + risperidone 0.4 mg/day for those weighing 20-45 kg, up to a maximum of 2.5 mg/day for 10 weeks. Participants weighing > 45 kg a maximum dose of 3.5 mg/day of risperidone Comparator: placebo capsules containing starch + risperidone 0.4 mg/day for those weighing 20-45 kg, up to a maximum of 2.5 mg/day for 10 weeks. Participants weighing > 45 kg a maximum dose of 3.5 mg/day of risperidone
Outcomes	Primary outcomes: ABC-Irritability (Aman 1985); AEs Secondary outcomes: tolerability
Notes	Study start date: August 2018 Study end date: January 2020 Funding: "This study was supported by a grant from Tehran University of Medical Sciences to S.A. (Grant Number: 38138)." Conflicts of interest: "The authors have no conflicts of interest to declare." Trial registry - IRCT20090117001556N112

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a computer-generated code, patients were randomly allocated to 2 treatment arms by the permuted randomisation block method in a 1:1 ratio.
Allocation concealment (selection bias)	Low risk	The assigned group number for each participant was kept hidden in a sealed opaque envelope until data analysis.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Pregnenolone and matching placebo capsules were identical in terms of shape, colour, size, and smell. All measures were under management of an independent group not involved elsewhere in the study. Both participants and the research team were blinded to the group assignments.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All measures were under management of an independent group not involved elsewhere in the study. Both participants and the research team were blinded to the group assignments."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition, no other obvious issues with outcome data reporting

Ayatollahi 2020 *(Continued)*

Selective reporting (reporting bias)	High risk	CARS noted in registration but not reported
Other bias	High risk	• The contact author is also on the ethics committee at the university funding the study. • The contact author is a peer-reviewer for one of the journals in which some of their studies are published.

Batebi 2021

Study characteristics	
Methods	10-week parallel trial of folinic acid + risperidone versus placebo + risperidone
Participants	Inclusion criteria: • aged 4-12 years • symptoms compatible with the DSM-5. Diagnosis and severity of ASD were also verified by a qualified child psychiatrist based on the behavioural observations and semi-structured interviews with the parents (ADI-R) • medication-free for at least 6 weeks before registration Exclusion criteria: • children with symptoms that were not severe enough to be considered for treatment with risperidone • concurrent prominent psychiatric disorders (e.g. depression, mania, anxiety, and bipolar disorder) • pre-existent medical or disease conditions such as epileptic disorders and febrile seizures • severe intellectual disability (i.e. IQ < 70) • tardive dyskinesia • history of antipsychotic or behavioural therapy during the past 6 months prior to registration Location/setting: outpatient children with ASD attending Roozbeh Hospital, Tehran, Iran Sample size: 66 Reason for dropouts/withdrawals: folinic acid + risperidone: 5 withdrew consent prior to week 5; placebo + risperidone: 6 withdrew consent prior to week 5 (all withdrew consent) Mean age: folinic acid average age 8.36; placebo group average age 7.52 Mean IQ: not reported Gender: folinic acid 42.9% female, placebo group 29.6% female Baseline ABC-I or other BoC scores: folinic acid 22.82, placebo 22.67 Concomitant medications: folinic acid and risperidone were initiated simultaneously. No other concomitant medication was allowed for neither of the trial groups. Previous medications: not reported
Interventions	Intervention: risperidone twice daily initiating at a dose of 0.5 mg with a dose increase of 0.5 mg/week (for the first 3 weeks). The maximum risperidone dose for children < 20 kg was 1 mg/day, and for children 20 kg or heavier was 2 mg/day, respectively. Folinic acid (C20H23N7O7) dosage was 2 mg/kg up to 50 mg/day for the entire course of the study. At the same time, the control group received placebo capsules. Comparator: placebo + risperidone (1-3.5 mg/day) for 10 weeks

Batebi 2021 *(Continued)*

Outcomes	Primary outcomes: irritability, measured using the ABC-Irritability subscale (Aman 1985); adverse events Secondary outcomes: tolerability
Notes	Study start date: November 2018 Study end date: April 2019 Funding: "This study was funded by Tehran University of Medical Sciences and Health Services (Grant number 38898)." Conflicts of interest: "The authors declare that they have no conflict of interest" trial registry: IRCT20090117001556N114

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using the Microsoft Office Excel software, a specific random code was allocated to each patient. The randomisation and allocation were conducted using block randomisation (with blocks of size 4) by the primary investigator of the study, who was not involved in the diagnosis and follow-ups.
Allocation concealment (selection bias)	Low risk	The allocations were kept in confidential and sealed opaque envelops and were exposed at the end of the trial.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Separate individuals implemented randomizations, drug administration, rating, data entry, and statistical analysis. Moreover, patients, parents, and researchers were blinded to the allocations."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Separate individuals implemented randomizations, drug administration, rating, data entry, and statistical analysis. Moreover, patients, parents, and researchers were blinded to the allocations."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	17% dropout without actual reasons given (just says "consent withdrawal"), thus can't assess whether reasons for incomplete data could be related to outcome
Selective reporting (reporting bias)	High risk	The 2 primary outcomes listed on the trials registry were ABC and subscales, and CARS. CARS was not reported.
Other bias	High risk	• The contact author is also on the ethics committee at the university funding the study • The contact author is a peer-reviewer for one of the journals in which some of their studies are published.

Behmanesh 2019

Study characteristics

Methods	12-week parallel study of propentofylline + risperidone versus placebo + risperidone
Participants	Inclusion criteria:

Behmanesh 2019 *(Continued)*

- children 4-11 years
- DSM-5 diagnosis of ASD
- presence of aggression, irritability or self-injurious behaviour

Exclusion criteria:

- presence of any active medical problem
- other psychiatric diagnosis except for mild to moderate Intellectual disability
- receiving any psychotropic medications except for risperidone during past 2 weeks prior to the trial
- severe hepatic disease
- history of allergy to risperidone and intolerance of it
- history of seizure requiring change of antiepileptic dose during the last month
- seizure during the last 6 months

Location/setting: children attending Roozbeh Hospital, Iran

Sample size: 48 (24 in each group)

Mean age: 7 years

Mean IQ: not reported

Gender: 75% of all participants were boys

Baseline ABC-I scores: intervention 25.79 (5.39); placebo 26.29 (4.70)

Reason for dropouts/withdrawals: 9 discontinued from each group. Propentofylline + risperidone: 5 withdrew consent and 4 excluded due to "lack of collaboration of their parents". Placebo + risperidone: 6 withdrew consent, 3 excluded due to "lack of collaboration of their parents"

Concomitant medications: "no other concomitant intervention or medication was permitted neither for the propentofylline nor the placebo group"

Previous medications: not reported

Interventions	Intervention (propentofylline + risperidone): 300 mg propentofylline once daily in capsule form. The dosage of propentofylline was increased to 600 mg/day (300 mg twice daily) after week 2, and for those heavier than 45 kg, the dose was increased to 900 mg/day (300 mg thrice daily). Risperidone began at a dose of 0.5 mg with a dose increase of 0.5 mg each week for the first 3 weeks. The maximum dose for participants < 20 kg was 1 mg/day and for participants ≥ 20 kg was 2 mg/day. Comparator (placebo + risperidone): risperidone began at a dose of 0.5 mg with a dose increase of 0.5 mg each week for the first 3 weeks. The maximum dose for participants < 20 kg was 1 mg/day and for participants ≥ 20 kg was 2 mg/day.
Outcomes	Primary outcomes: irritability (change from baseline) using the ABC-I (Aman 1985); AEs Secondary outcomes - tolerability
Notes	Study start date: November 2018 Study end date: April 2019 Funding: this study was supported by a grant from Tehran University of Medical Sciences to Prof Shahin Akhondzadeh (grant number 3899). Conflicts of interest: "The authors have no conflict of interest to disclose." Trial registry: IRCT20090117001556N113

Risk of bias

Behmanesh 2019 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using the Microsoft Office Excel software, the participants of the study were randomly assigned into 2 groups
Allocation concealment (selection bias)	Low risk	The assignments were retained in confidential and sealed opaque envelops and were unveiled at the study endpoint for statistical analysis
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Separate individuals were responsible for randomisations, drug administration, rating, data entry, and statistical analysis. The participants research investigators, nurses, and interviewers were all blinded to the treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Separate individuals were responsible for randomisations, drug administration, rating, data entry, and statistical analysis. The participants, research investigators, nurses, and interviewers were all blinded to the treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	27% dropout from each group /missing outcome data
Selective reporting (reporting bias)	Low risk	ABC-C and CARS prespecified outcomes, though trial endpoint timing different (10 weeks vs 12 weeks in protocol)
Other bias	High risk	• The contact author is also on the ethics committee at the university funding the study. • The contact author is a peer-reviewer for one of the journals in which some of their studies are published.

Belsito 2001

Study characteristics	
Methods	Placebo-controlled trial of lamotrigine versus placebo
Participants	Inclusion criteria: "children 3-11 years with a primary diagnosis of autistic disorder, either with early signs or following regression after a period of normal development were enrolled." Exclusion criteria included "children with autistic disorder associated with comorbid medical etiologies, such as Fragile X syndrome or metabolic disorders" Location/setting: John Hopkins medical institutions Sample size: 35 Number of withdrawals/dropouts: lamotrigine 5; placebo 2 Gender: 33 boys, 2 girls Mean age: median age 5.8 (1.75) IQ: not reported Baseline ABC-I scores or other BoC: not reported Concomitant medications: not reported

Belsito 2001 *(Continued)*

	History of previous medications: not reported
Interventions	Intervention (lamotrigine) for 18 weeks: 0.5 mg/kg lamotrigine twice daily titrated to a maximum of 5.0 mg/kg twice daily over 12 weeks or placebo twice daily Comparator (placebo) for 18 weeks: "participants received a placebo twice daily prepared in identically appearing tablets (shape, size, color, and taste)"
Outcomes	Primary outcomes: irritability, measured as change in ABC- I subscale scores (Aman 1985); AEs Secondary outcomes: none reported Timing of outcome assessment: baseline, 4, 8, 12 and 18 weeks
Notes	Study start date: not reported Study end date: not reported Funding source: Glaxo Wellcome Conflicts of interest: none declared Trial registry - not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the blinded sequence by which each patient received lamotrigine or placebo was determined by randomization at the end of baseline evaluations. Subjects were randomised via a computer-generated cluster method which made user-selected block assignments. Within each block, an equal number of patients received placebo or drug".
Allocation concealment (selection bias)	Low risk	Quote: "Codes were accessible to the investigational drug pharmacists and to the appointed safety committee".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described apart from, "Codes were accessible to the investigational drug pharmacists and to the appointed safety committee."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described apart from, "Codes were accessible to the investigational drug pharmacists and to the appointed safety committee."
Incomplete outcome data (attrition bias) All outcomes	High risk	22% LTFU - lamotrigine: 4 children (3 due to insomnia, and 1 due to increased stereotypies; 2 LTFU in placebo group: 1 increased stereotypies, and 1 for increased echolalia
Selective reporting (reporting bias)	High risk	The paper reports that outcome measures were completed at baseline, 4, 8, 12 and 18 weeks. Results were only presented graphically. Paper reports to measure changes in ABC-I and other subscales however "changes in irritability, lethargy, and hyperactivity were also insignificant between the groups" and only P values provided.
Other bias	Unclear risk	Quote: "The trial was supported by GlaxoWellcome".

Bernaerts 2020

Study characteristics	
Methods	4-week parallel trial of oxytocin versus placebo
Participants	Inclusion criteria: • diagnosis of ASD based on DSM-4-TR • male • aged 18-35 years Exclusion criteria: any neurological or genetic disorder, or contraindication for MRI Location/ setting: autism centre at the Leuven University Hospital, Belgium Sample size: oxytocin 22; placebo 18 Reasons for dropouts/withdrawal: the reason was not provided for the 1 participant from the placebo group who was not included in the analysis. Mean IQ: approx 103 for both groups Mean age: 24.5 years Gender: details not provided Baseline ABC-I or other BoC scale: oxytocin: WHO QoL 82.91 (14.04); placebo 85.24 (9.63) Concomitant medications: 6/22 in oxytocin group were on psychostimulants. Other medications included antidepressants, aripiprazole, unspecified antipsychotics and carbamazepine (Tegretol). 2/18 in placebo group were on psychostimulants. Other medications included antidepressants, and risperidone. Previous medications - not reported
Interventions	Intervention (oxytocin): 4 weeks of intranasal oxytocin (24 IU), once daily in the morning Comparator (placebo): nasal spray for 4 weeks, once daily in the morning Timing of outcome assessments: baseline and endpoint (4 weeks)
Outcomes	Primary outcomes: AEs Secondary outcomes: QoL (change from baseline) measured using the WHO QoL scale (WHO 1998)
Notes	Study start date: April 2015 Study end date: December 2016 Funding: this research was supported by the Branco Weiss fellowship of the Society in Science - ETH Zurich and by grants from the Flanders Fund for Scientific Research (FWO projects KAN 1506716N, KAN 1521313N, G040112 & G079017N). Conflicts of interest: S.B. is supported by a fund of the Marguerite-Marie Delacroix foundation. Trial registry: European Clinical Trial Registry (Eudract 2014-000586-45)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomised order

Bernaerts 2020 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Details regarding allocation concealment not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Except for the manager of randomisation, all research staff conducting the trial, participants, and their parents and/or partners were blinded to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Except for the manager of randomisation, all research staff conducting the trial, participants, and their parents and/or partners were blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data were analysed using an ITT format with LOCF to replace missing data
Selective reporting (reporting bias)	Low risk	All primary and secondary outcomes listed on clinical registry were reported.
Other bias	Low risk	No other obvious sources of bias identified

Buitelaar 1990

Study characteristics	
Methods	4-week crossover trial of adrenocorticotrophic hormone (synthetic analog of ACTH 4-9 (Org 2766)) versus placebo
Participants	Inclusion criteria: • children 5-13 years • outpatients from the Department of Child Psychiatry of the Utrecht University Hospital • met the DSM-4 criteria for infantile autism full syndrome, or for atypical PDD Exclusion criteria: "patients who suffered from gross neurological disorders, and internal and endocrinological diseases were excluded". Location/setting: child psychiatry outpatient clinic at Utrecht university hospital, The Netherlands Sample size: 14 Number of withdrawals/ dropouts: none reported Gender: 12 male, 2 female Mean age: 8.5 years IQ: Group 1 (Org 2766/ placebo): 65.3; Group 2 (placebo/Org 2766): 62.3 Concomitant medications: not reported History of previous medications: not reported Baseline ABC-I scores or other BoC: parent-rated ABC-I: 9.4 (6.8) Exclusion criteria included "having gross neurological disorders, and internal and endocrinological diseases; used psychotropic, or had used anticonvulsive or related medications 3 months prior to or during the trial".

Buitelaar 1990 *(Continued)*

Interventions	Adrenocorticotrophic hormone (4-9) for 4 weeks: Org 2766 was given at 20 mg/day for 4 weeks, after a 2-week placebo period Placebo for 4 weeks: equivalent placebo
Outcomes	Primary outcomes: irritability, measured using the ABC-Irritability subscale (Aman 1985) Secondary outcomes: none reported Timing of outcome assessment: baseline, after intervention phase and after placebo phase
Notes	Study start date: not reported Study end date: not reported Funding source: not reported Conflicts of interest: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details provided
Allocation concealment (selection bias)	High risk	Tablets of Org 2766 or identical matching placebo tablets were provided by Organon International B.V. and labelled by the local pharmacy. Assignment to treatment order occurred at random
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "During the trial the behavior of the child was rated once every 2 weeks at home by the parents or caretakers, and at school or day care unit by teacher or nurse".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All children completed the trial however Quote: "because of intermittant physical illness one child could not visit his day care unit for several periods of time. Behaviour checklist ratings from teachers were dismissed for this child".
Selective reporting (reporting bias)	Low risk	The primary outcome measures were play observations and the ABC (all subscales), which were all measured and reported in full.
Other bias	High risk	Tablets of Org 2766 and identical matching placebo tablets were provided by Organon International B.V.

Campbell 1987

Study characteristics

Methods	Parallel trial of fenfluramine versus placebo
Participants	Inclusion criteria:

Campbell 1987 *(Continued)*

- children 2-7 years
- met the DSM-III criteria for infantile autism, full syndrome
- patients in Bellevue Hospital, Children's Psychiatric inpatient service
- free of psychoactive drugs for a minimum of 2 weeks prior to the study

Exclusion criteria: "children who had a known cause of autism"

Location/setting: children's psychiatric inpatient service, USA

Sample size: 11 (6 fenfluramine, 5 placebo)

Number of withdrawals/dropouts: none reported

Gender: 9 male, 2 female

Mean age: 4.48 (1.16) years

IQ: "adaptive developmental quotients ranged from 34-83"

Baseline ABC-I scores or other BoC: not reported/ applicable

Concomitant medications: 0%

History of previous medications: not reported

Interventions	Intervention (fenfluramine) for 8 weeks: fenfluramine was started at 1.0 mg/kg/day in 2 daily doses. The maximum dose would not exceed 60 mg/day Comparator (placebo) for 8 weeks: "for placebo, the optimal doses ranged from 1.8-3.3 mg/kg/day (mean = 2.2); the maximum explored dose was 3.3 mg/kg/day.'
Outcomes	Primary outcomes: AEs Secondary outcomes: none reported Timing of outcome assessment: baseline, week 4, week 8
Notes	Study start date: not reported Study end date: not reported Funding source: supported, in part, by USPHS grant MH-32212 from the National Institute of Mental Health Conflicts of interest: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided

Campbell 1987 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition
Selective reporting (reporting bias)	High risk	Only selected items from the CGI and CPRS were reported. "None of the items on the CPRS nor their sum produced a statistically significant interaction. The effects of fenfluramine were thus indistinguishable from those of placebo".
Other bias	Unclear risk	No group differences published

Campbell 1993

Study characteristics	
Methods	3-week parallel trial of naltrexone versus placebo
Participants	Inclusion criteria: • hospitalised • aged 2-7 years • diagnosed as having ASD infantile onset (before 36 months of age) according to the DSM-III-R criteria Exclusion criteria: “children with identifiable causes of autism (eg. congenital rubella, inborn errors of metabolism, etc.), tardive or withdrawal dyskinesia or those who had other associated movement disorders (eg. Tourette's syndrome, chorea), systemic disease (renal, vascular), history of cardiac disease or nephrosis, seizure disorder or history of seizure disorder, history of hyperthyroidism or hypothyroidism, concurrent administration of any psychoactive medication, hypersensitivity to naltrexone, and opioid dependence”. Location/setting: pediatric inpatient clinic, Bellevue Hospital Centre, USA Sample size: 41 participants (naltrexone 23, placebo 18) Number of withdrawals/dropouts: 4 from naltrexone group "because error was made in labelling the blood samples for naltrexone levels." Gender: 34 boys, 7 girls Mean age: 4.9 years IQ: naltrexone group mean adaptive developmental quotient was 56.8; placebo group mean adaptive developmental quotient was 44.9 Baseline ABC-I or other BoC: not reported Concomitant medications: 0% History of previous medications: not reported
Interventions	Intervention (naltrexone) for 3 weeks: naltrexone maximum 1.0 mg/kg/day Comparator (placebo) for 3 weeks: placebo equivalent
Outcomes	Primary outcomes: AEs

Campbell 1993 *(Continued)*

	Secondary outcomes: none reported Timing of outcome assessment: once/week an hour after drug administration
Notes	Study start date: not reported Study end date: not reported Funding source: "supported in part by USPHS grants MH-32212 and MH-18915 from the NIMH, the Hirschell and Deanna E. Levine Foundation, and the Marion O. and Maximilian E. Hoffman Foundation, Inc Conflicts of interest: none declared Trial registry: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	These ratings were done independently by 2 child psychiatrists (CPRS; CGI) and a research nurse (Nurses' Global Impressions [NGIl and Aggression Rating Scale) who were all blinded to the child's treatment condition. "The teacher, also blinded, rated the children in the classroom."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	45 children completed the study; the data of 4 were not analysed because error was made in labeling the blood samples for naltrexone levels
Selective reporting (reporting bias)	Unclear risk	Several scales were used to measure outcomes and all were reported on, however only comparisons between baseline and endpoint were given (as F values and P values) and the aggression scale reported as absent/mild etc
Other bias	High risk	Quote: "New York Health and Hospitals Corporation, I.E. du Pont de Nemours & Company for supplying naltrexone (Trexan) and matching placebo tablets and for supporting in part the statistical analyses"

Carey 2002

Study characteristics

Methods	48-week cross-over trial of secretin versus placebo
Participants	Inclusion criteria: • aged 2-8 years • met DSM-4 criteria for diagnosis of autism or PDD

Carey 2002 *(Continued)*

- had not had a recent case of acute pancreatitis
- had not previously received an infusion of secretin

Exclusion criteria: not reported

Location/setting: Developmental and Behavioral Pediatrics Division at the Medical College of Ohio, USA

Sample size: 8 in total

Number of withdrawals/dropouts: not reported

Gender: 8 boys

Mean age: 5 years

IQ: "general developmental level based on parent report on the Child Development Inventory ranged from 16 to 39 months".

Baseline ABC-I or other BoC: ABC-I secretin 24.5, placebo 15.5

Concurrent drug use: details not provided

History of previous medications: details not provided

Interventions	Intervention (single dose of secretin): single dose of 2 IU of secretin/kg of body weight Comparator (single dose of placebo): equivalent single dose of placebo
Outcomes	Primary outcomes: irritability, measured using the ABC-I subscale (Aman 1985); AEs Secondary outcomes: none reported Timing of outcome assessment: ABC-I: prior to infusion and then weekly for 8 weeks
Notes	Study start date: not reported Study end date: not reported Funding source: not reported Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	All participants were randomised into 2 groups.
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinded, however no further details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not provided
Incomplete outcome data (attrition bias)	High risk	Complete parent and teacher data were obtained for 8 of the total 21 project participants.

Carey 2002 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Protocol was not provided so unclear if all outcomes were reported
Other bias	High risk	Participants were recruited from a list of children whose parents contacted the Developmental and Behavioral Pediatrics Division at the Medical College of Ohio to request a trial of secretin for their child.

Chez 2020

Study characteristics	
Methods	8-week cross-over trial of dextromethorphan + quinidine versus placebo
Participants	Inclusion criteria: • 18–60 years of age • diagnosis of ASD based on DSM-4-TR criteria, developmental history, and autism diagnostic observation scale (ADOS) or confirmed to have ASD during childhood through similar methods. • demonstrated behavioural irritability or rapid mood changes that correlated with labile emotional state (frontal lobe type perseveration issues) • have a collateral informant who attended visits and answered questionnaires pertaining to participants' behaviour • no medication changes for 30 days or new medications during the course of the study with the exception of medications for non-related conditions • Sexually active women of child-bearing potential were required to be on reliable form of contraception Exclusion criteria: • "participants who had uncontrolled epilepsy (as defined as having clinical convulsive episodes within the past 6 months) prior to the study or cardiovascular conditions including cardiac or structural malformation heart fail-ure, prolonged QT interval (>450 for males and >470 for females), history of torsades de pointes, or AV [atrioventricular] blocks were excluded". • "Other exclusion criteria included pregnancy, hepatitis, bone marrow depression, thrombocytopenia, lupus-like syndrome, head injuries, brain tumors; genetic disorders other than known genetic variants of autism, frontal lobe brain structural abnormalities, known allergy to dextromethorphan or quinidine, concurrent or recent (within 30 days) use of MAOI antidepressants, lamotrigine, felbamate or other NMDA agonists or antagonists; and any clinically significant physical or neurological conditions that could compromise the study or be detrimental to the subject. Patients with ASD who also had Fragile X, Downs, or Rett Syndrome were excluded." Location/ setting: single-centre study in the USA Sample size: 15 were randomised although 7 in each group received at least 1 dose of intervention or placebo. Reasons for dropouts: 2 participants withdrew after 17 weeks. Both had collateral informants who decided to withdraw from the study due to behavior deterioration. Mean IQ: details not provided Mean age: 21.92 (3.30) years Gender: 3/14 were female Baseline ABC-I or other BoC scale: dextromethorphan + quinidine 17.42 (9.23); placebo 17.5 (11.74)

Chez 2020 *(Continued)*

	Concomitant medications: participants were not allowed to use MAOI antidepressants, lamotrigine, felbamate or other NMDA agonists or antagonists. Previous medications: not reported
Interventions	Intervention: participants received 20 mg dextromethorphan/10 mg quinidine in tablet form (Nuedexta) once daily for 7 days and then every 12 h for the next 7 weeks. Comparator: equivalent placebo for 8 weeks
Outcomes	Primary outcomes: ABC-Irritability (Aman 1985) Secondary outcomes: tolerability Timing of outcome assessments: phase 1: baseline and week 8 Phase 2: baseline (after 4 week washout) and week 8
Notes	Study start date - details not provided Study end date - details not provided Funding: "This study was supported by an investigator initiated research Grant from Avanir Corporation (Grant No. 947135-1107629)" Conflicts of interest: "Dr. Michael Chez has been a speaker for pediatric epilepsy issues for Eisai, Lundbeck, UCB, and Sunnovion for the past 2 years. No other authors have any conflicts of interest".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The parents, neuropsychologists, clinical research coordinators (CRC), and investigators were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The parents, neuropsychologists, clinical research coordinators (CRC), and investigators were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition and all participants accounted for
Selective reporting (reporting bias)	Unclear risk	Without a clinical trial record or protocol, it is difficult to know if all outcomes were reported.
Other bias	High risk	Pharma funded - Avanir Corporation

Chugani 2016

Study characteristics

Chugani 2016 *(Continued)*

Methods	24-week parallel trial of 2.5 mg buspirone and 5.0 mg buspirone versus placebo
Participants	Inclusion criteria: • met DSM-4 criteria for ASD • met the criteria in Autism Diagnostic Interview-Revised (ADI-R) • met the Autism Diagnostic Observation Schedule (ADOS) cut-off scores using revised algorithms • age 2 to < 6 years, male and female Exclusion criteria: • "presence or history of neurologic disorders, (abnormal EEG without seizures will not be excluded), including seizure disorders, phenylketonuria, tuberous sclerosis complex, Rett syndrome, Fragile X syndrome, Down syndrome, and traumatic brain injury, and other medical or behavioural problems that required medications that are centrally active" • "Clinical or laboratory evidence of renal or hepatic disease (SGPT, GGT > 2 x normal value, and serum creatinine > 1.5 x normal value).' Receiving 'treatment with drugs known to alter the activity of CYP3A4" • "Use of centrally acting drugs during the 6 weeks prior or during the study. These drugs include but are not limited to neuroleptics, benzodiazepines, anticonvulsants and antidepressants. Shorter times may be considered depending on the half life of the drug." • "Prior treatment for periods longer than two weeks with buspirone or selective serotonin reuptake inhibitors. This includes herbal substances such as St John's Wort which have similar pharmacological actions." Location/setting: “6 academic medical centres: Wayne State University School of Medicine, Children's Hospital of Michigan; Case Western Reserve University, Rainbow Babies Hospital; University of Texas South Western; Cleveland Clinic Foundation; University of California Davis; an New York University School of Medicine”. USA Sample size: 166 (2.5 mg buspiraone n = 54; 5.0 mg buspirone n = 55; placebo n = 57) Number of withdrawals/ dropouts: "twenty-four participants (14%) discontinued the study during the treatment phase (adverse event [n = 12, 6 in the placebo group, 3 in the 2.5-mg group, 3 in the 5.0-mg group], withdrew consent [n = 3], lost to follow-up [n = 3], started exclusionary medication [n = 2], clinical decision [n = 2], participant moved [n = 1], time commitments [n = 1])." Gender: 137 male, 29 female Mean age: 4.4 years IQ: not reported Baseline ABC-I or other BoC scores: Repetitive Behaviour Scale (self-injurious behaviour), 2.5 mg buspirone 46.9 (3.5), 5.0 mg buspirone 31.5 (3.5), placebo 36.7 (3.5) Concurrent medications: “participants who used a stable dose of melatonin for sleep before entry into the study were allowed to continue use during the study." History of previous medications: not reported
Interventions	Buspirone 2.5 mg/day for 24 weeks: liquid, 2.5 mg in 1 mL, once/day in the evening for the first week of administration and thereafter twice a day 12 h apart for the entire study Buspirone 5.0 mg/day for 24 weeks: buspirone liquid, 5.0 mg in 1 mL, once/day in the evening for the first week of administration and thereafter twice a day 12 h apart for the entire study Placebo for 24 weeks: “placebo liquid, in 1 mL, once/day in the evening for the first week of administration and thereafter twice a day 12 h apart for the entire study”
Outcomes	Primary outcomes: AEs; self-injurious behaviour, measured with the Repetitive Behaviour Scale (Bodfish 2000)

Chugani 2016 *(Continued)*

	Secondary outcomes: tolerability Timing of outcome assessments: AEs were assessed twice monthly. Self-injurious behaviour was measured at baseline, 24 weeks and 48 weeks.
Notes	Study start date: 14 July 2009 Study end date: 8 January 2013 Source of funding: supported by the National Institute of Neurological Disorders and Stroke Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Exact method not mentioned. Quote: "Within each site, participants were randomised in blocks for age groups (2 to <4 years, and 4 to <6 years) to treatment groups of 2.5mg, 5mg, or placebo".
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "all site personnel were blinded to treatment during both phases of treatment. A medical monitor at a different site not involved in the enrollment of participants evaluated the adverse events"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Details not provided although an external person evaluated the adverse effects
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Outcome data could not be obtained for 11 of 24 participants who discontinued early because families declined to return for the final visit testing or were lost to follow-up, however an ITT analysis was used.
Selective reporting (reporting bias)	Low risk	The main outcome reported on clinicaltrials.gov was "To evaluate the effects of twice-daily oral buspirone on core features of autism in autistic children 2-6 years measuring the change from baseline in ADOS (Autism Diagnostic Observation Schedule) Composite Total scores compared to placebo at 6 months". the ADOS total scores were reported for each intervention group.
Other bias	Unclear risk	We contacted study authors for details on Repetitive Behaviour Scale subscale 4 results but no reply

Dai 2021

Study characteristics

Methods	
Participants	Inclusion criteria: "The patients, aged from 3 to 6 years old, were given the diagnosis of ASD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) , by a team of autism experts; Scores for Children Autism Rating Scale (CARS) were more than 30; Signed Informed Consents were provided by parents."

Dai 2021 *(Continued)*

	Exclusion criteria: "Liver and kidney dysfunction; With a history of allergy to sulfa drugs; abnormal ECG; chromosomal abnormality; suffering from nervous system diseases (such as epilepsy, schizophrenia, and so on); using the melatonin treatment for sleep disorders or withdrawal less than three weeks." Location/setting: Shanghai, China Sample size: bumetanide 59; placebo 60 (119 in total) Reasons for withdrawals/dropouts: bumetanide 1 dropped out due to non-adherence; placebo 2 dropped out (1 due to hand and foot disease, the other "met the criteria for withdrawal") Gender: bumetanide group 51 male, 8 female; placebo group 49 male, 11 female Mean age: bumetanide group 4.03 years; placebo 4.22 years IQ: details not provided except that 75% in the intervention and 65% placebo groups had ASD plus intellectual or developmental disability Baseline ABC-I or other BoC scale: not an outcome Concomitant medications: details not provided Previous medications: details not provided
Interventions	Intervention (bumetanide) for 3 months: bumetanide tablets, oral intake, 0.5 mg, twice daily, respectively at 8 am and 4 pm Comparator (placebo) for 3 months: "placebo tablets, oral intake, 0.5 mg, twice daily, respectively at 8 am and 4 pm"
Outcomes	Primary outcomes: AEs Secondary outcomes: self-injurious behaviour, change from baseline; measured using the Repetitive Behaviour Scale (Bodfish 2000) Timing of outcome assessments: not clear
Notes	Study start date: May 2017 Study end date: July 2019 Funding: various grants Conflicts of interest: details not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Participants were randomly assigned in a 1:1 ratio to receive 0.5 mg oral bumetanide or placebo twice daily for 3 months by using a block randomization scheme." "The generation of random allocation sequence and the preparation of trial medication were done by investigators in an external consultancy who do not participate in other aspects of the study."
Allocation concealment (selection bias)	Unclear risk	"The study medication (bumetanide or placebo tablet) was provided in sequentially numbered envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study medication (bumetanide or placebo tablet) was provided in sequentially numbered envelopes"

Dai 2021 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated that "Patients and their caregivers, investigators, experienced psychiatrists, and data analysts remained masked to the treatment allocation until the study database was locked"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 withdrew because "they met the criteria for withdrawal"
Selective reporting (reporting bias)	Unclear risk	2 of the outcomes on the trial registry have not been reported.
Other bias	High risk	The baseline Repetitive Behaviour Scale (self-injury) scores were double that in the placebo group.

Danfors 2005

Study characteristics	
Methods	6-month cross-over trial of tetrahydrobiopterin versus placebo
Participants	Inclusion criteria: • a diagnosis of ASD according to the DSM-4 • aged 3-7 years • an age-adjusted IQ score of ≥ 30 on Griffiths Developmental Scale • cerebrospinal fluid tetrahydrobiopterin < 30 pmol/mL Exclusion criteria: • no previous history of asthma or epilepsy • no previous pharmacological treatment against ASD • IQ < 30 Location/setting: outpatients from 4 different departments of child and adolescent psychiatry in Sweden Sample size: 12 in total Number of withdrawals/dropouts: "all 12 children completed the tetrahydrobiopterin treatment study". Gender: 11 male, 1 female Mean age: 5.3 years IQ: 32-93 Concurrent medications: participants could not have taken pharmacological treatments for ASD prior to or during the study. History of previous medications: see above
Interventions	Intervention (tetrahydrobiopterin): individual doses of tetrahydrobiopterin at 3 mg/kg of body weight were prescribed in capsule form (in single-dose pack) to be taken twice daily. Comparator (placebo): twice-daily capsules
Outcomes	Primary outcomes: adverse events

Danfors 2005 *(Continued)*

	Secondary outcomes: none reported
Notes	Study start date: details not provided Study end date: details not provided Funding: "This research was supported by grants from the Subfemtomole Biorecognition Project, ICORP, Japan Science and Technology Agency (JST), The Swedish Research Council (grant 8645) the Sven Jerring Fund, Holmia insurance company, the Gillbergska Foundation, the Samaritan Foundation, the Linnea and Josef Carlssons Foundation, and the child-neurology fund of Uppsala University" Conflicts of interest: none declared Trial registry: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The local hospital pharmacy produced the capsules and performed the randomisation of the patients
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; the assessors remained blinded throughout the study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind; the assessors remained blinded throughout the study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	AEs were not provided for both groups despite being recorded every 3 months.
Selective reporting (reporting bias)	Unclear risk	Difficult to determine without a protocol
Other bias	Low risk	None identified

Danforth 2018

Study characteristics

Methods	4-week parallel trial of MDMA + psychotherapy versus placebo + psychotherapy
Participants	Inclusion criteria: • aged ≥ 21 years • have at least two years of college education or the equivalent • complete the autism diagnostic observation schedule - 2 Module 4 (adult) by a designated Independent Rater (IR) who was research reliability certified • have moderate to severe symptoms of social anxiety with a combined Liebowitz Social Anxiety Scale score of at least 60

Danforth 2018 *(Continued)*

- able to safely discontinue any current psychotropic medications that could interfere with action of the experimental drug.

Exclusion criteria: psychiatric exclusion criteria included family history in first-degree relatives of schizophrenia or bipolar I disorder, or participant diagnoses of active or past psychotic disorder, borderline personality disorder, dissociative identity disorder, eating disorder or active suicidal ideation.

Setting: Los Angeles Biomedical Research Institute in Torrance, CA, USA

Sample size: placebo (n = 4); MDMA (n = 8)

Reason for dropouts/withdrawals: from MDMA group, 1 treatment discontinuation due to not meeting inclusion criteria

Current or previous medications: previous medications MDMA: antidepressants (5), anxiolytics (1), antipsychotics (1), stimulant (3), other (3). Placebo: antidepressants (2), antipsychotics (1), stimulant (1)

Mean age: placebo mean age 28.3 years, MDMA mean age 32.8 years

Mean IQ: details not provided

Gender: MDMA 25% female, placebo all male

Baseline ABC-Irritability scores: not an outcome

Concomitant medications - not reported

Previous medications: previous medications: MDMA antidepressants (5), anxiolytics (1), antipsychotics (1), stimulant (3), other (3). Placebo antidepressants (2), antipsychotics (1), stimulant (1)

Interventions	Intervention (MDMA + psychotherapy): "after three 60- to 90-min non-drug preparatory psychotherapy sessions, participants received two blinded experimental sessions with MDMA or placebo, spaced approximately 1 month apart. Following each experimental session, three 60- to 90-min non-drug integrative psychotherapy sessions occurred over 3 weeks" Comparator (placebo + psychotherapy): "after three 60- to 90-min non-drug preparatory psychotherapy sessions, participants received two blinded experimental sessions with MDMA or placebo, spaced approximately 1 month apart. Following each experimental session, three 60- to 90-min non-drug integrative psychotherapy sessions occurred over 3 weeks"
Outcomes	Primary outcomes: adverse events Secondary outcomes: tolerability Timing of outcome assessments: baseline, post-intervention, and 6 months
Notes	Study start date: February 2014 Study end date: April 2017 Funding: "The trial was sponsored and funded by the Multidisciplinary Association for Psychedelic Studies (MAPS), a 501(c)(3) nonprofit organization. MAPS Public Benefit Corporation (MPBC), wholly owned by MAPS, was the trial organizer." Conflicts of interest: in receipt of various grants and some authors were eployed by the funder of the study. Other: clinical trial registry - NCT02008396

Risk of bias

Bias	Authors' judgement	Support for judgement

Danforth 2018 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants, therapists, and IR [Independent Rater] were blinded to drug assignment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An independent rater (IR) administered the Leibowitz Social Anxiety Scale (LSAS) at baseline, 1 day, 2 weeks, and 4 weeks after each experimental session and readministered it before the blind was broken at 6 months.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis, only one dropout
Selective reporting (reporting bias)	Low risk	Same primary outcomes on clinical trial registration
Other bias	High risk	The trial was sponsored and funded by the Multidisciplinary Association for Psychedelic Studies.

Dean 2019

Study characteristics	
Methods	24-week trial of N-acetyl cysteine (NAC) versus placebo
Participants	Inclusion criteria: "diagnosis of Autistic Disorder according to DSM-4-TR (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision) criteria (American Psychiatric Association, 2000) and were aged between 3 and 9 years, inclusive". Exclusion criteria: "had a known or suspected clinically relevant systemic medical disorder or known genetic or metabolic cause of developmental delay, such as fragile X or Rett syndrome; had a prior sensitivity or allergy to NAC were considered likely to be unable to comply with the treatment protocol, e.g., having a highly restricted diet leading to refusal to take NAC; had parents/guardians who were non-fluent in English; had a history of asthma or epilepsy, as these are equivocally influenced by NAC, or were already receiving any treatment containing NAC, glutathione or their precursors". Location/setting: Australia Sample size: ITT sample was 98: NAC 48; placebo 50 Reason for dropouts/withdrawals: • NAC: 6 withdrew between baseline and week 4 (2 parents withdrew consent, 3 protocol violations, and 1 withdrew due to behavioural changes); 4 withdrew between week 4 and week 12 (1 parent withdrew consent, 1 protocol violation, 1 withdrew because of behavioural changes, and 1 withdrew for health reasons); 3 withdrew between week 12 and week 24 (2 LTFU and 1 protocol violation) • Placebo: 6 withdrew between baseline and week 4 (2 parents withdrew consent, 2 protocol violations, 1 serious AE, 1 withdrew for health reasons); 3 withdrew between between week 4 and week 12 (1 parent withdrew consent, 1 protocol violation, 1 LTFU); 4 LTFU between week 12 and 24 Mean age: 6.4 years

Dean 2019 *(Continued)*

	Mean IQ: 73 Gender: 79 male, 19 female Baseline ABC-Irritability scores: Repetitive Behaviour Scale (self-injury) 2.2 (2.9) in intervention group, 1.7 (2.6) in placebo group Current or previous medications: "children undergoing any pharmacological treatment for autistic disorder were allowed to continue with that treatment, as usual". Not specified per group but outlined 26.5% on a psychotropic medication (most commonly; melatonin 12/2% and risperidone 5.1%). Other medications included health supplements (most commonly fish oil 19.4%), anti-allergy medication (total use 5.1%), skin medication (total use 4.1%) and 9.1% of children were on a range of other medications (e.g. paracetamol).
Interventions	Intervention: fixed dose 500 mg once daily of N-acetyl cysteine Comparator: equivalent placebo
Outcomes	Primary outcomes: self-injurious behaviour, measured with the Repetitive Behaviour Scale (Bodfish 2000); AEs Secondary outcomes: tolerability Timing of outcome assessments: baseline, week 4, 12 and 24
Notes	Study start date: details not provided Study end date: details not provided Funding: "This work was supported by the Simons Foundation Autism Research Initiative (SFARI) [Grant 201473]. A pilot award and scholarship support for Kristi-Ann Villagonzalo was obtained from Australian Rotary Health. Michael Berk is supported by an NHMRC Senior Principal Research Fellowship (1059660)". Conflicts of interest: "No potential conflict of interest was reported by the authors". Trial registry: ACTRN12610000635066

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were randomised sequentially into either the NAC or placebo groups using a computer program designed for clinical trial randomisation (randomization.com)". "An independent researcher, who had no contact with any participants, coordinated the computer-generated randomisation codes"
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, their parents/guardians, trial staff and the statistician were blind to treatment arm allocation for the duration of the study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, their parents/guardians, trial staff and the statistician were blind to treatment arm allocation for the duration of the study
Incomplete outcome data (attrition bias)	High risk	Large amount of attrition by 6 months (> 25% in both groups). Not clear if AEs is for all participants or just those at 6 months' follow-up

Dean 2019 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Outcomes have not been listed on the clinical trials registry and so it is difficult to know if all outcomes have been reported.
Other bias	Unclear risk	The study medication was gifted by BioMedica

DeVane 2019

Study characteristics	
Methods	10-week trial of aripiprazole versus risperidone
Participants	Inclusion criteria: • aged 6-17 years • weighing at least 15 kg • meet DSM-4 criteria for ASD • ABC-Irritability subscale score of > 18 at baseline • mental age of at least 18 months • medication-free or adequate washout period (2-4 weeks prior) of psychotropic medications Exclusion criteria: • psychiatric disorder that is being treated with psychotropic drugs • prior diagnosis or evidence of other disorders that may interfere with assessment (e.g Fragile X, fetal alcohol syndrome) • prior use of aripiprazole or risperidone for > 2 weeks • seizure during the last 6 months • medical condition that may place the participant at increased risk of significant AEs • dependent on other substances excluding nicotine or caffeine • positive urine pregnancy test at baseline. Location/setting: 3 academic medical centres and a single private paediatric practice in the USA Mean age: range 6-15.1 years in aripiprazole group; 6.3-17.5 years in risperidone group IQ: details not provided Gender: 19% and 23% of aripiprazole and risperidone groups were female. Current or previous medications: aripiprazole, 4/31 had previously taken the study drug (but not within the last 3 years), risperidone, 1/31 had previously taken the study drug (but not within the last 3 years). Baseline ABC-Irritability scores: > 18 at baseline Sample size: 61 (31 aripiprazole; 30 risperidone) Number analysed: aripiprazole 31, risperidone 30 Reason for dropouts: aripiprazole, 4 discontinued all due to AEs, risperidone, 6 discontinued (3 due to missed visits, 2 AEs, and 1 withdrew on physician's advice) Timing of outcome assessments: "safety, physical, and psychological assessment were recorded at clinic visits that took place weekly or every 2 weeks".
Interventions	Intervention (risperidone): "children weighing 20-45 kg will receive an initial dose of 0.5 mg daily that will be increased to twice daily on day 4 (morning and bedtime). The dosage will be gradually increased

DeVane 2019 *(Continued)*

	in 0.5 mg increments to a maximum dose of 2.5 mg per day (1.0 mg in the morning and 1.5 mg at bedtime) by the fourth treatment week. A slightly accelerated dosage will be allowed for children who weigh more than 45 kg for a maximum dosage of 3.5 mg /day" Comparator (aripiprazole): starting dosage of 2.0 mg/day. "The dosage will be allowed to increase to 5.0 mg/day on day 4 and can be increased thereafter to a maximum dosage of 15 mg/day. The dosage will only be increased in 5.0 mg intervals. No dosage adjustments will be allowed for either drug after 4 weeks".
Outcomes	Primary outcomes: ABC-Irritability (Aman 1985); AEs Secondary outcomes: tolerability
Notes	Study start date: September 2011 Study end date: June 2015 Funding: "The study was funded by Grant No. R01HD62550 from the National Institute of Child Health and Human Development, National Institutes of Health". Conflicts of interest: "The authors have declared no conflicts of interest for this article". Trial registry: NCT01333072

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given on how random sequence was generated
Allocation concealment (selection bias)	Unclear risk	No details given on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All research personnel blinded except for RA who prepared meds and study pharmacist who checked meds
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Physicians (who conducted physical neurological evaluation) and caregiver (who completed questionnaires) were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for and included in the analysis.
Selective reporting (reporting bias)	High risk	Protocol available at ClinicalTrials.gov Identifier: NCT01333072 Primary outcome was "Changes in the Irritability Subscale of the Larger ABC (Abberent Behavior Checklist) That Occur From Baseline to 10 Weeks" but they've tested for P values at each week as there was no statistically significant difference at 10 weeks. This is reported misleadingly in the abstract Quote: "Improvement was greatest in the risperidone group at every assessment period"
Other bias	Low risk	None identified

Dollfus 1992

Study characteristics	
Methods	Cross-over trial of amisulpride versus bromocriptine
Participants	Inclusion criteria: "children 4-13 years inclusive who meet the DSM-III diagnostic criteria for infantile autism. Severity of autism according to the Childhood Autism Rating Scale was at least 36 indicating 'severely autistic'." Exclusion criteria: details not provided Location/setting: inpatients and outpatients at Salpetriere hospital, Paris Sample size: 9 in total (cross-over study). Amisulpride first group (5); bromocriptine first group (4) Number of withdrawals/dropouts: none in first phase of cross-over. Only one dropped out of the study during the second treatment phase (amisulpride) on week 12 for reasons unrelated to the treatment Gender: 4 girls, 5 boys Mean age: 6.9 years IQ: "the severity of the autistic syndrome did not allow IQ tests to be given. It may be presumed, therefore, that the children are likely to have been severely mentally retarded". Baseline ABC-I or other BoC: not an outcome Concurrent medications: "two of the nine children had received neuroleptic treatment at the time of selection. Therefore, a 45-day neuroleptic washout period was required". No neuroleptic or other psychotropic drugs were allowed during the trial, except benzodiazepine, niaprazine, or hydroxyzine for severe sleep disorders, which 3 participants took concurrently during the trial (1 participant niaprazine; 1 participant niaprazine and flunitrazepam-hydroxyzine; 1 participant hydroxyzine) History of previous medications: not reported
Interventions	Intervention (amisulpride): 1.5 mg/kg/day for 4 weeks Comparator (bromocriptine): 0.15-0.20 mg/kg/day for 4 weeks
Outcomes	Primary outcomes: AEs Secondary outcomes: none reported Timing of outcome assessment: baseline and then every 2 weeks for 14 weeks
Notes	Study start date: not reported Study end date: not reported Source of funding: research protocol subsidised by MUSTELA Foundation (under the aegis of the Foundation of France) Conflicts of interest: none declared Trial registry: not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Details not provided

Dollfus 1992 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinding was used although specific details not provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The raters were blind to the treatment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 9 participants were involved in the trial, with only 1 person withdrawing from the trial during the second phase of the crossover trial. A LOCF was used for the analysis of this participant.
Selective reporting (reporting bias)	Unclear risk	The BSE was reported fully at baseline and endpoint for both phases of the cross-over, however the BSE is not relevant to the outcomes of interest. Non-specific BSE measures include items on aggressiveness which not reported specifically, rather included as part of total score.
Other bias	Unclear risk	No other sources identified but difficult to know without a protocol or trial registry

Eslamzadeh 2018

Study characteristics	
Methods	8-week parallel trial of atomoxetine + risperidone versus placebo + risperidone
Participants	Inclusion criteria: • meet the DSM-5 for ASD • 6-17 years of age Exclusion criteria: • concomitant ADHD • other psychiatric disorders • any other medical conditions • use of any psychotropic apart from risperidone • IQ < 50 Location/setting: outpatient clinic of Ibnesina hospital, Iran Mean IQ: details not provided Mean age: 8.0 years Gender: 6 female, 34 male Sample size: 40-20 each group Number analysed: 20 in each group completed the trial Reasons for dropouts: 3 from atomoxetine group discontinued due to withdrawing consent (1) and AEs (2) and 1 from placebo group did not start the trial.

Eslamzadeh 2018 *(Continued)*

	Baseline ABC-I or other BoC scale: not reported Timing of outcome assessments: "patients were evaluated at baseline, 4 weeks and 8 weeks after the administration of the drug". Concomitant medications: apart from risperidone, participants could not be taking any other psychotropic drugs. Previous medications - not reported
Interventions	Intervention (atomoxetine + risperidone): atomoxetine was given at 0.5 mg/kg/day at the start and increasing every 5 days up to a maximum of 1.2 mg/kg/day for 8 weeks. All participants were currently taking risperidone ranging from 1-4 mg/day Comparator (placebo + risperidone): placebo plus usual intake of risperidone for 8 weeks
Outcomes	Primary outcomes: AEs Secondary outcomes: tolerability
Notes	Study start date: August 2015 Study end date: September 2016 Funding: "This work was extracted from a residency thesis in the Mashhad University of Science. There was no organizational financial support". Conflicts of interest: "There are no conflicts of interest". Other: trial registry IRCT2016022826802N1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind". No further details provided
Blinding of outcome assessment (detection bias) All outcomes	High risk	The trial registry stated that investigators were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The numbers that discontinued in the treatment group do not match what was analysed (i.e they report 3 dropouts but 4 not included in the analysis).
Selective reporting (reporting bias)	Low risk	The outcomes listed on the clinical registry were reported
Other bias	High risk	• The contact author is also on the ethics committee at the university funding the study.

Eslamzadeh 2018 *(Continued)*

- The contact author is a peer-reviewer for one of the journals in which some of their studies are published.

Fankhauser 1992

Study characteristics	
Methods	Cross-over trial of clonidine versus placebo
Participants	Inclusion criteria: • aged 5-33 years • DSM-III-R diagnosis of an autistic disorder • no medication use in the 2 weeks before the study Exclusion criteria: • a history of schizophrenia or profound intellectual disability • unstable medical condition requiring medication • abnormal laboratory results Location/setting: USA Sample size: 9 in total (cross-over) Number of withdrawals/dropouts: 2 from clonidine group Gender: all male Mean age: 12.9 years IQ: not reported Baseline ABC-I or other BoC: baseline RFRLRS (affectual responses: 1.02) Concurrent medications: 0% History of previous medications: 0%
Interventions	Intervention (clonidine): weekly patch delivering approximately 0.005 mg/kg /day for 4 weeks Comparator (placebo): transdermal placebo patch for 4 weeks
Outcomes	Primary outcomes: irritability, measured using the RFRLRS (Freeman 1986) Secondary outcomes: tolerability Timing of outcome assessment: baseline, 2 weeks, 4 weeks
Notes	Study start date: not reported Study end date: not reported Source of funding: Boehringer Ingelheim Pharmaceuticals supplied the patches Conflicts of interest: none declared Trial registry: not reported
Risk of bias	

Fankhauser 1992 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	2 of 9 participants were lost to follow-up, 1 because of irritability and sedation while on clonidine LTFU: 2 unexplained
Selective reporting (reporting bias)	High risk	AEs were not reported.
Other bias	Unclear risk	This was highly divergent sample (5-33 years) with low sample numbers (9)

Findling 2014

Study characteristics	
Methods	Parallel trial of aripiprazole versus placebo
Participants	Inclusion criteria • Male or female children or adolescents with a mental age of at least 24 months • 6-17 years of age, inclusive, at the time of the baseline visit • Meets current diagnostic criteria of the DSM 4-TR for autistic disorder • Displays behaviors such as tantrums, aggression, self-injurious behaviour, or a combination of these problems. An ABC subscale score ≥ 18 AND a CGI-S score ≥ 4 at the screening and baseline visits Exclusion criteria • Previous treatment with aripiprazole for at least 3 weeks' duration at an adequate daily dose, without demonstrating a clinically meaningful response • Lifetime diagnosis of psychiatric disorder such as bipolar disorder, psychosis, or schizophrenia, or a current diagnosis of PDD-NOS, Asperger's syndrome, Rett's syndrome, childhood disintegrative disorder, or Fragile X syndrome • At significant risk for suicide • Unstable epilepsy or history of severe head trauma or stroke • Other unstable medical conditions Location/setting: child and adolescent psychiatry, Johns Hopkins Hospital, USA Sample size: 85 (41 aripiprazole, 44 placebo)

Findling 2014 *(Continued)*

	Number of withdrawals/dropouts: 19 dropouts in aripiprazole group due to: withdrawal (5), LTFU (1), lack of efficacy (13); 25 dropouts in placebo group due to: adverse event (1), lack of efficacy (23), non-compliance (1) Mean age: aripiprazole 10.1 years, placebo 10.8 years IQ: mental age of at least 24 months Gender: aripiprazole male 30/41; placebo 38/44 male Baseline ABC-I or other BoC: not reported (only change from baseline) Concurrent medications: "allowed antipsychotics apart from aripiprazole include antidepressants, benzodiazepines (for procedures only), stimulants, alpha-agonists, mood stabilizers, and atomoxetine. Diphenhydramine for sleep or serious behaviur problems, nonbenzodiazepine sleep aids for insomnia, and melotonin for insomnai were permitted". History of previous medications: not reported
Interventions	Intervention (aripiprazole): "Phase 1 (single blind): Participants received an initial dose of aripiprazole 2 mg daily, titered up to 5, 10, or 15 mg once daily to optimize clinical benefit, for a maximum of 26 weeks. Phase 2 (randomised): Aripiprazole was continued at the (fixed) dose prescribed at the end of Phase 1, once daily for 16 weeks. The dose (within the range of 2-15 mg/day) could have been adjusted based on efficacy and tolerability". Comparator (placebo): equivalent placebo for 16 weeks
Outcomes	Primary outcomes: irritability (change from baseline), measured using the ABC-Irritability subscale (Aman 1985); AEs Secondary outcomes: QoL, measured with the PedsQL Timing of outcome assessment: ABC-I and AEs were assessed every 2 weeks and PedsQL every 4 weeks
Notes	Study start date: March 2011 Study end date: June 2012 Source of funding: Bristol-Myers Squibb Conflicts of interest: "Dr Findling receives or has received research support from, acted as a consultant to, received royalties from, and/or served on a speaker's bureau for Abbott, Addrenex, Alexza, American Psychiatric Press, AstraZeneca, Biovail, Bracket, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Forest, GlaxoSmithKline, Guilford Press, Johns Hopkins University Press, Johnson & Johnson, Kem-Pharm, Lilly, Lundbeck, Merck, National Institutes of Health, Neuropharm, Novartis, Noven, Organon, Otsuka, Pfizer, Physicians Postgraduate Press, Rhodes Pharmaceuticals, Roche, Sage, Sanofi-Aventis, Schering-Plough, Seaside Therapeutics, Sepracore, Shionogi, Shire, Solvay, Stanley Medical Research Institute, Sunovion, Supernus, Transcept, Validus, WebMD and Wyeth".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided about sequence generation
Allocation concealment (selection bias)	Unclear risk	Details not provided about allocation concealment
Blinding of participants and personnel (performance bias)	Unclear risk	Details not provided about blinding

Findling 2014 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not provided about blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Paper mentions the PedQoL and Caregiver Strain Questionnaire that were administered every 4 weeks in the double-blind phase. Neither outcome was reported in the paper. LTFU: aripiprazole 19/39 did not complete the trial (withdrawal (5); LTFU (1); Lack of efficacy (13)) Placebo: 25/43 did not complete the trial (adverse event (1), poor/noncompliance (1), lack of efficacy (23))
Selective reporting (reporting bias)	High risk	Quote: "Safety assessments were made every 2 weeks in the double blind phase". Relatively few AEs reported for double-blind phase suggesting reporting bias.
Other bias	High risk	There is an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed".

Ghaleiha 2013a

Study characteristics	
Methods	Parallel trial of memantine versus placebo
Participants	Inclusion criteria: • children aged 4-12 years • meet the DSM-4-TR criteria for diagnosis of autism • ABC-C I subscale score of ≥ 12 at screening at baseline Exclusion criteria: • concomitant schizophrenia or psychotic disorders • severe intellectual disabilities • active clinical seizures • history of drug or alcohol abuse or tardive dyskinesia • any antipsychotic drug treatments in the previous 6 months • previously used memantine • any significant active medical problem Location/setting: speciality clinic for autism in the children's outpatient clinic, Iran Sample size: 40 (20 memantine/risperidone; 20 placebo/risperidone) Number of withdrawals/ dropouts: none reported Gender: memantine 11 boys, 9 girls; placebo 12 boys, 8 girls Mean age: memantine 7.42 years; placebo 7.97 years IQ: not reported Baseline ABC-I or other BoC: ABC-I memantine 18.25, placebo 17.65

Ghaleiha 2013a *(Continued)*

	Concurrent medications: 0% (participants had to be drug-treatment-free in 6 months prior to trial) History of previous medications: not reported
Interventions	Intervention (memantine + risperidone) for 10 weeks: participants started on 5 mg (tablets) once daily, which was titrated up or down in 5 mg increments each week up to a maximum of 15 mg/day for children 10-40 kg and 20 mg/day for children > 40 kg. Risperidone was titrated up to 2 mg/day (starting at 0.5 mg with dose increases of 0.5 mg increments weekly for the first 3 weeks) for children weighing 10-40 kg, titrated up to 3 mg/day for children > 40 kg Comparator (placebo + risperidone) for 10 weeks: placebo was identical to memantine in appearance, shape, size, colour and taste. Risperidone was titrated up to 2 mg/day (starting at 0.5 mg with dose increases of 0.5 mg increments weekly for the first 3 weeks) for children weighing 10-40 kg, titrated up to 3 mg/day for children > 40 kg
Outcomes	Primary outcomes: irritability, measured using the ABC-Irritability subscale (Aman 1985); AEs Secondary outcomes: none reported Timing of outcome assessments: ABC-I was rated at baseline, weeks 2, 4, 6, 8 and 10; AEs were recorded every 2 weeks
Notes	Study start date: January 2009 Study end date: January 2011 Source of funding: Tehran University of Medical Sciences Conflicts of interest: none declared Trial registry - IRCT1138901151556N10

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised to receive memantine or placebo in a 1:1 ratio using a computer-generated code"
Allocation concealment (selection bias)	Unclear risk	Quote: "the assignments were kept in sealed, opaque envelopes until data analysis." But it is not clear how they were allocated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Throughout the study the person who administered the medications, the rater and the patients were blind to assignments.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Throughout the study, the person who administered the medications, the rater and the patients were blind to assignments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There appeared to be no LTFU
Selective reporting (reporting bias)	Low risk	All data appear to have been reported
Other bias	High risk	• The contact author is also on the ethics committee at the university funding the study.

Ghaleiha 2013a *(Continued)*

- The contact author is a peer-reviewer for one of the journals in which some of their studies are published.

Ghaleiha 2013b

Study characteristics	
Methods	Parallel trial of riluzole + risperidone versus placebo + risperidone
Participants	Inclusion criteria: "male and female outpatients aged 5-12 years with a diagnosis of autistic disorder based on the DSM-4-TR criteria and a score of >12 on the ABC-C irritability subscale who had discontinue other medication because of lack of efficacy". Participants also had to be drug-free for at least 6 weeks prior to study entry". Exclusion criteria: • any significant medical problem e.g. hepatic disease, seizure disorder • DSM-4 axis I or II psychiatric disorder (based on a structured diagnostic interview) • severe intellectual disabilities, which makes the diagnosis of autism inconclusive • history of hypersensitivity to riluzole • drug or alcohol abuse • tardive dyskinesia • any psychotropic medication within 6 weeks prior to enrolment Location/ Setting: autism speciality clinic in the children's outpatient clinic of Roozbeh Hospital, Iran Sample size: riluzole + risperidone 25; placebo + risperidone 24 Number of withdrawals/dropouts: riluzole + risperidone: 3 restlessness, 2 no improvement. Placebo + risperidone: 1 restlessness; 3 withdrew consent Gender: 17/20 male riluzole/risperidone group; 16/20 male placebo/risperidone group Mean age: riluzole + risperidone 8.4 years; placebo + risperidone 7.6 years IQ: not reported Baseline ABC-I or other BoC: ABC-I of ≥ 12 Concurrent medications: 0% on psychotropic medications History of previous medications: 16/20 and 18/20 (riluzole and placebo group respectively) risperidone; Ritalin (methylphenidate) 6 and 7/20; biperiden 5 and 3/20; haloperidol 1 and 2/20; clonidine 2 and 3/20; fluoxetine 2 in both groups; levocarnitine 2 in riluzole group; valproic acid 1 in both groups; lamatrogine 1 and 2/20; lithium 1 in riluzole group; perphanazine 1 in placebo group; ginseng 1 in riluzole group; desmopressin 1 in riluzole group; pentoxifylline 1 in placebo group
Interventions	Intervention (riluzole + risperidone) for 10 weeks: riluzole (Rilutek; Sanofi-Aventis) was titrated from 25 mg/day to 50 mg/day for children weighing between 10 kg and 40 kg or 100 mg/day for children weighing > 40 kg. Risperidone (Risperdal; Janssen Pharmaceuticals) was titrated from 0.5 mg/day up to 2 mg/day for children weighing up to 40 kg or 3 mg/day for children weighing > 40 kg. Comparator (placebo + risperidone) for 10 weeks: risperidone (Risperdal; Janssen Pharmaceuticals) was titrated from 0.5 mg/day up to 2 mg/day for children weighing up to 40 kg or 3 mg/day for children weighing more than 40 kg.
Outcomes	Primary outcomes: irritability, measured using the ABC-Irritability subscale (Aman 1985); AEs Secondary outcomes: tolerability

Ghaleiha 2013b *(Continued)*

	Timing of outcome assessments: baseline, week 5, week 10
Notes	Study start date: August 2011 Study end date: September 2012 Source of funding: supported by a grant from Tehran University of Medical Sciences to Prof Shahin Akhonzadeh (grant number 14037) Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated code was used in order to randomly assign the patients to the riluzole or placebo group in a 1:1 ratio"
Allocation concealment (selection bias)	Low risk	Quote: "The assignments were kept in sequentially numbered, sealed, opaque envelopes until the end of the study."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The patients, their parents, and the physicians who referred them were all blind to the treatment assignments, as were the rater and the person who administered the medications. Separate persons were responsible for random allocation and rating of the patients" Quote: "The placebo was identical in appearance (shape, size, color, and taste) to riluzole and was dispensed by the investigational drug pharmacist."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: 'The patients, their parents, and the physicians who referred them were all blind to the treatment assignments, as were the rater and the person who administered the medications. Separate persons were responsible for random allocation and rating of the patients'.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All 40 participants who completed at least one post-baseline visit were included in the analysis. 9 of 49 randomised participants did not attend a post-baseline visit, 5 in the riluzole group and 4 in the placebo group.
Selective reporting (reporting bias)	Low risk	All outcomes were reported (ICRT checked)
Other bias	High risk	• The contact author is also on the ethics committee at the university funding the study. • The contact author is a peer-reviewer for one of the journals in which some of their studies are published.

Ghaleiha 2014

Study characteristics

Methods	Parallel trial of galantamine + risperidone versus placebo + risperidone
Participants	Inclusion criteria: • outpatients • aged 4-12 years • met the criteria for diagnosis of autism (DSM-4-TR) (≥ 6 symptoms, as per DSM 4-TR) • score of ≥ 12 on the ABC-I

Ghaleiha 2014 *(Continued)*

	Exclusion criteria: • any other diagnosis of a psychiatric disorder on the DSM-IV axis I or II, based on a structured diagnostic interview. • severe intellectual disability • any unstable medical illness, hepatic disease, active epilepsy, genetic syndrome or other clinically significant abnormality • history of tardive dyskinesia or previous hypersensitivity with the use of galantamine or risperidone • use of psychotropic medication in the 6 weeks prior to enrolment in the stud Location/setting: psychiatric academic hospital affiliated with Tehran University of Medical Sciences Sample size: galantamine 25; placebo 23 Number of withdrawals/dropouts: galantamine (5) because of withdrawn consent; placebo (3) because of withdrawn consent Gender: galantamine 17/20 male; placebo 18/20 male Mean age: galantamine 6.85 years; placebo 5.9 years IQ: galantamine 6 had mild intellectual disability, 2 had moderate intellectual disability; placebo 5 had mild intellectual disability, 4 had moderate intellectual disability Baseline ABC-I or other BoC: ABC-I baseline of ≥ 12 Concurrent medications: none permitted History of previous medications: galantamine 1 had taken valproic acid; placebo 1 sodium valproate, 1 carbamazepine, 1 vigabatrin, 1 phenobarbital
Interventions	Intervention (galantamine + risperidone) for 10 weeks: the initial dosage of galantamine was 2 mg/day and increased weekly in increments of 2 mg if tolerated and clinically indicated. The maximum dose was 12 mg/day for children weighing < 20 kg, 16 mg/day for children weighing 20–30 kg, 20 mg/day for children weighting 30–40 kg and 24 mg/day for children weighing ≥ 40 kg. Risperidone: titrated up to 1 mg/day for children weighing < 20 kg, and 2 mg/day for children weighing ≥ 20 kg Comparator (placebo + risperidone) for 10 weeks: risperidone was titrated up to 1 mg/day for children weighing < 20 kg, and 2 mg/day for children weighing ≥ 20 kg. The equivalent placebo was also administered.
Outcomes	Primary outcomes: • irritability, measured using the ABC-I (Aman 1985) • response (partial or complete defined as a minimum 25% reduction and a minimum 50% reduction in ABC-Irritability scores from baseline respectively) • AEs Secondary outcomes: tolerability Timing of outcome assessments: baseline, week 5, week 10
Notes	Study start date: April 2012 Study end date: January 2013 Source of funding: Tehran University of Medical Sciences (grant number 13216 to SA) Conflicts of interest: none declared Trial registry: IRCT201204081556N40

Ghaleiha 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization codes were generated by excel software by an independent person who was not involved elsewhere in the research project"
Allocation concealment (selection bias)	Low risk	Quote: "assignments were kept in sequentially-numbered, sealed, opaque envelopes and were opened sequentially, only after the participant details were written on the envelope"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the patients, their parents and the physicians who referred them were all blind to the treatment assignments, so were the research investigators and the person who administered the medications. Placebo capsules and their ingredients were made to be identical to galantamine capsules"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The research investigators were blinded to the treatment assignments. Separate people were responsible for rating and random allocation of the patients.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data analysed for 20 participants completing in each group
Selective reporting (reporting bias)	Low risk	All ABC domains reported
Other bias	High risk	• The contact author is also on the ethics committee at the university funding the study. • The contact author is a peer-reviewer for one of the journals in which some of their studies are published.

Ghaleiha 2015

Study characteristics

Methods	Parallel trial of pioglitazone + risperidone versus placebo + risperidone
Participants	Inclusion criteria: • male and female • outpatients • aged 4–12 years • diagnosis of autism based on DSM-4-TR criteria and confirmed by an expert child psychiatrist based on behavioural observations and semi-structured interviews with parents • a score of at least 12 on the ABC-I • presenting with chief complaint of severely disruptive symptoms related to autism • drug-free for at least 6 weeks Location/setting: autism speciality clinic of the children's outpatient clinic of Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, Iran Sample size: 22 in each group. Number of withdrawals/dropouts: 2 in each group withdrew consent

Ghaleiha 2015 *(Continued)*

	Gender: treatment 15/20 male; placebo 17/20 male Mean age: treatment group 6.95 years; placebo 6.2 years IQ: not reported Baseline ABC-I or other BoC: ABC-I 18.25; placebo 19.00 Concurrent medications: not reported History of previous medications: treatment group: risperidone 15/20 participants, Ritalin (methylphenidate) 4, valproic acid 2, lamotrigine 1. Placebo: risperidone 16/20, Ritalin (methylphenidate) 6, valproic acid 2, lamotrigine 2 Exclusion criteria: any active medical condition, diagnosis of DSM-IV axis I or II disorder, use of any psychotropics in previous 6 weeks, history of hepatic disease or seizure; having insulin-dependent diabetes, liver disease, or congestive heart failure Number randomised: pioglitazone 22; placebo 22 Number analysed: pioglitazone 20; placebo 20
Interventions	Intervention (pioglitazone + risperidone) for 10 weeks: pioglitazone (Actos, Takeda/Eli Lilly) 30 mg/day (15 mg twice/day) fixed dose. Risperidone(Risperdal; Janssen Pharmaceuticals, Belgium) initial dose 0.5 mg/day increased by 0.5 mg every week to a maximum of 1 mg/day for participants weighing < 20 kg and 2 mg/day for those who were ≥ 20 kg Comparator (placebo + risperidone) for 10 weeks: placebo tablets with identical appearance. Risperidone (Risperdal; Janssen Pharmaceuticals, Belgium) initial dose 0.5 mg/day increased by 0.5 mg every week to a maximum of 1 mg/day for participants weighing < 20 kg and 2 mg/day for those who were ≥ 20 kg
Outcomes	Primary outcomes: • irritability, measured using the ABC-I (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessments: baseline, week 5, week 10
Notes	Study start date: March 2012 Study end date: February 2014 Source of funding: "This study was supported by a grant from Tehran University ofMedical Sciences to Prof Shahin Akhondzadeh (grant number16043). The funding organization had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript and the decision to submit the paper for publication." Conflicts of interest: none declared Trial registry: IRCT201204081556N40

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation codes were generated by Microsoft Office excel software and each participant was assigned to one specific code"

Ghaleiha 2015 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "Assignments were kept in confidential sealed opaque envelopes and were disclosed after the end of the study for statistical analysis"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants, parents and referring physicians were totally blinded to the assignments. Additionally, responsible individuals for administration of the medications, rating and statistical analysis were also blinded to the assignments.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The participants, parents and referring physicians were totally blinded to the assignments. Additionally, responsible individuals for administration of the medications, rating and statistical analysis were also blinded to the assignments.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Two of 22 were LTFU in both groups
Selective reporting (reporting bias)	Low risk	All data were reported.
Other bias	High risk	• The contact author is also on the ethics committee at the university funding the study. • The contact author is a peer-reviewer for one of the journals in which some of their studies are published.

Ghaleiha 2016

Study characteristics	
Methods	10-week parallel study of minocycline + risperidone versus placebo + risperidone
Participants	Inclusion criteria: • children 3-12 years • diagnosis of ASD based on DSM-4 criteria • ABC-I score of at least 12 at baseline • presence of behavioural problems such as aggression Exclusion criteria: "Children with concomitant psychotic disorders, severe intellectual disability that made the diagnosis inconclusive (based on clinical judgment and reviewing prior neurocognitive testing and records), other DSM-IV axis I or II disorders, seizure disorder, a history of alcohol or drug abuse, tardive dyskinesia, administration of antipsychotic medications within the past 6 months, as well as behavior therapy, and the presence of any significant active medical condition were excluded from the study". Setting: psychiatric hospital Dropouts/withdrawals: 2 participants in each group withdrew consent prior to week 5 (1st outcome measurement point) Sample size: 50 (25 each group) Mean age: 7.6 years Gender: minocycline 17/23 male; placebo 18/23 male IQ: details not provided

Ghaleiha 2016 *(Continued)*

	Baseline ABC-I or other BoC: ABC-I intervention group 21.26 (4.82), comparator group 19.91 (7.20) Concomitant medications: participants were not allowed to be taking antipsychotics concomitantly. Previous medications: details not provided
Interventions	Intervention (minocycline + risperidone): minocycline 100 mg/day + tablet risperidone 1-2 mg/day as intervention 10 weeks Comparator (placebo + risperidone): risperidone 1-2 mg/day + capsule placebo as control for 10 weeks. The maximum target dose of risperidone was defined as 1 mg/day for children weighing < 20 kg and 2 mg/day for those weighing ≥ 20 kg
Outcomes	Primary outcomes: • ABC-I (change from baseline) (Aman 1985) • AEs Secondary outcomes: none reported
Notes	Study start date: March 2013 Study end date: March 2015 Funding: "This study was supported by a grant from Tehran University of Medical Sciences to Dr. Shahin Akhondzadeh (Grant No. 20288)". Also, "The authors also affirm that there was no source of funding" Conflicts of interest: 'the authors do not have any conflicts of interest" Trial registry: IRCT201302201556N50

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised to receive either minocycline or placebo in a 1:1 ratio using a computer-generated code.
Allocation concealment (selection bias)	Low risk	The assignments were kept in sealed opaque envelopes until data analysis.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Throughout the study, the person who administered the medications, the rater, the participants, and parents were blind to assignments. Independent people were responsible for treatment allocation and participant interviews.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo was identical to the intervention medication (minocycline) in shape, size, colour, and taste and was dispensed by the investigational drug pharmacist. Throughout the study, the person who administered the medications, the rater, the participants, and parents were blind to assignments. Independent people were responsible for treatment allocation and participant interviews
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 participants in each group discontinued (8% each group) and imputation was not used
Selective reporting (reporting bias)	Low risk	Outcomes reported match protocol
Other bias	High risk	• The contact author is also on the ethics committee at the university funding the study.

Ghaleiha 2016 *(Continued)*

- The contact author is a peer-reviewer for one of the journals in which some of their studies are published.

Ghanizadeh 2013

Study characteristics	
Methods	Parallel trial of N-acetylcysteine (NAC) + risperidone versus placebo + risperidone
Participants	Inclusion criteria: • children and adolescent outpatients from child and adolescent psychiatry clinics • met DSM-4 diagnostic criteria for ASD • aged 3.5-16 years. • ll diagnostic interviews were conducted by an expert child and adolescent psychiatrist. Exclusion criteria: • the use of any concomitant medications • patients with psychotic disorders, unstable medical conditions, evidence of active liver disease, seizure disorder, unstable hypertension or cardiac disease, unstable asthma, and kidney disease Location/setting: child and adolescent psychiatry clinics affiliated with Shiraz University of Medical Sciences Sample size: 40 (20 to each group) Number of withdrawals/dropouts: NAC: lack of efficacy 0, declined to return 3, severe sedation 1. Placebo: lack of efficacy 3, declined to return 4, severe sedation 0 Gender: NAC 13/17 boys; placebo 12/14 boys Mean age: NAC 8.8 years; placebo 7.9 years IQ: not reported Baseline ABC-I or other BoC: ABC-I NAC + risperidone 13.2; placebo + risperidone 16.7 Concurrent medications: clonidine NAC (5), placebo (3); folic acid NAC (2), placebo 0; imipramine NAC (1), placebo (0); biperiden 1 each group; nortriptyline 1 (NAC group); topiramate NAC (0), placebo (2) History of previous medications: not reported
Interventions	Intervention (NAC + risperidone) for 8 weeks: 1200 mg/day in twice-daily doses. Risperidone started at the dose of 0.5 mg/day, titrated up to 2 mg/day during 3 weeks for children weighing < 30 kg. The dose for children > 30 kg was up to 3 mg/day. Comparator (placebo + risperidone) for 8 weeks: placebo tablets were administered in the form of effervescent. The shape, size, taste, and colour of NAC and placebo were identical. Risperidone started at the dose of 0.5 mg/day, titrated up to 2 mg/day during 3 weeks for children weighing < 30 kg. The dose for children > 30 kg was up to 3 mg/day.
Outcomes	Primary outcomes: • irritability, measured using the ABC-I (Aman 1985) • AEs Secondary outcomes: tolerability Timing of outcome assessments: baseline, 4 weeks and 8 weeks (endpoint)

Ghanizadeh 2013 *(Continued)*

Notes	Study start date: 2011 Study end date: 2012 Source of funding: "This study was supported by a grant from Shiraz University of Medical Sciences (Grant No: 5545)." Conflicts of interest: none declared Trial registry: IRCT201106103930N6

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly allocated into one of the two groups using a random number generator"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The patients, parents, and independent assessor were blind to the allocation of patients"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the independant assessor was blind to the allocation of patients"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data analysed for 17/20 in NAC group and 14/20 in placebo group
Selective reporting (reporting bias)	Low risk	Relevant ABC domains reported
Other bias	Unclear risk	Unclear whether there were differences in the dose of risperidone between groups. 5 in the NAC group and 3 in the placebo group also received clonidine. 2 in the placebo group but none in the NAC group received topiramate.

Ghanizadeh 2015

Study characteristics

Methods	Parallel trial of buspirone + risperidone versus placebo + risperidone
Participants	Inclusion criteria: • children 4-17 years • DSM-4 diagnosis of autism, a CGI-Severity score of C4, range 0-7 at baseline • able to swallow medication • if taking concomitant medications must maintain them at a constant dose during the study Exclusion criteria: • primary diagnosis of a psychotic disorder

Ghanizadeh 2015 *(Continued)*

- active substance abuse or dependence
- unstable medical condition, active liver disease, an unstable hypertension or cardiac disease, unstable asthma, kidney disease as determined by the investigator
- allergic to medications
- initiation of a new behavioral therapy

Location/setting: "child and adolescent psychiatry clinic affiliated with Shiraz University of Medical Sciences [Iran] clinics specializing in the treatment of child and adolescent psychiatry problems".

Sample size: 40 (20 in each group)

Number of withdrawals/dropouts: 16 completing trial in the busperone group; 18 in placebo group

Gender: buspirone 12/16 boys, placebo 15/18 boys

Mean age: buspirone 7.05 years, placebo 7.5 years

IQ: not reported

Baseline ABC-I or other BoC: ABC-I buspirone 25.7, placebo 24.7

Concomitant medications: not reported

History of previous medications: not reported

Interventions	Intervention (buspirone + risperidone) for 8 weeks: buspirone was titrated to a maximum 10 mg/day given twice daily for children weighing < 40 kg, and up to 20 mg/day for children weighing > 40 kg. The dose of risperidone was up to 2 mg/day for children weighing < 40 kg and up to 3 mg/day for children weighing > 40 kg. The dosage was increased to this target/maximum dose from week 1 to week 2, and modified at any time in response to clinical efficacy and AEs. Comparator (placebo + risperidone) for 8 weeks: the dose of risperidone was up to 2 mg/day for children weighing < 40 kg and up to 3 mg/day for children weighing > 40 kg. The dosage was increased to this target/maximum dose from week 1 to week 2, and modified at any time in response to clinical efficacy and AEs.
Outcomes	Primary outcomes: • irritability, measured with the ABC (Aman 1985) • response rate Secondary outcomes: tolerability Timing of outcome assessment: baseline, week 4, week 8
Notes	Study start date: 2012 Study end date: 2013 Source of funding: supported by a grant from Shiraz University of Medical Sciences to Professor Ahmad Ghanizadeh (grant no. 6978) Conflicts of interest: none declared Trial registry: IRCT201307303930N28

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A random number list provided by a random number generator was used for the allocation of the patients into the groups".

Ghanizadeh 2015 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "both risperidone and placebo were administered in the form of similar tablets"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported to be double-blinded however, the "physician who interviewed the patients and allocated the patients into the groups was not blinded".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The person who allocated the patients into the group and the person who rated the outcome measure were different.
Incomplete outcome data (attrition bias) All outcomes	High risk	Mentioned assessment at week 4 but these outcomes were not reported LTFU: 2 people did not respond to calls (1 in each group). 1 person's symptoms of crying and isolation were exacerbated (buspirone group)
Selective reporting (reporting bias)	High risk	The Iranian clinical trial registry does not include results (neither does the paper include week 4 measures) and the trial was retrospectively registered online.
Other bias	High risk	The study authors retrospectively registered the trial on the Iranian clinical trials website - it is unknown whether 8 weeks was the original length of the trial or not.

Ghanizadeh 2014

Study characteristics	
Methods	Parallel trial of aripiprazole versus risperidone
Participants	Inclusion criteria: • children and adolescents with ASD (diagnosed according to DSM-4-TR and according to ADI-R. • clinician rating of at least moderate severity of autistic symptoms (CGI-S score of C4, range 0-7) Exclusion criteria: • history of medically significant or uncontrolled medical conditions such as hypothyroidism, diabetes or cancer • history of drug or alcohol abuse • received risperidone or aripiprazole during the last 2 weeks prior to enrolment in the study • received any additional behavioural intervention Location/setting: child psychiatry outpatient clinic affiliated with Shiraz University of Medical Sciences, Iran Sample size: 59 were randomised (29 aripiprazole, 30 risperidone) Number of withdrawals/dropouts: 3 children dropped out of aripiprazole group because of severity of symptoms (1), exacerbation of epilepsy (1) and severe sedation (1). 3 children dropped out of the risperidone group due to lack of efficacy (1), refused to return (1), agitation and crying (1) Gender: aripiprazole 25/29 male; risperidone 23/30 male Mean age: aripiprazole 9.6 years, risperidone 9.5 years IQ: not reported

Ghanizadeh 2014 *(Continued)*

	Baseline ABC-I or other BoC: ABC-I aripiprazole 26.2; risperidone 21.5 Concomitant medications: concurrent medications were allowed apart from antipsychotics provided they were stable throughout the trial and commenced at least two weeks prior to the trial. History of previous medications: details not provided
Interventions	Intervention (aripiprazole) for 8 weeks: maximum dose of aripiprazole for children weighing < 40 kg was up to 10 mg/day and up to 15 mg/day for children > 40 kg. The dose of aripiprazole was titrated over 2 weeks (1.25 mg/day starting dose); mean daily dose of 5.5 mg/day (approximately 0.163 mg/kg/day) Comparator (risperidone) for 8 weeks: maximum dose for children weighing < 40 kg was 2 mg, and for those > 40 kg was up to 3 mg/day. Risperidone was titrated over 2 weeks (0.25 mg starting dose); risperidone mean daily dose 1.12 mg/day (or 0.033 mg/kg/day)
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessments: baseline, 1 month and 2 months (endpoint)
Notes	Study start date: not reported Study end date: not reported Source of funding: "grant (No: 3135) from Shiraz University of Medical Sciences to Professor Ahmad Ghanizadeh. MB is supported by the Simons Autism Foundation. MB has received Grant/Research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, MBF, NHMRC, Beyond Blue, Rotary Health, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Organon, Novartis, Mayne Pharma and Servier, has been a speaker for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Merck, Pfizer, Sanofi Synthelabo, Servier, Solvay and Wyeth, and served as a consultant to Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck Merck and Servier, and is a co-inventor of two provisional patents regarding the use of NAC and related compounds for psychiatric indications". Conflicts of interest: none declared Trial registry - IRCT201110233930N15

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	The clinician who administered the medications was not blind to assignment and "about 7 of the parents (12%) of the parents were not blinded to the group assignment because they could correctly guess the group allocation or requested to be not blinded to it".
Blinding of outcome assessment (detection bias)	High risk	Some parents knew of their allocation and contamination could have occurred.

Ghanizadeh 2014 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed both the first and second follow-up and an ITT analysis was used. LTFU aripiprazole: severity of symptoms (1); exacerbation of epilepsy (1); and severe sedation (1) LTFU risperidone: lack of efficacy (1); refused to return (1); agitation and crying (1)
Selective reporting (reporting bias)	High risk	The most common AEs associated with risperidone were not reported (sedation and weight gain)
Other bias	Low risk	None identified

Gordon 1993

Study characteristics	
Methods	Cross-over trial of clomipramine, desipramine, and placebo
Participants	Inclusion criteria: • meet the DSM-III-R and ADI criteria for ASD • free of significant medical problems, including seizures • free of psychotropic medications for at least 3 months prior to the study Exclusion criteria: • significant medical problems, including seizures, by history, physical examination, and laboratory examination • used psychoactive medications during the 3 months prior to the study. Location/setting: outpatient clinic, USA Sample size: 24 in total (cross-over) Number of withdrawals/dropouts: 1 in clomipramine group and 1 other dropout although group was not specified. Gender: 15/24 male Age range: 6-18 years IQ range: 30-107 Baseline ABC-I or other BoC: not reported Concomitant medications: not reported History of previous medications: not reported
Interventions	Intervention 1 (clomipramine) for 5 weeks: mean final dose was 152 mg/day (SD 56), 4.3 mg/kg/day (SD 0.8). The initial dosage was 25 mg/day, and titrated to a maximum of 5 mg/kg per day or 250 mg/day usually between weeks 2 and 3 Intervention 2 (desipramine) for 5 weeks: mean final dose was 127 mg/day (SD 52). 4.0 mg/kg/day (SD 1.2). The initial dosage was 25 mg/day, titrated to a maximum of 5 mg/kg per day or 250 mg/day usually between weeks 2 and 3

Gordon 1993 *(Continued)*

	Comparator (placebo) for 5 weeks: equivalent placebo
Outcomes	Primary outcomes: AEs Secondary outcomes: none reported Timing of outcome assessment: week 5 (endpoint)
Notes	Study start date: not reported Study end date: not reported Source of funding: not reported Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation was performed by the National Institutes of Health pharmacy using a random-number table".
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details of blinding were not provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not provided
Incomplete outcome data (attrition bias) All outcomes	High risk	LTFU: clomipramine/desipramine 2; 1 in the clomipramine/ desipramine group because of violent outbursts and 1 because the group home administered his medicine to the wrong participant.
Selective reporting (reporting bias)	Unclear risk	Outcomes that were mentioned in the paper were reported. No protocol was available.
Other bias	Unclear risk	No baseline comparisons were reported by group.

Guastella 2015a

Study characteristics

Methods	8-week parallel trial of oxytocin versus placebo
Participants	Inclusion criteria: • male adolescents 12-18 years • confirmed diagnosis of ASD based on the DSM-4-TR Exclusion criteria: "females, severe depressive or psychotic symptoms, including suicidal thoughts and/or actions, cardiovascular disease, kidney disease, smoking more than 15 cigarettes a day, sub-

Guastella 2015a *(Continued)*

	stance dependence, or sensitivity to preservatives (in particular, E 216, E 218, and chlorobutanol hemihydrate)". Location/setting: autism clinic at the Brain & Mind Research Institute, University of Sydney, Australia Sample size: oxytocin (26), placebo (24) Number of withdrawals/dropouts: placebo, 1, parent unwilling to attend follow-up assessment, 2 discontinued (1 parent withdrew, 1 AEs) Gender: all male Age range: oxytocin 13.85. placebo 14.00 years IQ range: mean IQ oxytocin 80.04, placebo 93.14 Baseline ABC-I or other BoC: self-injurious behaviour (measured using the Repetitive Behaviour Scale (self-injurious subscle), oxytocin baseline 1.96 (2.27); placebo 3.13 (3.75) Concurrent medications: adjunctive psychotropic medication use (oxytocin = 9, placebo = 9) included stimulants (35.7%), antipsychotics (28.6%), antidepressants (25%), mood stabilisers (7.1%), and benzodiazepines (3.6%) History of previous medications: not reported
Interventions	Intervention (oxytocin nasal spray): either 18 or 24 IU, administered twice daily for 8 weeks Comparator (placebo nasal spray): administered twice daily for 8 weeks.
Outcomes	Primary outcomes: self-injurious behaviour measured using the Repetitive Behaviour Scale (Bodfish 2000) Secondary outcomes: tolerability Timepoints - baseline, endpoint and 3-month follow-up
Notes	Study start date: February 2009 Study end date: January 2012 Funding: "This study was funded by a National Health and Medical Research Council Project Grant to authors A.J.G., K.M.G., N.J.R., and S.L.E. (632625)" Conflicts of interest: most authors were also receiving funding for other trials. Other: trial registry ACTRN12609000513213

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Nasal sprays were developed and randomised by a compounding chemist with an identical placebo containing all ingredients except the active oxytocin
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinded - no further details provided

Guastella 2015a *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Data were entered by research assistants blind to drug assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout. Analysed in ITT format, although "last-observations-carried-forward to replace missing data" was used which is a dubious method.
Selective reporting (reporting bias)	Low risk	Same primary outcome and measurement timepoints as clinical trial reg
Other bias	Low risk	No other sources of bias identified

Hagerman 2018

Study characteristics	
Methods	6-month trial of sertraline versus placebo
Participants	Inclusion criteria: • documentation of ASD as verified using both DSM-5 and ADOS-2 criteria • age between 24 and 72 months • stable medications (including antiepileptics, antipsychotics, and clonidine) in the 2 months prior to enrolment • concurrent enrolment in at least 1 community or school intervention for ASD Exclusion criteria: • changes in concomitant medications and interventions were discouraged unless medically necessary during the trial • current or past SSRI treatment • diagnosis of the fragile X syndrome full mutation, or any other serious co-morbid medical disorders affecting brain function and behaviour, including uncontrolled seizures Location/setting: USA Sample size: 58 (32 sertraline, 26 placebo) Number of withdrawals/dropouts: sertraline (8, 2 lost to follow-up, 6 withdrew consent); placebo (5, 1 lost to follow-up, 4 withdrew consent) Gender: details not provided Average age (SD) : 4.3 (0.8) and 3.7 (1.1) years in the sertraline and placebo groups IQ range: details not provided Baseline ABC-I or other BoC: N/A Concurrent medications: sertraline (9.38%); placebo (7.69%) History of previous medications: details not provided
Interventions	Intervention: the study drug was administered orally in liquid form (20 mg/mL), and dose was assigned based on age at enrolment: participants under 4 years received sertraline or placebo liquid in a dose of 2.5 mg/day (0.125 mL) for the duration of the trial, and participants ≥ 4 years received 5.0 mg/day (0.25 mL).

Hagerman 2018 *(Continued)*

	Comparator: placebo was administered orally in liquid form for 6 months.
Outcomes	Primary outcomes: AEs Secondary outcomes: tolerability
Notes	Study start date: April 2015 Study end date: July 2018 Funding: "This project was supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) under grant number R40MCH 27701". Conflicts of interest: "RH has carried out treatment studies in fragile X syndrome and autism spectrum disorder by Roche, Novartis, Neuren, Marinus, Alcobra, and Curemark and has also consulted with Zynerba and Fulcrum. FT received funds from Asuragen, Roche, and Zynerba. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest". Trial registry: NCT02385799

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The UC Davis Investigational Drug Services independently carried out randomization". No information on sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "The UC Davis Investigational Drug Services independently carried out randomization"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Apart from "double-blinded" no further details were provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Apart from "double-blinded" no further details were provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout < 20% and reasons reported
Selective reporting (reporting bias)	Low risk	Same primary outcomes as trial reg (MSEL expressive language raw score and age equivalent combined score)
Other bias	Low risk	No other sources of bias identified

Hajizadeh-Zaker 2018

Study characteristics

Methods	10-week trial of L-carnosine versus placebo
Participants	Inclusion criteria: • children 3-12 years

Hajizadeh-Zaker 2018 *(Continued)*

- clinical diagnosis of autism based on the DSM-5 criteria
- outpatients at a speciality clinic
- ABC-I score of at least 12

Exclusion criteria:

- co-occurring schizophrenia or psychotic disorder
- severe intellectual disability
- history of seizures
- presence of hepatic disease
- history of alcohol or drug abuse
- tardive dyskinesia
- any significant medical condition

Location/setting: speciality clinic for autism in the children's outpatient clinic (Iran)

Sample size: 50

Number of withdrawals/dropouts: risperidone + L-carnosine (n = 4) 4 discontinued treatment (withdrew consent), risperidone + placebo (n = 4) 4 discontinued treatment (withdrew consent)

Gender: 35 male, 7 female

Mean age: L-carnosine + risperidone 8.24 (2.22), placebo + risperidone 7.90 (1.89)

Mean IQ: details not provided

Baseline ABC-I or other BoC: ABC-I > 22.0 at baseline

Concurrent medications: details not provided

History of previous medications: details not provided

Interventions	Intervention (L-carnosine + risperidone): L-carnosine was administered in tablet form, 400 mg twice daily, + tablet form of risperidone, 1-3.5 mg/day, for 10 weeks Comparator (placebo + risperidone): risperidone was administered in tablet form, 1-3.5 mg/day, plus placebo in tablet form for 10 weeks.
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: tolerability
Notes	Study start date: December 2015 Study end date: November 2016 Funding: "This study was supported by a grant from Tehran University of Medical Sciences to Prof. S.A. (Grant No. 29571). This study was supported by a grant from Tehran University of Medical Sciences (Grant No. 29571)". Conflicts of interest: "No competing financial interests exist". Other - trial registry: IRCT201512081556N83

Risk of bias

Bias	Authors' judgement	Support for judgement

Hajizadeh-Zaker 2018 *(Continued)*

Random sequence generation (selection bias)	Low risk	A computerised random number generator (allocation ratio 1:1) was applied to generate randomisation codes
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes were used to keep the assignments to mask the allocation throughout the study.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The children, parents, the physician who referred the children, the physician who arranged the medications, the rater, and the statistician were all blinded to the allocated treatment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The children, parents, the physician who referred the children, the physician who arranged the medications, the rater, and the statistician were all blinded to the allocated treatment."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	16% dropout in both groups.
Selective reporting (reporting bias)	Low risk	Outcome measures reported per protocol
Other bias	High risk	• The contact author is also on the ethics committee at the university funding the study. • The contact author is a peer-reviewer for one of the journals in which some of their studies are published.

Handen 2005

Study characteristics	
Methods	Cross-over trial of secretin versus placebo
Participants	Inclusion criteria: • children with autism • free of gastrointestinal disorders Exclusion criteria: • included current or lifetime diagnosis of bipolar disorder, schizophrenia, schizoaffective disorder, and psychotic disorder, NOS • uncontrolled epilepsy or taking ≥ 2 anticonvulsants • use of other psychotropic medications unless the medications have been stable for at least 1 month prior to the start of the trial and remained stable throughout the trial • any other significant medical conditions, gastrointestinal symptoms including diarrhoea and constipation, or pancreatitis Location/setting: research centre at the Children's Hospital of Pittsburgh Sample size: 8 in total (cross-over) Number of withdrawals/dropouts: none reported Gender: 7 male, 1 female Mean age: 7 years, 6 months

Handen 2005 *(Continued)*

	IQ: "IQs ranged from moderate mental retardation [intellectual disability] to gifted (with two subjects functioning within the moderate range of mental retardation, three within the mild range, one with borderline intellectual functioning, one with average abilities and one functioning within the gifted range)". Baseline ABC-I or other BoC: ABC-I 11.4 Concurrent medications: not reported History of previous medications: not reported
Interventions	Intervention (porcine secretin): 2 infusions of porcine secretin at a dose of 2 IU/kg at the start of the secretin phase and 2 months later Comparator (placebo): single 2 IU/kg dose of placebo
Outcomes	Primary outcomes: • irritability, measured using the ABC-I (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessment: baseline, 1 month and 2 months post-infusion
Notes	Study start date: not reported Study end date: not reported Source of funding: "this research was supported by a small grant to the authors from the General Clinical Research Center at Children's Hospital of Pittsburgh" Conflicts of interest: none disclosed Trial registry: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Allocated by hospital pharmacist
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear how many participants were originally randomised to the study
Selective reporting (reporting bias)	Unclear risk	The primary outcomes mentioned at the start of the paper are the ABC (and 5 subscales), the CGI, the Dosage Record and Treatment Emergent Symptom

Handen 2005 *(Continued)*

		Scale (DOTES), and the Gilliam Autism Rating Scale (GARS). Adverse events were not recorded, although the other 3 scales were recorded in full.
Other bias	Unclear risk	Cross-over study and all participants appear to have completed both phases of the study

Handen 2008

Study characteristics	
Methods	Cross-over trial of guanfacine versus placebo
Participants	Inclusion criteria: • diagnosis of intellectual disability (based on the most recent school psychological assessment) and/or autism (ASD or pervasive developmental disorder) • diagnosed with ADHD or present with clinically significant deficits in the areas of overactivity and inattention • scored ≥ 15 points on the CPRS/or Teacher Hyperactivity Index Exclusion criteria: • any known genetic disorders • continued current use of prescribed stimulant medications Location/setting: outpatient speciality clinic serving children with developmental disorders Sample size: 11 in total Number of withdrawals/dropouts: 1 from placebo group due to non-compliance Gender: 10 male, 1 female Mean age: 7.3 years IQ: cognitive functioning ranged from severe intellectual disability to average IQ. Baseline ABC-I or other BoC: details not provided Concomitant medications: Adderall (2), mirtazapine (1); risperidone, zolpidem, tartrate and carbamazepine (1); nortriptyline (1); lamotrigine (1); methylphenidate (1); and bupropion and clonidine (1) History of previous medications: details not provided
Interventions	Intervention (guanfacine): began on a maximum of 3.0 mg/day titrated doses over a 19-day period. After 8 days on the highest dose, a 6-day washout period commenced (1.5 mg/day for 3 days and 0 mg/kg per day for 3 days) Comparator (placebo): equivalent placebo for 8 days
Outcomes	Primary outcomes: irritability, measured using the parent-rated ABC-I subscale (Aman 1985) Secondary outcomes: tolerability Timing of outcome assessments: baseline then at 4 additional visits
Notes	Study start date: not reported Study end date: not reported

Handen 2008 *(Continued)*

	Source of funding: not reported Conflicts of interest: not reported Trial registry: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided, only that it is a double-blinded trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "we did not have complete sets of parent and/or teacher data for some subjects (e.g., one parent whose child was in the summer program was unreliable in completing questionnaires; some trials that occurred across a school vacation resulted in incomplete teacher data). Our solution was to use parent data as our primary source when available and to use teacher data if parent data were missing."
Selective reporting (reporting bias)	High risk	The authors note that the ABC was measured at baseline and an additional four visits. Neither baseline nor additional visit scores were recorded.
Other bias	High risk	Quote: "no standardized instruments were used to assess autistic disorder and comorbid psychiatric diagnoses" (among other limitations)

Handen 2011

Study characteristics

Methods	Parallel trial of donepezil versus placebo
Participants	Inclusion criteria: • children and adolescents aged 8-17 years • IQ > 75 • diagnosed with ASD using ADI-R and ADOS • score at least one SD lower than the mean on the Card Sorting test, verbal fluency, or Executive Function tests Exclusion criteria: not reported Location/setting: not reported Sample size: 34 (donepezil 18, placebo 16)

Handen 2011 *(Continued)*

	Number of withdrawals/dropouts: "one subject terminated due to an increase in aggression and irritability. Two other subjects were unable to tolerate the 10mg/day dose and were maintained on a 5mg/day dose". Gender: details not provided Mean age: treatment group 8 years 7 months, placebo group 9 years 7 months IQ: mean 96.8 (treatment group), 96.7 (placebo group) Baseline ABC-I or other BoC: baseline CBCL (aggression) 9.72; RFRLRS (affectual responses i.e. irritability) 0.90 Concurrent medications: concurrent psychotropic medications allowed provided the dose levels are maintained during the trial. 5 participants were taking SSRIs, 4 were taking stimulants and 2 were taking atomoxetine. History of previous medications: not reported
Interventions	Intervention - donepezil max 5 mg/day for 4 weeks followed by donepezil maximum 10 mg/day for 4 weeks if tolerated. Participants began on 2.5 mg/day increasing to 5 mg/day after 1 week. After 4 weeks at 5 mg/day doses were increased to 7.5 mg/day for 1 week, up to a maximum of 10 mg/day for the remaining for 4 weeks (for 16/18 who could tolerate higher doses). Comparator (placebo) for 10 weeks: equivalent placebo
Outcomes	Primary outcomes: • aggression, measured using the CBCL (Achenbach 2000) • irritability, measured using the RFRLRS Affectual Responses subscale (Freeman 1986) Secondary outcomes: none reported Timing of outcome assessments: "following randomisation, subjects were seen for a total of 4 clinic visits (following one week on 2.5mg/day, following four weeks on 5.0mg/day, one week on 7.5mg/day, and four weeks at 10mg/day".
Notes	Study start date: not reported Study end date: not reported Source of funding: NIMH Grant 5R21 MH64941-03 as well as a gift by Pfizer and Eisai Pharmaceutical companies Conflicts of interest: none declared Trial registry: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study pharmacist conducted the randomization for each subject"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described though study authors stated the trial was double-blind

Handen 2011 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF analysis used for the one of 34 randomised participants who did not complete the trial
Selective reporting (reporting bias)	Low risk	All outcome data appear to have been reported
Other bias	High risk	A gift was given by Pfizer and Eisai Pharmaceutical companies (who also provided the medication and placebo for this trial). The placebo group were one year older (9 years 7 months) compared to the donepezil group (8 years 7 months). Baseline scores for aggression (9.72 vs 7.47) and irritability (0.90 vs 0.80) were also higher for the donepezil group.

Handen 2015

Study characteristics	
Methods	Parallel trial of atomoxetine versus placebo
Participants	Inclusion criteria: • aged 5-14 years • minimum mental age of 24 months • meet criteria for an ASD (autistic disorder, Asperger's disorder, PDD-NOS), based upon the ADI-R and expert clinical evaluation using a DSM-4-TR interview • exhibit significant symptoms of overactivity and/or inattention at both home and school, based on a mean item score of at least 1.50 on the parent and teacher SNAP scales and a CGI–S score of ≥ 4 • free of psychotropic medications for 2 weeks before randomisation (except stable doses of melatonin or low-dose clonidine for sleep and anticonvulsant for seizure control) Exclusion criteria: • Rett disorder, childhood disintegrative disorder, diagnosis of schizophrenia or other psychotic disorder, bipolar disorder, current diagnosis of major depression or obsessive-compulsive disorder • significant medical conditions or abnormalities on routine laboratory tests or ECG • prior trial of atomoxetine for ≥ 4 weeks, within the last 2 years • regular usage of b-adrenergic blocking agents, asthma medicine • prior involvement in a highly structured parent training programme Location/setting: University of Pittsburgh Medical Centre, Ohio State University, and University of Rochester, USA Sample size: atomoxetine 32, placebo 32 Number of withdrawals/dropouts: inadequate improvement (2 placebo group); behavioural AEs especially irritability 2 atomoxetine group, 3 placebo group; physical AE 2 placebo group; LTFU 1 from each group; other LTFU/unknown 3 placebo group Gender: atomoxetine 26/32 boys; placebo 24/32 boys Mean age: atomoxetine 8.6 years; 8.2 years placebo IQ: atomoxetine group: 78.7; placebo group: 86.7

Handen 2015 *(Continued)*

	Baseline ABC-I or other BoC: ABC-I atomoxetine group: 16.00; placebo group 16.97 Concomitant medications: “a single anticonvulsant for seizure control was allowed, provided that stable doses and seizure-free status had been 6 months or more”. History of previous medications: details not reported
Interventions	Intervention (atomoxetine) for 10 weeks: the initial dose was 0.3 mg/kg/day (rounded to the nearest 5 mg) with weekly escalations by 0.3 mg/kg/day, unless there were limiting side effects or no further improvement, to a target dose of 1.2 mg/kg/day, but could be increased to a maximum of 1.8 mg/kg/day. Mean final dose of atomoxetine was 1.38 mg/kg/day. Comparator (placebo) for 10 weeks: sugar pill administered twice daily
Outcomes	Primary outcomes: • irritability, measured using parent-reported ABC-I subscale (Aman 1985) • AEs Secondary outcomes: tolerability Timing of outcome assessment: “study visits occurred weekly to assess medication response, to monitor adverse events (AEs), and to adjust doses. Final dose adjustments were made at week 6, with subsequent monitoring visits at weeks 8 and 10"
Notes	Study start date: October 2008 Study end date: April 2014 Source of funding: grants from the National Institute of Mental Health to Ohio State University (5R01MH079080), University of Pittsburgh (5R01MH079082-05), and University of Rochester (5R01 MH083247), by Eli Lilly and Co, who provided atomoxetine and placebo, and by the University of Rochester CTSA (UL1 RR024160) and Ohio State University CTSA (UL1TR001070) from the National Center for Research Resources and the National Center for Advancing Translational Sciences of the National Institutes of Health Conflicts of interest: none declared Trial registry: NCT00844753

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The study biostatistician generated the randomisation sequence using a computer algorithm"
Allocation concealment (selection bias)	Low risk	Quote: "a designated team member at each site obtained the assignment for each participant via a Web portal maintained by the data centre"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "ATX [atomoxetine] assignment was double-blinded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"ATX [atomoxetine] assignment was double-blinded". Independent evaluators blinded to treatment assignment until completion of the study rated participants on the CGI scale.
Incomplete outcome data (attrition bias)	Unclear risk	High LTFU across groups 29/128 although data were estimated from Missing At Random models and sensitivity tested using LOCF.

Handen 2015 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Protocol and archived versions available NCT00844753
Other bias	Unclear risk	More than twice as many (72%) in special education compared to placebo group (34%)

Hardan 2012

Study characteristics	
Methods	Parallel trial of N-acetylcysteine versus placebo
Participants	Inclusion criteria: • outpatients • 3-12 years • physically healthy male and female • diagnosis of autism based on the DSM-4-TR criteria • CGI-S rating of ≥ 4 • stable concomitant medications and biomedical treatments for at least 2 weeks before enrolment • no planned changes in psychosocial interventions during the trial Exclusion criteria: • DSM-4 diagnosis of schizophrenia, schizoaffective disorder or psychotic disorder not otherwise specified • prior adequate trial of N-acetylcysteine • active medical conditions, unstable seizures or significant physical illness • pregnant or sexually active female participants • taking antioxidant agents and glutathione prodrugs, except where they have been off these compounds for at least 4 weeks Setting/location: autism clinic at Stanford University, USA Sample size: 33 (15 randomised to NAC and 18 to placebo) Number of withdrawals/dropouts: 2 from NAC group (1 AE, 1 dislike taste); 6 from placebo group (3 dislike the taste, 2 withdrawal, 1 LTFU) Gender: 31 male, 2 female Mean age: NAC group 7.0 years, placebo 7.2 years IQ: details not provided Baseline ABC-I or other BoC: NAC group ABC-I 16.9, repetitive behaviour scale (Scales of Independent Behaviour) 3.9; placebo group ABC-I 14.8, Repetitive Behaviour Scale (Scales of Independent Behaviour) 3.4 Concomitant medications: "14 subjects were on at least on psychotropic medication with three being on more than one. The most commonly prescribed classes of medication were second generation antipsychotics and SSRIs". History of previous medications: details not provided

Hardan 2012 *(Continued)*

Interventions	Intervention (N-Acetylcysteine) for 12 weeks: NAC was initiated at 900 mg/day for the first 4 weeks, then 900 mg twice/day for 4 weeks, then 900 mg 3 times/day for 4 weeks (or matching placebo) Comparator (placebo) for 12 weeks: sugar pill
Outcomes	Primary outcomes: • irritability, measured using the ABC-I (Aman 1985) • self-injurious behavior, measured with the Repetitive Behaviour Scale - Scales of Independent Behaviour (Bodfish 2000) • AEs Secondary outcomes: tolerability Timing of outcome assessment: baseline, 4, 8 and 12 weeks
Notes	Study start date: March 2009 Study end date: September 2010 Source of funding: "grant from the Escher Family Fund at the Silicon Valley Community Foundation to AYH. Dr AY Hardan has received research support from the companies: Bristol-Myers Squibb Company and Forest Pharmaceuticals. Dr Frazier has received research support from, acted as a consultant to, or received travel support from Shire Development, Inc. and Bristol-Myers Squibb Company. Dr LA Herzenberg and Dr R Tirouvanziam are listed as inventors on two patents licensed by Bioadvantex, Inc, the supplier of the N-acetylcysteine and placebo for this study, covering the use of N-acetylcysteine in cystic fibrosis". Conflicts of interest: none declared Trial registry: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomisation was done by the Stanford pharmacist using www.randomization.com, which randomises each subject by using the method of randomly permuted blocks"
Allocation concealment (selection bias)	Low risk	Quote: "each participant received a supply of the compound (NAC or placebo) labeled with a reference number"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Parents and investigators involved in the study were blinded to participant status". "The study coordinator was not involved in randomisation and clinical ratings, received information about the group assignments and distribute the compound to the parents"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "investigators involved in the study were blinded to participants' status"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Participants did not complete intervention after randomisation - unclear if ITT analysis or other approach was used to account for these losses.
Selective reporting (reporting bias)	Unclear risk	Without knowing what was in the trial protocol, it is difficult to know if outcomes and measures originally undertaken were reported

Hardan 2012 *(Continued)*

Other bias	High risk	Pharmaceutical company provided both active treatment and placebo for study. 2 study authors are inventors of two patents listed with this same company.

Hardan 2019

Study characteristics	
Methods	-week trial of memantine versus placebo
Participants	Inclusion criteria: • had completed open-label trial preceding the double-blind trial, was classified as a 'responder' (The responder criterion was defined as having at least a 10-point improvement (reduction in score) in the Social Responsiveness Scale (SRS) total raw score relative to the Visit 1 total raw score in Study MEM-MD-91) during the open-label trial • children 6-12 years of age • diagnosis of Asperger's or ASD based on DSM-5 criteria • IQ score #50 on the Kaufman BriefIntelligence Test, Version 2 (or other standardized IQ test), • ABC-I score < 17 Exclusion criteria: • children with a concurrent medical condition that may confound the interpretation of study results • significant risk of suicidality • history of significant renal, hepatic, cardiovascular, respiratory, gastrointestinal, neurologic, endocrine, or other disorders Setting/location: paediatric outpatient settings at multiple study sites (92 sites in 15 countries) Sample size: 158 and 160 randomised to memantine and placebo groups respectively and 108 and 116 completed the trial Number of withdrawals/dropouts: 8 (placebo 1 protocol violation, 1 consent withdrawal; memantine reduced dose 1 did not meet eligibility criteria; memantine full dose 1 did not meet eligibility criteria, 3 protocol violation, 1 LTFU) Gender: placebo 88.8% were male, memantine 84.1% were male Mean age: placebo mean age 8.9 years, memantine mean age 9.2 years IQ: placebo mean IQ 93.3, memantine mean IQ 91.1 Baseline ABC-I or other BoC: not reported Concomitant medications: "83.8% of participants were taking concomitant medications and supplements, most commonly (≥ 10.0%) melatonin (17.0%), multivitamin (15.9%), ibuprofen (11.4%), risperidone (10.6%), and paracetamol (10.3%)" History of previous medications: not reported
Interventions	Intervention (memantine): doses were based on weight; ≥ 60 kg maximum 15 mg/day, 40-59 kg maximum 9 mg/day, 20-39 kg maximum 6 mg/day, < 20 kg maximum 3 mg/day. These doses were reduced to 6 mg/day, 3 mg/day, 3 mg/day and 3 mg every other day, for each respective group. Comparator (placebo): matching placebo for 12 weeks
Outcomes	Primary outcomes:

Hardan 2019 *(Continued)*

	• irritability (ABC-I) (Aman 1985) • AEs Secondary outcomes: tolerability
Notes	Study start date: May 2009 Study end date: August 2012 Funding: "Funding for these studies was provided by Forest Research Institute (Jersey City, NJ), the sponsor at the time the studies were conducted." Conflicts of interest: none declared Trial registry: NCT00872898

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Premier, Inc. provided Interactive Web Response System (IWRS) services for randomization."
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind - no further details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind - no further details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout; an ITT analysis was used that included all participants with at least 1 post-baseline outcome assessment.
Selective reporting (reporting bias)	High risk	ABC-I (change from baseline) was mentioned as an outcome in the paper, but it was not reported, only "At week 12, no clinically meaningful changes from baseline were observed between treatment groups on the additional efficacy variables, CGI-I and CGI-S, ABC-C, or SRS [Social Responsiveness Scale] subscales and SRS total raw score."
Other bias	High risk	Funding for these studies was provided by Forest Research Institute (Jersey City, NJ), the sponsor at the time the studies were conducted. Writing support was funded by Allergan plc (formerly Forest Research Institute; Madison, NJ). Two of the listed study authors were employed by the sponsor.

Harfterkamp 2014

Study characteristics

Methods	Parallel trial of atomoxetine versus placebo
Participants	Inclusion criteria:

Harfterkamp 2014 *(Continued)*

	• 6-17 years of age • IQ of at least 60 • dual diagnosis of ASD (based on DSM-4) and ADHD Exclusion criteria: • weight of < 20 kg • presence of psychosis, bipolar disorder, or substance abuse • a serious medical illness • history of seizures • ongoing use of psychoactive medications other than the study drug • intended start of a structured psychotherapy or inpatient treatment Location/setting: 9 Dutch child and adolescent psychiatry centres, 6 university centres, (Amsterdam, Groningen, Leiden, Maastricht, Nijmegen, and Utrecht), and 3 non-university centres (The Hague, Hoorn, an Oosterhout). Sample size: 48 in atomoxetine group, 49 in placebo group Number of withdrawals/dropouts: placebo group: protocol violation (2), physician decision (1). Atomoxetine group: AE (1), protocol violation (2), lack of efficacy (1), parent/ caregiver decision (1) Gender: atomoxetine 42/48 male, placebo 41/49 Mean age: atomoxetine 9.9 years, placebo 10.0 years IQ: atomoxetine 91, placebo 94.6 Baseline ABC-I or other BoC: atomoxetine ABC-I 17.3, placebo ABC-I 16.2 Concomitant medications: participants were not permitted to be using psychoactive medications prior to study on an ongoing basis History of previous medications: atomoxetine 18/48 and placebo 18/49 had not received any prior psychopharmacological treatment
Interventions	Intervention (atomoxetine) for 8 weeks: maximum of 1.2 mg/kg/day daily dose. First week 0.5 mg/kg/day; 2nd week 0.8 mg/kg/day; 1.2 mg/kg/day for 6 weeks Comparator (placebo) for 8 weeks: maximum of 1.2 mg/kg/day daily dose. First week 0.5 mg/kg/day; 2nd week 0.8 mg/kg/day; 1.2 mg/kg/day for 6 weeks
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: tolerability Timing of outcome assessments: baseline and 8 weeks (endpoint)
Notes	Study start date: October 2006 Study end date: March 2008 Source of funding: funded by Eli Lilly and company. "Myriam Harfterkamp has accepted invitations for congress travels from Eli Lilly and Eurocept. Ruud B. Minderaa was advisor for Eli Lilly. Jan K. Buitelaar has been a consultant to/member of advisory board of, and/or speaker for Bristol-Myer Squibb, Eli Lilly, Janssen Cilag BV, Medice, Organon/Shering Plough, Servier, Shire, and Union Chimique Belge (UCB). Gigi van de LooNeus has received honoraria for a presentation from Eli Lilly and wasmember oftheadvisory boardforUCBPharma B.V. andShire. Rutger-Jan van der Gaag has no financial disclosures. Pieter J. Hoekstra has received honoraria for presentations or advice from Desitin, Eli Lilly, and Shire".

Harfterkamp 2014 *(Continued)*

Conflicts of interest: none declared

Trial registry: NCT00380692

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details were not provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	An ITT analysis was used and all participants who received at least 1 dose of the drugs were included in the analysis
Selective reporting (reporting bias)	Low risk	Results reported on clinicaltrials.gov (NCT00380692)
Other bias	High risk	Sponsor: Eli Lilly and Company Information provided by: Eli Lilly and Company

Hellings 2005

Study characteristics

Methods	Parallel trial of valproate versus placebo
Participants	Inclusion criteria: • aged 6-20 years (mean age 9.46 +/- 2.46) • comorbid DSM-4 Axis I diagnoses, except Tourette's Disorder • significant aggression to self, others, or property at least 3 times/week • presence of a PDD Exclusion criteria: • previous adequate valproate trial for any indication or clinical seizures within the past year • history of degenerative neurological changes or metabolic disorders • Tourette's Disorder • history of thrombocytopenia, hepatitis, pancreatitis, pregnancy, or polycystic ovarian syndrome; • concomitant psychotropic or antiseizure medications Location/setting: recruitment was through University of Kansas MR/Autism outpatient, USA Sample size: 30 in total (16 to valproate, 14 to placebo)

Hellings 2005 *(Continued)*

	Number of withdrawals/dropouts: 13/16 valproate participants completed the trial, 12/14 in placebo group completed the trial. 1 severely hyperactive and 1 spreading skin rash dropped out on advice from principal investigator and unblinded child psychiatrist, remaining 3 dropped out due to "manifested dangerous aggression". Gender: 20 boys, 10 girls Mean age: 11.2 years Mean IQ: 54 Baseline ABC-I or other BoC: ABC-I valproate 23.33, placebo 21.93; aggression valproate 10.05, placebo 10.50. Concomitant medications: psychotropic or anticonvulsant medications were not allowed to be taken concurrently. History of previous medications: details not provided
Interventions	Intervention (valproate acid 20 mg/kg/day) for 8 weeks: after an initial 1-week placebo lead-in phase, valproate liquid (250 mg/5 mL) was gradually introduced with an additional 250 mg added every 3rd day, replacing the equivalent amount of placebo liquid, to achieve a dosage of 20 mg/kg/day. Comparator (placebo) for 8 weeks: placebo administered in a liquid form resembling valproate for 8 weeks
Outcomes	Primary outcomes: • ABC-Irritability (Aman 1985) • aggression, measured using the Parent Overt Aggression Scale (Yudofsky 2003) • AEs Secondary outcomes: tolerability Timing of outcome assessments: weekly
Notes	Study start date: 1998 Study end date: 2003 Source of funding: "funding sources for this work were the National Institute of Mental Health (1K08MH01561-01), National Institute of Child Health and Human Development (HD26927, HD02528), and Abbott Pharmaceuticals, Abbott Park, Illinois (Unrestricted $5,000 grant)." Conflicts of interest: none declared Trial registry: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "an 8-week trial of two parallel groups of subjects, randomised to liquid VPA or placebo by the study pharmacist."
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The investigators, parents, and teachers were blinded regarding medication or PBO [placebo] status"

Hellings 2005 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The investigators were blinded regarding medication or PBO [placebo] status"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	An ITT analysis was used however 1 participant is not accounted for LTFU: 1 in valproate group and 1 in placebo group discontinued due to AEs, and 1 in valproate group withdrew due to non-efficacy
Selective reporting (reporting bias)	Low risk	The ABC-I was measured and reported at baseline and endpoint.
Other bias	Unclear risk	Potential bias with pharmaceutical company funding but "unrestricted" implies no involvement beyond financial. No significant differences in age, gender, current placement home, day placement school, years in current placement, parental marriage status, and aggression as the worst presenting symptom.

Hendouei 2019

Study characteristics	
Methods	10-week trial of resveratrol + risperidone versus placebo + risperidone
Participants	Inclusion criteria: • DSM-5 clinical diagnosis of ASD • children between the ages of 3 and 12 years • presence of behavioural problems such as aggression, overactivity or repetitive behaviours (indication of treatment with risperidone) • Both "male and female outpatients referred to our clinic from different parts of Iran with probable autistic signs and symptoms". Exclusion criteria: • presence of any active medical problem • other psychiatric diagnosis except for mild to moderate intellectual disability • receiving any antipsychotic medications during past month prior to the trial • severe hepatic disease • history of allergy to risperidone and intolerance of it • history of seizure requiring change of antiepileptic dose during the last month • seizure during the last 6 months Location/setting: autism clinic in children's outpatient clinic of Roozbeh Hospital (Tehran University of Medical Sciences, Tehran, Iran) Sample size: resveratrol (35); placebo (35) Number of withdrawals/dropouts: resveratrol (4, 2 ineligible to continue, 2 consent withdrawn); placebo (4, 4 consent withdrawn) Gender: 50 male, 12 female Mean age: resveratrol 7.8 (2.1); placebo: 8.1 (1.9) IQ: details not provided Baseline ABC-I or other BoC: ABC-I of > 22 at baseline across both groups

Hendouei 2019 *(Continued)*

	Concomitant medications: apart from resveratrol and risperidone no other concomitant medications were allowed in either group. History of previous medications: antipsychotics could not be taken in month prior to the study and any anticonvulsant use could not have changed in month prior to study
Interventions	Intervention (resveratrol + risperidone): both groups were treated with risperidone twice daily, starting at a dose of 0.5 mg, with a dose increase of 0.5 mg per week (for the first 3 weeks). Resveratrol dosage was 250 mg twice per day from the beginning of the study. Comparator (placebo + risperidone): both groups were treated with risperidone twice daily, starting at a dose of 0.5 mg with a dose increase of 0.5 mg/week (for the first 3 weeks) plus placebo for 10 weeks.
Outcomes	Primary outcomes: • irritability, measured using the ABC-I (Aman 1985) • AEs Secondary outcomes: tolerability Timing of outcome assessments: baseline, week 5 and week 10 (endpoint)
Notes	Study start date: January 2018 Study end date: April 2019 Funding: "This study was supported by a grant from Tehran University of Medical Sciences to Prof. Shahin Akhondzadeh (Grant No: 36420)" Conflicts of interest: "None of the authors in this study had conflict of interest of any kind with the parties that might be involved." Trial registry: IRCT20090117001556N104

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using the Microsoft Office Excel software, each patient was assigned to a specific random code."
Allocation concealment (selection bias)	Low risk	The assignments were retained in confidential and sealed opaque envelops and were unveiled at the study endpoint for statistical analysis.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "all individuals involved in this study, such as patients and researchers, were blinded to the assignments."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Separate individuals were responsible for randomisations, drug administration, rating, data entry and statistical analysis. Furthermore, all individuals involved in this study, such as patients and researchers, were blinded to the assignments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition, and all participants were accounted for
Selective reporting (reporting bias)	High risk	Doesn't report CARS (primary outcome on trial reg) and measurement time points different to trial reg

Hendouei 2019 *(Continued)*

Other bias	High risk	• The contact author is also on the ethics committee at the university funding the study. • The contact author is a peer-reviewer for one of the journals in which some of their studies are published.

Herscu 2020

Study characteristics	
Methods	14-week parallel trial of fluoxetine versus placebo
Participants	Inclusion criteria: • 5-17 years of age • meets DSM-4 criteria for ASD • CYBOCS-PDD score of at least 10 at screening Exclusion criteria: "diagnosis of Asperger Syndrome or Pervasive Developmental Disorder Not Otherwise Specified, Rett Syndrome, Childhood Disintegrative Disorder, Patients planning to commence cognitive behaviour therapy during the period of the study or those who have begun cognitive behaviour therapy within 8 weeks prior to enrolment, or Patients who are currently taking fluoxetine or who have previously taken it". Location/setting: an autism network consisting of 18 centres Sample size: 158 (78 fluoxetine, 80 placebo) Reason for dropouts/withdrawals: fluoxetine 22 withdrawn (7 AEs, 6 withdrew consent, 1 sponsor decision, 2 lack of efficacy, 6 LTFU); placebo 15 withdrawn (5 AEs, 7 withdrew consent, 2 lack of efficacy, 1 LTFU). Mean age: 9.0 years Mean IQ: not reported Gender: 13% and 16% of the fluoxetine and placebo groups respectively were female Baseline ABC-Irritability or other BoC: not reported Concomitant medications: participants were not allowed to be taking psychotropic medications. Previous medications: not reported
Interventions	Intervention (fluoxetine): all randomised participants initiated treatment with 2 mg/day fluoxetine, which could be titrated flexibly every 2 weeks to 4 mg, 6 mg, 9 mg, 13 mg, and a maximum of 18 mg/day. Comparator (placebo): all randomised participants initiated treatment with 2 mg/day placebo, which could be titrated flexibly every 2 weeks to 4 mg, 6 mg, 9 mg, 13 mg, and a maximum of 18 mg/day
Outcomes	Primary outcomes: AEs Secondary outcomes: tolerability Timing of outcome assessments: weeks 2, 4, 8, 10, 12 and 14 (endpoint)
Notes	Study start date: September 2007 Study end date: January 2009

Herscu 2020 *(Continued)*

Funding: "This study was funded by Neuropharm Plc. in collaboration with the Autism Speaks Autism Clinical Trials Network."

Conflicts of interest: various consulting with and funding by pharmaceutical companies

Trial registry: NCT00515320

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment group was assigned centrally through the use of an automated clinical trials database.
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinded - no further details provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Scoring was by a site clinician who was blind both to drug/placebo assignment and to AEs (which could have biased the rater).
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout (23%); ITT analysis based on percent change from baseline to endpoint (Week 14 or the **last assessment for those withdrawing**)
Selective reporting (reporting bias)	Low risk	Same primary outcome as clinical trial reg
Other bias	High risk	Funded by Neuropharm Plc. One person dropped out due to "sponsor decision" to withdraw from treatment group

Hollander 2005

Study characteristics

Methods	Cross-over trial of fluoxetine versus placebo
Participants	Inclusion criteria: • aged 5-17 years • meet the criteria for ASD (autism, Asperger's, or PDD-NOS) according to the DSM-4-TR Exclusion criteria: • responded well to previous interventions or had only mild global severity • other DSM-4 psychotic disorders • history of seizures • any clinically significant medical illness Location/setting: details not provided

Hollander 2005 *(Continued)*

	Sample size: 44 children or adolescents Number of withdrawals/dropouts: "three subjects were dropped due to noncompliance and one was dropped because of lack of efficacy, all prior to week 4". Gender: 30 boys, 9 girls Mean age: 8.18 +/- 3.04 IQ: 63.7 Baseline ABC-I or other BoC: not reported Concomitant medications: none were allowed History of previous medications: details not provided
Interventions	Intervention (fluoxetine) for 8 weeks: fluoxetine was started at 2.5 mg/day for a week, then titrated based on weight to a maximum dose of 0.8 mg/kg/day; 0.3 mg/kg for week 2, 0.5 mg/kg/day for week 3, and 0.8 mg/kg/day for weeks 4–8. Dose prescribed on day 28 (end of week 4) was maintained for the remainder of the 8-week phase unless indicated due to side effects, in which case the stable dose was lowered. This was followed by a 4-week washout period before cross-over to placebo. Comparator (placebo) for 8 weeks: the dosing schedule began at 2.5 mg/day of placebo once a day for 1 week. The following 7 weeks followed a flexible titration schedule up to a maximum of 0.8 mg/kg/day (0.3 mg/kg for week 2, 0.5 mg/kg/day for week 3, and 0.8 mg/kg/day weeks 4-8)
Outcomes	Primary outcomes: AEs Secondary outcomes: tolerability Timing of outcome assessments: baseline and every 4 weeks until week 20
Notes	Study start date: not reported Study end date: not reported Funding: "this work was supported by Orphan Products Division of the Food and Drug Administration Grant # FD-R-00152001-03, NIH STAART Center of Excellence Grant #1U54 MM066673-01A1, NARSAD Young Investigator Award for Dr Novotny, and the Seaver Foundation. Lilly Research Laboratories provided liquid fluoxetine and matching placebo for the study" Conflicts of interest: none declared Trial registry: NCT00004486

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided
Blinding of outcome assessment (detection bias)	Low risk	Quote: "subjects were monitored and assessed weekly by the treating physician, who was blind to treatment condition, during the first 4 weeks of each

Hollander 2005 *(Continued)*

All outcomes		fluoxetine/placebo phase of the study". "In addition, all CY-BOCS and CGI-AD outcome assessments were completed by an independent evaluator (IE) who did not have access to side effect data and who was blind to treatment condition, at baseline and every 4 weeks throughout the study, until week 20 or termination."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants were accounted for and an ITT analysis was used on the 39 participants who completed the trial. LTFU: 1 participant not included in the analysis because of "lost pharmacy records, which made it impossible to be certain of the subject's randomization condition" and three participants were dropped due to noncompliance and 1 was dropped because of lack of efficacy, all prior to week 4.
Selective reporting (reporting bias)	Unclear risk	The CY-BOCS, CGI, the Vineland Adaptive Behavior Scale, Wechsler Preschool and Primary Intelligence Scale-Revised (WPPSIR), Wechsler Intelligence Scale for Children (WISC-III) (ages 7–16) or the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) (age 17). The CY-BOCS was reported in full at weeks 0, 4 and 8, however the CGI scores were only reported at endpoint.
Other bias	Unclear risk	"This work was supported by Orphan Products Division of the Food and Drug Administration Grant # FD-R-001520- 01-03, NIH STAART Center of Excellence Grant #1U54 MM066673-01A1, NARSAD Young Investigator Award for Dr Novotny, and the Seaver Foundation. Lilly Research Laboratories provided liquid fluoxetine and matching placebo for the study. We acknowledge Charles Cartwright MD, Katherine Delaney PhD, and Sallie Jo Hadley MD for their clinical contributions to this study."

Hollander 2006a

Study characteristics	
Methods	8-week parallel study of divalproex sodium versus placebo
Participants	Inclusion criteria: • meet DSM-4 and ADI-R criteria for an ASD • score as moderately ill on CGI-Autistic Disorder (Guy 1976) • not selected on the basis of levels of repetitive or aggressive behaviours on study measures Exclusion criteria: "medical illnesses (with the exception of stable seizure disorder), past history of psychotic disorders, and recent or current use of divalproex, terfenadine (Seldane), or astemizole (Hismanal). Subjects using any psychoactive medication were allowed to participate in the trial only if the dose remained stable for at least 3 months prior to and during the trial". Location/setting: "patients were recruited and screened for the presence of ASDs at the Seaver and New York Autism Center of Excellence" (USA) Number and reason for discontinuing: "one subject dropped out in week 5 due to lack of efficacy (on medication) and 12 subjects completed the trial". Mean IQ: IQ scores for the majority of participants were in the mild to moderate intellectual disability range, with a mean IQ score of 60 (range = 30–104) Gender: details not provided Mean age: 9.5 years (12 were children or adolescents (< 18 years), and 1 adult was aged 40) Baseline ABC-I or other BoC: not an outcome

Hollander 2006a *(Continued)*

	Concomitant medications: "only one participant was on a stable dose of risperidone prior to the study and continued throughout the 8 wk of the study. No other participant was on concomitant medications." Previous medications: not reported
Interventions	Intervention (divalproex sodium) for 8 weeks: started with 125 mg/day and was increased by 125 mg every 4 days during the first 2 weeks of treatment. The recommended divalproex serum level was 50–100 mg/mL by week 2, and the maximum dose was 30 mg/kg/day. Comparator (placebo) for 8 weeks: started with 125 mg/day and was increased by 125 mg every 4 days during the first 2 weeks of treatment. The recommended serum level was 50–100 mg/mL by week 2, and the maximum dose was 30 mg/kg/day.
Outcomes	Primary outcomes: AEs Secondary outcomes: tolerability Timing of outcome assessments: baseline, weeks 1, 2, 3, 4, 6, and 8 (endpoint)
Notes	Study start date: details not provided Study end date: details not provided Funding: "Funding was received from Abbott Laboratories as an investigator-initiated study, the Seaver Foundation, and STAART Autism Center of Excellence Grant no. 5 U54 MH06673-02". Conflicts of interest "Dr Hollander has served on an advisory board of Abbott Laboratories." Trial registry: NCT00211757

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The randomisation schedule had a goal of establishing a 2:1 ratio of patients in the active vs placebo groups
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported to be double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	An unblinded person reported serum divalproex levels of < 50 mg/mL or > 100 mg/mL to the investigators so that the dose of study drug could be adjusted appropriately. In order to preserve the study blind, sham divalproex levels were reported for selected placebo participants.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if > 13 were randomised and thus selective reporting. Quote: "Twenty-five subjects were screened. Thirteen subjects were randomized, had at least one post-treatment outcome measure, and were included in the intent-to-treat (ITT) group"
Selective reporting (reporting bias)	High risk	The CGI and ABC were reported as outcomes on trial registry however not reported in the paper. The primary outcome (CYBOCS) was reported graphically and using t-scores.

Hollander 2006a *(Continued)*

Other bias	Low risk	No other sources identified

Hollander 2006b

Study characteristics	
Methods	Parallel trial of olanzapine versus placebo
Participants	Inclusion criteria: • age 6-17 years • meet DSM-5 and ADI-R criteria with a rating of at least moderate (≥ 4) on the CGI Scale • free of psychotropic medications for at least 4 weeks prior to starting the study drug except stable dose (at least 3 months) of anticonvulsants for seizures or clonidine or chloral hydrate given only at bedtime for sleep • "children in an established programme for at least 3 months prior to starting the trial and kept constant throughout the medication trial could be included in the study". Exclusion criteria: • responded well to prior pharmacological treatment • psychotic disorders • history of any clinically significant medical illness (with the exception of a stable seizure disorder) Location/setting: details not provided Sample size: 11 in total, 6 olanzapine group, 5 placebo Number of withdrawals/dropouts: "one child dropped out right after randomization due to parental disagreement regarding study participation. Two others dropped out during the study because their parents were noncompliant with their follow up appointments." Gender: all were male in the olanzapine group, placebo 3/5 were male Mean age: olanzapine 9.25 years, placebo 8.9 years IQ: 2 in olanzapine group had severe intellectual disability, 5 participants had mild intellectual disability (2 and 3 in placebo), 4 had normal cognitive function (2 in each group) Baseline ABC-I or other BoC: not applicable Concomitant medications: 0% History of previous medications: not reported
Interventions	Intervention (olanzapine) for 8 weeks: "in children weighing less than 40kg, the dosage started with 2.5mg of olanzapine every other day; after 3 days, the dose increased to 2.5mg every day. In children weighing more than 40kg, the dose started at 2.5mg every day and was increased to 5mg/day after 3 days/ Thereafter, the dosage for both weight groups was increased in 5-mg increments weekly to a maximum of 20mgday" Comparator (placebo) for 8 weeks: equivalent placebo
Outcomes	Primary outcomes: AEs Secondary outcomes: none reported Timing of outcome assessments: baseline, weekly for 1st 4 weeks then biweekly for last 4 weeks

Hollander 2006b *(Continued)*

Notes	Study start date: not reported Study end date: not reported Source of funding: "this study was supported by an investigator-initiated research grant from Lilly Research Laboratories. Olanzapine and matching placebo were supplied by Lilly Research Laboratories" Conflicts of interest: "Dr Hollander serves on the advisory board of Abbott, Wyeth, Solvay, Somaxon Pharmaceuticals and receives research grants from Lilly, Abbott, Pfizer, UCB-Pharma, and OrthoMcNeil Pharmaceuticals. All other authors have no financial relationships to disclose". Trial registry: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided except for, quote: "Patients were evaluated weekly for the first 4 weeks and biweekly for the next 4 weeks in a double-blind fashion by the treating psychiatrist."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Paper reports that a secondary outcome is the Overt Aggression Scale irritability and aggression subscales however scores are not reported (only P values and z scores)
Incomplete outcome data (attrition bias) All outcomes	High risk	Available data from this relatively small sample of 11 participants (6 treatment and 5 control), we used mixed regression analysis to assess differences in the improvement ratings between the treatment and control groups. This analysis did not eliminate participants, but instead estimated effects using the data available for each participant. The reasons for missing data were children who discontinued the study before 8 weeks and missed treatment visits.
Selective reporting (reporting bias)	High risk	Quote: "The Overt Aggression Scale as listed as one of the outcome measures", however, "we did not find any evidence for significant change on the CYBOCS, the OAS-M [Overt Aggression Scale-Modified] irritability measure, or the OAS-M [Overt Aggression Scale - Modified] aggression measure".
Other bias	High risk	Both active treatment and placebo supplied by the same pharmaceutical company that financially supported the study

Hollander 2010

Study characteristics

Methods	Parallel trial of divalproex sodium versus placebo
Participants	Inclusion criteria: aged • 5-17 years • outpatients

Hollander 2010 *(Continued)*

- met the DSM-4 criteria for ASD
- CGI-S score of at least 4
- ABC-I score of at least 18
- Overt Aggression Scale-Modified (OAS-M) score of at least 13
- seizure-free for at least 6 months and on a stable dose of anticonvulsants other than divalproex sodium or related formulations
- non-medicated children with a history of seizures and 6-month seizure-free, or with an abnormal EEG but no clinical seizures

Exclusion criteria:

- pregnant or nursing mothers
- sexually active women of childbearing potential who are not using adequate birth control measures
- overall adaptive behavior scores < 2 years on the Vineland Adaptive Behavior Rating Scale
- active or unstable epilepsy
- any of the following past or present mental disorders: schizophrenia, schizoaffective disorder or organic mental disorders
- serious suicidal risk
- clinically significant or unstable medical illness that would contraindicate participation in the study, including hematopoietic or cardiovascular disease, pancreatitis, liver toxicity, and polycystic ovary syndrome
- history of encephalitis, phenylketonuria, tuberous sclerosis, fragile X syndrome, anoxia during birth, pica, neurofibromatosis, hypomelanosis of Ito, hypothyroidism, Duchenne muscular dystrophy, and maternal rubella
- history of the following:
  - gastrointestinal, liver, or kidney, or other known conditions which will presently interfere presently with the absorption, distribution, metabolism, or excretion of drugs
  - cerebrovascular disease or brain trauma
  - clinically significant unstable endocrine disorder, such as hypo- or hyperthyroidism
  - recent history or presence of any form of malignancy
- treatment within the previous 30 days with any drug known to a well-defined potential for toxicity to a major organ
- clinically significant abnormalities in laboratory tests or physical exam
- likely to require electroconvulsive therapy or any other psychotropic medication during the study, unless otherwise permitted
- unable to tolerate taper from psychoactive medication if necessary
- history of hypersensitivity or severe side effects associated with the use of divalproex sodium, or an ineffective prior therapeutic trial of divalproex sodium (serum levels within range of 50-100 ug/mL for 6 weeks)
- received any of the following interventions within the prescribed period before starting treatment:
  - investigational drugs within the previous 30 days
  - depot neuroleptic medication
  - psychotropic drugs not permitted for concurrent use in the study within the previous 7 days
  - fluoxetine within the previous 5 weeks
- any new alternative non-medication treatments, such as diet, vitamins, and psychosocial therapy, begun within the previous 3 months
- any organic or systemic disease or patients who require a therapeutic intervention, not otherwise specified, which would confound the evaluation of the safety of the study medication
- currently reside in a remote geographical area who do not have regular access to transportation to the clinical facility

Location/setting: not mentioned

Sample size: 16 (intervention group), 11 (placebo group)

Number of withdrawals/dropouts: placebo group 1 withdrawal; intervention group 1 withdrawal for lack of efficacy.

Hollander 2010 *(Continued)*

	Gender: 23 male, 4 female Mean age: 9.46 years IQ: placebo 76.1, intervention 52.92. Overall mean IQ 63.3 Baseline ABC-I or other BoC: ABC-I intervention group 20.3, placebo 22 Concomitant medications: 0% History of previous medications: details not provided
Interventions	Intervention (divalproex sodium) for 12 weeks: started at 125 mg/day for children weighing up to 40 kg and titrated to a maximum of 250 mg twice/day over 1 week. For children weighing ≥ 40 kg, the starting dose was 250 mg/day and titrated to a maximum of 500 mg twice/day over 1 week. Comparator (placebo) for 12 weeks: participants received a placebo comparative to the study drug divalproex sodium
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: tolerability Timing of outcome assessments: AEs recorded at baseline then weekly for 4 weeks then biweekly for next 4 weeks
Notes	Study start date: not reported Study end date: not reported Source of funding: funded by NINDS R21 NS4 3979-01, E Hollander, PI. Grant no. M01-RR00071 from the National Centre for Research Resources (NCRR) Conflicts of interest: "Eric Hollander received consultation fees from Abbott, Neuropharm, Nastech, BMS, and Forest; received research grants from Abbott, and UBS Pharma; and has intellectual property related to oxytocin and memantine and ASD. Evdokia Anagnostou received a consultation fee by Inte-Gragen. The rest of the authors have nothing to disclose". Trial registry: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The children were randomised in a 1:1 fashion
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided except, quote: "all clinicians involved in efficacy or safety assessments were blinded to the randomisation condition", and "feedback on subjects randomised to placebo was based on a blocked schedule, so that all study clinicians remained blinded to the condition of randomisation."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not provided

Hollander 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No direct mention of ITT methods to account for 3 participants who didn't complete intervention, however implied in the total number analysed
Selective reporting (reporting bias)	Low risk	Final ABC-I scores were not provided however were on the clinicaltrials.gov website
Other bias	High risk	Quote: "adverse event monitoring took place every week for the first four weeks and every 2 weeks thereafter. Questions were focused on known side effects of divalproex sodium, followed by open-ended questions."

Hollander 2012

Study characteristics	
Methods	Parallel trial of fluoxetine versus placebo
Participants	Inclusion criteria: • people between the ages of 18 and 60 years • met the DSM-4 criteria for an ASD • CGI score of ≥ 4 • medication-free status Exclusion criteria: • history of hypersensitivity or side effects while receiving fluoxetine treatment • abnormal electrocardiogram, laboratory test, or physical examination findings • schizophrenia, schizoaffective disorder, bipolar disorder, active seizure disorder, or significant hematopoietic or cardiovascular disease Location/setting: details not provided Sample size: 37 (fluoxetine 22, placebo 15) Number of withdrawals/dropouts: 2 dropouts did not comply with study procedures, 1 discontinued because of relocation, and 1 discontinued because of poor tolerability Gender: 26 male, 11 female Mean age: 34.31 years IQ: 103.25 Baseline ABC-I or other BoC: not applicable Concomitant medications: 0% History of previous medications: not reported
Interventions	Intervention (fluoxetine) for 12 weeks: dosage followed a fixed schedule, starting at 10 mg/day and increasing, as tolerated, up to 80 mg/day; mean final dose 9.9 mg/day Comparator (placebo) for 12 weeks: equivalent placebo
Outcomes	Primary outcomes: • AEs • irritability, measured using the ABC-I subscale (although not reported) (Aman 1985)

Hollander 2012 *(Continued)*

	Secondary outcomes: none reported Timing of outcome assessments: AEs were measured biweekly
Notes	Study start date: not reported Study end date: not reported Source of funding: "funded by Food and Drug Administration orphan product g rant FD-R-0 0 2 0 2 6 -0 1 and supported by Studies to Advance Autism Research and Treatment (STAART) Center of Excellence grant 1U5 4 MH- 0 6 6 6 7 3 from NIMH, by the Seaver Foundation, and by the Mount Sinai General Clinical Research Center. Mount Sinai School of Medicine licensed an orphan designation for fluoxetine in autism to Neuropharm, Ltd". Conflicts of interest: "Dr Hollander has been a consultant to Abbott, Forest, and Neuropharm in the past. Dr Anagnostou has consulted without fees to Neuropharm, Novartis, and Proximagen. The other authors report no financial relationships with commercial interests". Trial registry - NCT00004486

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up by group not reported for all outcomes
Selective reporting (reporting bias)	High risk	ABC irritability data not reported
Other bias	High risk	Higher proportion of men (80%) in placebo group compared to fluoxetine group (64%); higher proportion who were white (86%) in the fluoxetine group compared to placebo group (53%); higher proportion had Asperger's (rather than ASD) (73%) in the fluoxetine group compared to placebo group (53%). No other differences in age, IQ, and baseline scores

Hollander 2020a

Study characteristics

Methods	Cross-over trial of *Trichuris suis* ova versus placebo

Hollander 2020a *(Continued)*

Participants	Inclusion criteria: "age 18-35, inclusive, at the time of consent, Outpatient, meet criteria for the diagnosis of Autism Spectrum Disorder according to the DSM-4-TR, and supported by the ADOS or ADI-R, have an IQ of 70 or greater, participants who are taking other medications prior to enrollment had to be on a stable dose of concomitant medication, including psychotropic, anticonvulsant, or sleep aid for at least 3 months prior to baseline ratings. Other inclusion criteria included being judged reliable for medication compliance and agree to keep appointments for study contacts and tests as outlined in the protocol (both subjects and guardians) and have a personal or family history of allergies". Exclusion criteria • History of bipolar or other psychiatric disorders (such as schizophrenia or schizoaffective disorders) • Previous diagnosis of Rett's Disorder or Childhood Disintegrative Disorder • Uncontrolled seizure disorders (defined as seizures within the past 6 months) • Pregnant or breastfeeding at screening or at any time during the study • Other chronic medical conditions • Treatment in the last 12 weeks with cyclosporine, methotrexate, infliximab or immunomodulatory agents, treatment in the last 2 weeks with antibiotics, antifungal or antiparasitic medications • history of previous treatment with *Trichuris suis* Ova (TSO) Location/setting: autism programme at Montefiore Medical Center, Albert Einstein College of Medicine, USA Sample size: 10 total (cross-over) Number of withdrawals/ dropouts: none reported Gender: 9 male, 1 female Mean age: 21.15 years IQ: 87.89 Baseline ABC-I or other BoC: parent-rated ABC-I 12.5 Concomitant medications: details not provided History of previous medications: details not provided
Interventions	Intervention (*Trichuris suis* ova) for 12 weeks: *Trichuris suis* ova were administered in vials prepared by Coronado Biosciences. Vials were diluted with a commercial drink and given to participants orally to ingest. Participants received a dose of 2500 ova every 2 weeks for 12 weeks. Comparator (placebo) for 12 weeks: placebo was administered on site every 2 weeks.
Outcomes	Primary outcomes: • irritability, measured using the ABC-Irritability subscale (Aman 1985) • self-injurious behaviour, measured using the Repetitive Behaviour Scale Revised (RBS-R) - Self-injurious subscale (Bodfish 2000) • AEs Secondary outcomes: none reported Timing of outcome assessment: baseline and every 2 weeks for 12 weeks
Notes	Study start date: November 2012 Study end date: June 2014 Source of funding: funding provided by the Simons Foundation. Drug/placebo and consulting provided by Coronado Biosciences: "Coronado Biosciences also provided both TSO and the matching placebo".

Hollander 2020a *(Continued)*

Conflicts of interest: none declared

Trial registry: NCT01040221

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Other than "double-blinded", details not provided
Incomplete outcome data (attrition bias) All outcomes	High risk	No dropouts were reported although only 9 were analysed for CGI scale
Selective reporting (reporting bias)	High risk	The ABC was apparently measured at baseline, 2, 4, 6, 8, 10, 12, 14, 16 weeks. Only pooled baseline and mean change from baseline to endpoint were reported
Other bias	High risk	No study results posted on ClinicalTrials.gov for this study even though it was completed July 2014. Active treatment prepared by pharmaceutical company

Hollander 2020b

Study characteristics

Methods	24-week parallel trial of balovaptan versus placebo
Participants	Inclusion criteria: • boys and girls aged 5-17 years who are fluent in English, meet the DSM-5 criteria for ASD, CGI score of at least 4 at screening, an IQ of at least 70 • "Language, hearing, and vision compatible with the study measurements as judged by the Investigator" • a parent or guardian who can accompany the participant to study visits and who is willing to provide consent for the participant • female participants cannot be breast-feeding during the trial and must have a negative pregnancy test, and must use a contraceptive method from screening until 28 days following the trial Exclusion criteria • Start or change in psychosocial intervention (including investigational) within 4 weeks prior to screening • Unstable or uncontrolled psychiatric and/or neurological disorder including uncontrolled epilepsy (defined as a seizure within the past 6 months)

Hollander 2020b *(Continued)*

- unstable cardiovascular disease, history of alcohol or substance abuse/dependence, or abnormality on ECG at screening
- Concomitant medical conditions that affect the pulmonary, gastrointestinal, hepatic, renal, metabolic, or immune systems
- Medications such as anticonvulsants were requred to be at a stable dose for at least 4 weeks prior to screening for the trial.

Location/setting: 44 sites across the USA

Sample size: 134

Number of withdrawals/dropouts: placebo, 26 dropped out (AEs (3); lack of efficacy (1); LTFU (3); physician decision (1); withdrawal by participant (18)). Balovaptan, unclear, groups are not clearly defined.

Gender*:* 83% and 84% were male in the intervention and placebo groups respectively.

Mean age: approximately 12 years in both groups

IQ: not reported

Baseline ABC-I scores or other BoC: not reported

Concomitant medications: not reported

History of previous medications*:* not reported

Interventions	Intervention (balovaptan) for 24 weeks: participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 mg/day of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks (up to 52 additional weeks for those enroled in the open-label extension). Comparator: participants received a matching placebo orally. Approximate treatment duration was up to 24 weeks.
Outcomes	Primary outcomes: none reported Secondary outcomes: QoL (change from baseline) measured using the PedsQL (Varni 2001). Higher scores suggest a higher QoL Timing of outcome assessments: baseline, weeks 12 and 24 (endpoint)
Notes	Study start date: 2016 Study end date: 2020 Source of funding: F. Hoffmann-La Roche Ltd (pharmaceutical company) Conflicts of interest: various grants and other support from pharmaceutical companies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided apart from "randomised study"
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias)	Unclear risk	Details not provided apart from "Masking: Double (Participant, Investigator)"

Hollander 2020b *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not provided apart from "Masking: Double (Participant, Investigator)"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Difficult to understand participant flow
Selective reporting (reporting bias)	High risk	The paper/presentation mentions the ABC-Irritability however, it wasn't reported and was not listed on the trial registry. Also, the study was "Terminated (The 24-week analysis indicated no clinical or statistical benefit for the primary endpoint for the overall study population. No new safety concerns identified.)"
Other bias	High risk	List of disclosures included payment by pharma company, for many of the study authors

Ichikawa 2017

Study characteristics	
Methods	8-week parallel trial of aripiprazole versus placebo
Participants	Inclusion criteria: • children and adolescents aged 6–17 years • diagnosis of autistic disorder (not ASD) defined by the DSM-4-TR criteria • behavioural problems such as irritability, agitation, self-injurious behaviour, or a combination of these symptoms • CGI-S score of ≥ 4 and an ABC Japanese Version (Ono 1996) score of ≥ 18 at screening and baseline Exclusion criteria: • complications or histories of schizophrenia, other psychosis, and mood disorders including bipolar disorder and major depression according to the DSM-4-TR criteria (diagnosed by the investigator) • diagnosis of Rett disorder, childhood disintegrative disorder, Asperger's disorder, or PDD-NOS according to the DSM-4-TR, or a diagnosis of fragile X syndrome • treatment resistance to antipsychotic medication • significant risk of committing suicide • profound intellectual disability • previously used aripiprazole, received any investigational drug within 30 days before providing informed consent, or received any concomitant drug or therapy specified as prohibited in the study protocol Location/setting: 50 sites in Japan Sample size: 47 aripiprazole, 45 placebo Number of withdrawals/dropouts: 3 from placebo discontinued, 1 due to AEs and 2 due to a physician decision Gender: 75 male, 17 female Mean age: approx 10 years IQ: approximately 35% in both groups had mild intellectual disability, 15% had moderate intellectual disability, and 13% had severe intellectual disability

Ichikawa 2017 *(Continued)*

	Baseline ABC-I or other BoC: aripiprazole ABC-I 27.1 (7.2); placebo 26.8 (6.5) Concomitant medications: concomitant psychotropic medications were not permitted during the trial. History of previous medications: not provided
Interventions	Intervention: aripiprazole was initiated at 1 mg/day, with a target dosage of 1, 3, 6, 9, 12, or 15 mg/day Placebo: equivalent placebo once daily for 8 weeks
Outcomes	Primary outcomes: • irritability (ABC Japanese Version Irritability Subscale Score) (Ono 1996) • AEs Secondary outcomes: tolerability
Notes	Study start date: June 2012 Study end date: June 2015 Funding: "This study was funded by Otsuka Pharmaceutical Co, Ltd (Tokyo, Japan)" Conflicts of interest: various authors received funding and other support from pharmaceutical companies. Trial registry: NCT01617447

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on method of generating this sequence
Allocation concealment (selection bias)	Low risk	Quote: "Clinicians were required to input information regarding eligible patients on the Interactive Web Response System (IWRS), and then the registration center assigned a trial drug code to each patient"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind - doesn't specify exactly who was blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind - doesn't specify exactly who was blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was low and all participants were accounted for.
Selective reporting (reporting bias)	Low risk	The trial registry reports that the ABC-Irritability and AEs were outcomes. Both of these were reported in full.
Other bias	High risk	A pharmaceutical company funded the study and 2 of the study authors are employees of the pharma company.

Jacob 2022

Study characteristics	
Methods	24-week parallel trial of balovaptan versus placebo
Participants	Inclusion criteria: • men and women at least 18 years of age who meet the DSM-5 criteria for an ASD diagnosis • an IQ of at least 70 • women who are sexually active are on contraception during the trial and for at least 28 days after the trial • other permitted medications must be maintained at a stable dose throughout the study Exclusion criteria: • pregnant or breastfeeding women • any changes to medications in prior 6 weeks to trial, unstable or uncontrolled psychotic disorders, substance use disorders within the past 12 months, neurological disorders including unstable epilepsy (seizures within the past 6 months) • other significant medical conditions including hypertension, peripheral neuropathy, syncope or cardiovascular disease; positive for Hepatitis B or C or HIV; history of bleeding disorders or other disease or condition that "could interfere with, or treatment of which might interfere with, the conduct of the study, or what would, in the opinion of the investigator, pose an unacceptable risk to the subject in this study". Location/setting: 46 sites across 6 countries (the USA, the UK, France, Italy, Spain, and Canada) Sample size: 321 (balovaptan group 163; placebo group 158) Number of withdrawals/dropouts: • balovaptan group, 61 withdrew in total (1 prior to receiving the intervention, 39 study termination by sponsor, 12 withdrawal by participant, 4 AEs, 1 lack of efficacy, 1 LTFU, 1 other reasons, 1 physician decision, 1 protocol deviation) • placebo group: 55 in total discontinued (33 study termination by sponsor, 9 withdrawal by participant, 4 AEs, 1 lack of efficacy, 4 LTFU, 1 non-compliance with study drug, 3 other reasons) Gender*:* 64 females, 257 males Mean age: 27.6 years IQ: approx 105 Baseline ABC-I scores or other BoC: Concomitant medications: details not provided History of previous medications*:* details not provided
Interventions	Intervention: 10 mg of oral balovaptan once daily for 24 weeks Comparator: equivalent placebo for 24 weeks
Outcomes	Primary outcomes: AEs Secondary outcomes: QoL, measured using the PedsQL, (Varni 2001) Timing of outcome assessments: AEs week 24 (endpoint); QoL: baseline, week 12 and 24 (endpoint)
Notes	Study start date: August 2018 Study end date: July 2020

Jacob 2022 *(Continued)*

Source of funding: Pharmaceutical company (Hoffmann-La Roche)

Conflicts of interest:

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly allocated (1:1) to receive balovaptan or placebo with an independent interactive voice or web-based response system (IxRS) using permuted blocks of four. Knowledge of block size was controlled to avoid randomisation predictability. Sites enroling a participant entered the participant's data in the IxRS, and the system assigned the participant to a trial group according to the allocation sequence. The randomisation provider was Signant Health; the sponsor did not have access to the live allocation sequence while the study was ongoing.
Allocation concealment (selection bias)	Low risk	Participants were randomly allocated (1:1) to receive balovaptan or placebo with an independent interactive voice or web-based response system (IxRS) using permuted blocks of four. Knowledge of block size was controlled to avoid randomisation predictability. Sites enroling a participant entered the participant's data in the IxRS, and the system assigned the participant to a trial group according to the allocation sequence. The randomisation provider was Signant Health; the sponsor did not have access to the live allocation sequence while the study was ongoing.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Apart from "Participants, study site personnel, and the sponsor were masked to treatment assignment" no further details were provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Apart from "Participants, study site personnel, and the sponsor were masked to treatment assignment" no further details were provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	Over half of all dropouts in both groups were "terminated by the sponsor".
Selective reporting (reporting bias)	Unclear risk	It appears that all outcomes listed on trial registry were reported however, with the early termination it is unclear if other factors contributed to the study terminating (especially with the involvement of the sponsor).
Other bias	High risk	The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

Jaselskis 1992

Study characteristics

Methods	Cross-over trial of clonidine versus placebo
Participants	Inclusion criteria: • children 5-11 years • diagnosed with ASD according to the DSM-III-R criteria • no history of medical or neurological illnesses

Jaselskis 1992 *(Continued)*

- had inattention, impulsivity, and hyperactivity that was excessive for their developmental level
- unresponsive or intolerant to or experienced AEs with other psychopharmacological treatments previously

Exclusion criteria:

- any neurological or medical illnesses
- use of medications in the month prior to starting the study

Location/setting: outpatients clinic, USA

Sample size: 8 in total (cross-over)

Number of withdrawals/dropouts:none reported

Gender: 8 male

Mean age: 8.1 years

IQ: 59

Baseline ABC-I or other BoC: none reported

Concomitant medications: 0%

History of previous medications: medications were not allowed in the month prior to the study.

Interventions	Intervention (clonidine) for 6 weeks: clonidine was provided at 0.025 mg strength. Clonidine was tapered up over 2 weeks to a dose of 4-10 ug/kg/day (0.15-0.20 mg/day) in 3 doses per day. Comparator (placebo) for 6 weeks: identical placebo tablets were provided in a 0.025 mg strength. Placebo was tapered up over 2 weeks to a dose of 4-10 ug/kg per day (0.15-0.20 mg/day) in 3 doses per day.
Outcomes	Primary outcomes: irritability, measured using the ABC-I subscale (Aman 1985) Secondary outcomes: none reported Timing of outcome assessment: ABC-I rated weekly by teachers; AEs recorded weekly however not reported
Notes	Study start date: not reported Study end date: not reported Source of funding: "supported in part by the Harris Center for Developmental Studies (Chicago, IL) and National Institute of Mental Health Child and Adolescent Mental Health Academic Award K07 MH00822 (to E.C.)" … "Catapres and matched placebo tablets were provided as a gift from Boehringer Ingelheim Pharmaceuticals Inc. (Ridgefield, CT)". Conflicts of interest: none declared Trial registry: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided except for, quote: "The subjects were randomly assigned by a non-rating clinician whose only clinical contact with patients and parents occurred during the diagnostic phase and after the completion of the study for each patient."

Jaselskis 1992 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	"Tablets were placed in sealed envelopes designated for each day of the study"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All raters (parents, teachers and clinicians) were blind to drug order until ratings were completed"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all raters (parents, teachers, and clinicians) were blind to drug order until ratings were completed"
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 8 participants were analysed in the trial and individual data were not recorded.
Selective reporting (reporting bias)	High risk	No baseline scores were recorded despite "three sessions that were done at baseline". "Clinician ratings were only made at the end of each treatment period" and "none of the clinician ratings showed significant differences between placebo and clonidine" and "weekly teacher ratings included the Abberant Behaviour Checklist". Side effects were monitored weekly however not reported.
Other bias	High risk	Quote: "clonidine and identical placebo tablets were provided...by Boehringer Ingelheim Pharmaceuticals, Inc"

Kent 2013

Study characteristics	
Methods	Parallel trial of risperidone versus placebo
Participants	Inclusion criteria: • DSM-4 diagnosis of autistic disorder and parent-rated ABC-I subscores of at least 18 • aged 5-17 years (inclusive) • weighing at least 20 kg Exclusion criteria: • previous or current DSM-4 diagnosis of psychotic disorder or PDD • determined neurological disorders • moderate or severe extrapyramidal symptoms or tardive dyskinesia • past lack of response to risperidone treatment • girls who were pregnant or breastfeeding Setting: multicenter study including "16 clinical and investigative settings", USA Sample size: 66 (risperidone 31, placebo 35) Number of withdrawals/dropouts: placebo 8 (AE 0, LTFU 0, withdrew consent 1, insufficient response 6, medication noncompliance 1, other 0). Risperidone 6 (AE 1, LTFU 1, withdrew consent 3, insufficient response 0, medication noncompliance 0, other 1) Gender: placebo 31 male, 4 female; risperidone 28 male, 3 female Mean age: all were aged under 18 years IQ: not reported

Kent 2013 *(Continued)*

	Baseline ABC-I or other BoC: ABC-I risperidone 28.0; placebo 28.9 Concomitant medications: participants were not allowed to be taking psychotropic medications for at least 1 week before baseline. Anticholinergics and antihistamines for the treatment of emergent extrapyramidal symptoms were restricted to the lowest dose and for the shortest duration possible. Similarly, hypnotic or sedative medications (lorazepam, 0.25–2 mg; or diphenhydramine up to 50 mg) were allowed if the patient had been stable on a particular dose for at least 30 days before study start. Antihistaminic drugs were the most commonly used concomitant medication; a higher percentage of participants in placebo (20%; n = 7) than risperidone group 3%, n = 1) were treated with these drugs. History of previous medications: not reported
Interventions	Intervention (risperidone) for 6 weeks: 1.25 mg/day children < 45 kg; or 1.75 mg/day children > 45 kg Comparator (placebo) for 6 weeks: placebo oral solution for 6 weeks
Outcomes	Primary outcomes: • ABC-I (change from baseline) and response rates (at least 25% improvement in ABC-I scores)(Aman 1985) • Improvement in irritability (defined as a minimum 25% improvement in ABC-Irritability scores (Aman 1985)) • AEs Secondary outcomes: none reported Timing of outcome assessment: baseline and the 6 weeks (endpoint)
Notes	Study start date: December 2007 Study end date: March 2010 Source of funding: Johnson & Johnson Pharmaceutical Research & Development, LLC Conflicts of interest: "Dr Aman was an investigator for this study and has received research support or been a consultant for Janssen Research & Development, LLC, Bristol-Myers Squibb, Pfizer, Forest Research, and Hoffman La Roche. Drs. Ness, Singh, Hough and Kent and Mr. Karcher are employees of Janssen Research & Development, LLC. Drs Ning and Kushner were employed by Janssen Research & Development, LLC during the design and conduct of this study. Dr Ning is currently employed by Purdue Pharma and Dr Kushner is at CFG Health Systems, LLC. All authors met ICMJE criteria and all those who fulfilled those criteria are listed as authors". Trial registry" NCT00576732

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the randomisation was conducted by using randomly permuted blocks and was stratified by centre and baseline weight"
Allocation concealment (selection bias)	Low risk	Quote: "To maintain blinding, the study drugs supplied were identical in appearance and packed in identical child-resistant containers."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Patients, parents or primary caregivers, and the site personnel were all blinded to treatment assignment."
Blinding of outcome assessment (detection bias)	Unclear risk	Not mentioned apart from "site personnel were all blinded"

Kent 2013 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias)
All outcomes
	High risk	• ITT analysis used
		• Sedation not reported for high-dose risperidone - only low-dose.
		• LTFU:
		  ◦ placebo (8): lack of efficacy (6); withdrew (1); protocol violation (1)
		  ◦ risperidone low-dose (5): adverse effects (1); withdrew (1); LTFU (1); other (2)
		  ◦ risperidone high-dose (6): adverse effects (1); withdrew (3); LTFU (1); other (1)

Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned were reported however without a trial protocol it is difficult to know if other outcomes were originally measured but not reported. Data were collected at 4 days, and weeks 1, 2, 4 and 6, or at the time of early withdrawal but only endpoint data were reported.
Other bias	Unclear risk	Participants were recruited from the investigators' practices There were no apparent differences in age, gender, race, BMI, diagnosis, symptoms or baseline scores.

Khalaj 2018

Study characteristics	
Methods	10-week parallel trial of palmitoylethanolamide versus placebo
Participants	Inclusion criteria: • children 4–12 years old • meet the DSM-V criteria for diagnosis of ASD • irritability symptoms of at least moderate severity, defined as scores ≥ 12 on the ABC-I subscale Exclusion criteria: • children in whom severity of symptoms were not pronounced enough to be considered for treatment with risperidone • children with concomitant psychiatric disorders, pre-existing medical or disease conditions (particularly epilepsy or seizure disorders) • severe intellectual disability • history of alcohol/drug abuse, tardive dyskinesia, or history of antipsychotic medication • behaviour therapy in the 6 months prior to the trial • children who had not received any other medications in the 6 weeks before trial commencement Location/setting: 2 Children's Outpatient Clinics at tertiary hospitals in Iran Sample size: 70 (35 each group) Number analysed: risperidone plus palmitoylethanolamide (n = 31), risperidone plus placebo (n = 31) Number of withdrawals/dropouts: risperidone plus palmitoylethanolamide (n = 4), risperidone plus placebo (n = 4). No reasons reported Gender: 47 male, 15 female Mean age: 6.84 (2.1); placebo 7.42 (2.35) years IQ: details not provided

Khalaj 2018 *(Continued)*

	Baseline ABC-I or other BoC: ABC-I intervention group 21.97 (5.06); placebo 20.97 (6.8) Concomitant medications: only children who were drug-free for at least 6 weeks before beginning of the study due to other reasons (discontinuation of drugs by their parents) were included. History of previous medications: details not provided
Interventions	Intervention (palmitoylethanolamide + risperidone): participants in both groups similarly received risperidone. It was started with an initial dose of 0.5 mg and stepwise 0.5 mg weekly increases for the first 3 weeks were implemented. Maximum dose of risperidone was 1 mg/d for children weighing < 20 kg and 2 mg/d for those with a body weight ≥ 20 kg. Additionally, individuals were administered 600 mg palmitoylethanolamide twice daily for 10 weeks. Comparator (placebo + risperidone): risperidone was started with an initial dose of 0.5 mg and stepwise 0.5 mg weekly increases for the first 3 weeks were implemented. Maximum dose of risperidone was 1 mg/d for children weighing < 20 kg and 2 mg/d for those with a body weight ≥ 20 kg. Additionally, individuals were administered 600 mg of placebo twice daily for 10 weeks.
Outcomes	Primary outcomes: • irritability using the ABC-Irritability (Aman 1985) • adverse events Secondary outcomes: tolerability
Notes	Study start date: February 2017 Study end date: October 2017 Funding: this study was funded by Tehran University of Medical Sciences and Health Services (grant number 33135). Conflicts of interest: "Authors declare no conflict of interest" Trial registry: IRCT201702171556N96

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear if random number generator or quasi Quote: "Randomization was performed by a radomization operator who was not otherwise involved in this trial"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by a radomization operator who was not otherwise involved in this trial." "Randomization codes were kept secure until data curation was completed."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; participants and their parents were blinded to group allocations.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind ; participants and their parents were blinded to group allocations. "Randomization codes were kept secure until data curation was completed"
Incomplete outcome data (attrition bias) All outcomes	High risk	Reason for withdrawals not described

Khalaj 2018 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Difficult to know without a protocol
Other bias	High risk	• The contact author is also on the ethics committee at the university funding the study. • The contact author is a peer-reviewer for one of the journals in which some of their studies are published.

King 2001

Study characteristics	
Methods	Parallel trial of amantadine hydrochloride versus placebo
Participants	Inclusion criteria: • aged 5-19 years • diagnosis of ASD according to DSM-4 and ICD-10 criteria • composite age equivalents > 18 months on the Vineland Adaptive Behavior Scales • ABC-I, ABC-hyperactivity (subscale IV) ≥ age-adjusted 75th percentile • idiopathic autism Exclusion criteria: • IQ (ratio, nonverbal) score < 35 as measured on the Mullen Scales of Early Learning (Mullen, 1995) or the Differential Ability Scale (Elliot, 1990) • fragile X syndrome and tuberous sclerosis complex (both of which may predispose to autistic symptoms) • receiving neuroleptic, anticonvulsant, or stimulant medication, or showed evidence for any clinically important medical illness Location/setting: 6 university medical centres, USA Sample size: 19 amantadine hydrochloride, 20 placebo Number of withdrawals/dropouts: none post-randomisation Gender: amantadine: 15/19 male; placebo: 19/20 male Mean age: 7 years IQ: > 35 Baseline ABC-I or other BoC: ABC-I amantadine 19.1; ABC-I placebo 18.7 Concomitant medications: SSRIs ("provided the dose had been stable for greater than 1 month prior to entry, and the dose did not change during the study period") amantadine group: 4/19; placebo 6/20 History of previous medications: not reported
Interventions	Intervention (amantadine hydrochloride) for 5 weeks: after a week-long placebo baseline phase, amantadine hydrochloride was started at 2.5 mg/kg once/day for first week of active treatment. "For each of the three remaining weeks of the treatment phase, amantadine hydrochloride as two doses of 0.25 mL/kg (i.e., 5 mg/kg per day)" Comparator (placebo) for 5 weeks: "taste and color-matched placebo was started as 0.25 mL/kg per day for a week during baseline phase. During the first week of the treatment phase, under double-blind

King 2001 *(Continued)*

	conditions, subjects received placebo at a single dose of 0.25 mL/kg per day. For each of the three remaining weeks, the subject was given placebo as two doses of 0.25 mL/kg (i.e., 0.5 mL/kg per day)".
Outcomes	Primary outcomes: AEs Secondary outcomes: none reported Timing of outcome assessments: screening, baseline start of the week, baseline end of the week, visits in weeks 2, 3, 4, 5
Notes	Study start date: not reported Study end date: not reported Source of funding: "funded by Cerebrus plc, Winnersh, UK" Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided except, "Treatment allocation was randomized and supplied in a blind manner"
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for and included in the analysis. The only participants who withdrew from the study did so before randomisation.
Selective reporting (reporting bias)	High risk	ABC-I endpoint scores not reported
Other bias	Unclear risk	Study was funded by Cerebus plc - unclear parameters around this funding. No significant differences in age, gender, weight, race, concomitant SSRI, CGI-rated illness severity, ABC irritability and hyperactivity scores at baseline

King 2009

Study characteristics

Methods	Parallel trial of citalopram versus placebo
Participants	Inclusion criteria: • meet the DSM-4-TR criteria for ASD, Asperger's disorder, or PDD • have an illness severity rating of at least moderate on the CGI-S

King 2009 *(Continued)*

	• score at least moderate on compulsive behaviours Exclusion criteria: details not provided Location/setting: s6 academic medical centres in the USA Sample size: 149 (73 children were randomised to citalopram and 76 to placebo) Number of withdrawals/dropouts: placebo: 13 withdrew (7 AEs, 1 protocol violation, 5 withdrew consent) Citalopram hydrobromide: 13 withdrew (1 serious AE, 8 AEs, 2 protocol violations, 2 withdrew consent) Mean age: 9.4 years Gender: 128/149 boys IQ: 43% had nonverbal IQ > 70 Baseline ABC-I or other BoC: citalopram ABC-I 13.2; placebo 11.2; self-injurious behaviour 2.8 (citalopram); 2.6 (placebo) Concomitant medications: psychotropic medication not allowed during the study. Only sleep medications allowed History of previous medications: details not provided
Interventions	Intervention (citalopram hydrobromide) for 12 weeks: 10 mg/5 mL. Mean maximum dose was 16.5 mg/day (± 6.5 mg) Comparator (placebo) for 12 weeks: equivalent placebo
Outcomes	Primary outcomes: • Irritability, measured using the ABC-Irritability subscale (Aman 1985) • self-injurious behaviour, measured using the Repetitive Behavior Scale-Self-Injurious subscale (Bodfish 2000) Secondary outcomes: none reported Timing of outcome assessments: AEs assessed at bi-weekly visits; ABC-I and self-injury measured at baseline and endpoint
Notes	Study start date: April 2004 Study end date: October 2006 Source of funding: all authors received salary contributions from the National Institutes of Health, which supported this study. Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned to citalopram or placebo using permuted blocks with randomly varying block sizes stratified by site and by age (5-11 vs 12-17 years)
Allocation concealment (selection bias)	Unclear risk	Details not provided

King 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Two masked clinicians met with participants during each scheduled evaluation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The evaluating clinician monitored efficacy and was blinded to AEs
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LTFU citalopram: 13 withdrew, 1 due to serious AE; 8 AEs; 2 protocol violations; 2 consent withdrawn LTFU placebo: 13 withdrawn, 7 AEs; 1 protocol violation; 5 consent withdrawn
Selective reporting (reporting bias)	Low risk	The trial protocol was recorded on Clinicaltrials.gov and outcomes were reported in the paper.
Other bias	High risk	Study authors all work with/for pharmaceutical companies

Klaiman 2013

Study characteristics	
Methods	Parallel trial of tetrahydrobiopterin versus placebo
Participants	Inclusion criteria: • meet the DSM-4-TR diagnostic criteria for an ASD • aged 3-7 years of age at the start of the study • developmental quotient > 50 as assessed by the Vineland Adaptive Behaviour Scale • not taken any psychoactive medications other than supplements, anticonvulsants, melatonin, or diphenhydramine for sleep or seizures within the 6 months prior to enroling in the study Exclusion criteria: • taken any psychoactive medications other than supplements, anticonvulsants, melatonin, or diphenhydramine for sleep or seizures within the 6 months prior to enroling in the study Location/setting: Children's Health Council in Palo Alto, California, USA Sample size: 46 (23 in both groups) Number of withdrawals/dropouts: tetrahydrobiopterin (BH4) AEs (2) and lack of efficacy (1), placebo lack of efficacy (1) Gender: tetrahydrobiopterin (BH4) 20 male, 3 female, 18 male, 5 female Mean age: 5 years IQ: not reported Baseline ABC-I or other BoC: ABC-I BH4 11.1, placebo 11.9 Concomitant medications: participants could not have been taking psychotropic drugs in 6 months prior to trial and not start any new medications during the trial. History of previous medications: not reported

Klaiman 2013 *(Continued)*

Interventions	Intervention (tetrahydrobiopterin) for 16 weeks: "individual doses of BH4 were prescribed in tablet form at 20mg/kg of body weight and taken once daily. The form of BH4 prescribed was given as tetrahydrobiopterin dihydrochloride. "The mean dose of BH4 at endpoint was 385mg/day or 19mg/kg/day" Comparator (placebo) for 16 weeks: matching placebo
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: tolerability Timing of outcome assessments: baseline, week 8 and week 16 (endpoint)
Notes	Study start date: not reported Study end date: not reported Source of funding: "study drugs and matching placebo were provided by BioMarin Pharmaceutical, Inc" Conflicts of interest: none declared Trial registry: NCT00850070

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Group assignment was generated by a randomization program on Microsoft Excel"
Allocation concealment (selection bias)	Low risk	One member of the research team (LH) was responsible for all randomisation; randomisation records were kept on a password-protected computer in a locked office.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	BH4 and placebo were supplied by the pharmacist as matching pills in identical packaging. "Participants, parents, and evaluators (GRE and CK) responsible for assessing the children all were blind to assignment; they remained blind until the final participant completed the trial."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Participants, parents, and evaluators (GRE and CK) responsible for assessing the children all were blind to assignment; they remained blind until the final participant completed the trial."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the analysis and an ITT analysis was used, including using LOCF. All outcomes were reported in full.
Selective reporting (reporting bias)	Low risk	All measures were reported in full.
Other bias	High risk	This research was funded by BioMarin Pharmaceutical, Inc. as an investigator-initiated study (#CHC0901).

Le 2022

Study characteristics	
Methods	6 week cross-over trial of oxytocin versus placebo
Participants	Inclusion criteria: • aged 3-8 years • meet the DSM-5 criteria for ASD diagnosis • meet the ADOS-2 criteria for ASD • not in receipt of any psychotropics in the previous 3 months • parent or participant consent to participate Exclusion criteria: • previous or current use of oxytocin • meet the DSM-5 criteria for any mental disorders • "ASD accompanied with severe behavioural disorders" • any serious medical conditions, including neurological, endocrine, cardiovascular, or gastrointestinal disorders • any chronic nasal disorders that impact the ability to use nasal sprays • hearing or vision impairments • allergic to oxytocin Location/setting: China Sample size: 41 (21 oxytocin, 20 placebo) Number of withdrawals/dropouts: none were lost to follow-up in the first phase of the cross-over trial Gender: male (38), female (3) Mean age: 5.0 years across both groups IQ: not reported Baseline ABC-I or other BoC scores: not an outcome Concurrent medications: details not provided History of previous medications: details not provided
Interventions	Intervention (oxytocin) followed by placebo: oxytocin nasal spray 24 IU every 2nd day for 6 weeks, followed by a 2-week wash-out period before starting the 2nd phase of the cross-over trial Comparator (placebo) followed by oxytocin: equivalent placebo (24 IU) every 2nd day for 6 weeks, followed by a 2-week wash-out period before starting the 2nd phase of the cross-over trial
Outcomes	Primary outcomes: AEs Secondary outcomes: not reported Timing of outcome assessments: unclear
Notes	Source of funding: University of Electronic Science and Technology of China, UESTC high-level research fostering project Conflicts of interest: "The authors have no conflicts of interest to declare"
Risk of bias	

Le 2022 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1:1 computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Intranasal spay bottles for oxytocin or placebo were identical in appearance and labelling with each having a unique code.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Intranasal spray bottles were labelled and distributed to carers by an individual not involved in any other aspect of the trial who was responsible for finally unmasking the treatment details at the end of the trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Intranasal spray bottles were labelled and distributed to carers by an individual not involved in any other aspect of the trial who was responsible for finally unmasking the treatment details at the end of the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 of 21 LTFU in oxytocin group and 1 in 22 in placebo group
Selective reporting (reporting bias)	Unclear risk	There were no serious AEs in either group but the only other AE that was reported was urination frequency.
Other bias	Low risk	No differences in age, gender, baseline scores of autism subtype

Lemonnier 2017

Study characteristics	
Methods	3-month parallel trial of bumetanide versus placebo
Participants	Inclusion criteria: • children and adolescents aged 2–18 years • fulfil diagnosis criteria of Childhood Autism (F84.0) or Asperger's Syndrome (F84.5) according to ICD-10; and ADOS G and ADI-R • CARS total score 434 points • weight ≥ 11 kg Exclusion criteria: • serious, unstable illnesses including, gastroenterological, respiratory, cardiovascular (QT interval lengthening), endocrinology, immunologic or hematologic disease; renal or hepatic dysfunction and neurological disorders such as seizures and microcephaly • psychotropic medications were not allowed during the trial and had to be discontinued at least 4 weeks before entering the trial Location/setting: France; the patients were enroled in six French specialised centres (hospitals of Brest, Limoges, Rouen, Nice, Lyon and Marseilles) Mean IQ: details not provided Mean age: 7.8 ± 4.1 (0.5 mg), 7.9 ± 4.6 (1.0 mg), 8.4 ± 4.6 (2.0 mg) and 8.8 ± 4.5 (placebo) Gender: 78 male, 10 female

Lemonnier 2017 *(Continued)*

	Sample size: 88 Reasons for dropouts: 0.5 mg - no LTFU reported, 1.0 mg - 3 AEs and 1 LTFU, 2.0 mg - 6 AEs, 3 LTFU; placebo - 1 AE, 2 LTFU Baseline ABC-I or other BoC scale: not an outcome Timing of outcome assessments: end of month 4 Concomitant medications: psychotropic medications (including antipsychotic, psychostimulant, antidepressant, anxiolytics, mood stabilisers and neuroleptic agents) had to be discontinued at least 4 weeks before entering the trial Previous medications: not reported
Interventions	Intervention (bumetanide) 0.5 mg, 1 mg or 2 mg twice daily for 90 days Comparator: equivalent placebo for 90 days
Outcomes	Primary outcomes: AEs Secondary outcomes: tolerability
Notes	Study start date: January 2014 Study end date: March 2015 Funding: "The study was sponsored by Neurochlore, a biotech company dedicated to the development of novel therapies to autism and other developmental disorders'. 'Funding of the trial comes from an investment of Symmetry Capital, a grant from France's Agence Nationale de la Recherche (ANR-12-RPIB-0001-01) and French Government loans". Conflicts of interest: "Three of the authors are founders and shareholders of the company funding the study. The remaining authors declare no conflicts of interest" Trial registry: NCT01078714

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated age-stratified randomisation schedule prepared by Amatsi group used
Allocation concealment (selection bias)	Unclear risk	No information beyond "randomised"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinded - no further details provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Each patient was seen and assessed by two clinicians who were unaware of the treatment assignment. Quote "Finally, the diuretic actions of bumetanide also impact the blinding procedure. To reduce this impact, the psychiatrist was separated from the pediatrician who treated the children and was thus blinded to the treatment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	LTFU participants included in final analyses

Lemonnier 2017 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Protocol not published
Other bias	High risk	Quote: "The study was sponsored by Neurochlore, a biotech company dedicated to the development of novel therapies to autism and other developmental disorders. EL, DR and YB-A are founders and shareholders of the company"

Levy 2003

Study characteristics	
Methods	Cross-over trial of single-dose secretin versus single-dose placebo
Participants	Inclusion criteria: diagnosis of ASD confirmed using the ADI-R. No other inclusion criteria outlined Exclusion criteria: • significant hearing or vision loss • other neurological disorders, e.g. cerebral palsy, phenylketonuria, tuberous sclerosis, neurofibromatosis, seizure disorders; • genetic disorders • prematurity (< 32 weeks gestation) • diagnosis of coeliac disease or other gastrointestinal disease associated with malabsorption • previous treatment with secretin • anaemia • lead poisoning Location/setting: Children's Hospital of Philadelphia, USA Sample size: 62 total (31 in each group) Number of withdrawals/dropouts: 2 participants dropped out post-randomisation however reasons were not provided Gender: all participants were male Mean age: secretin 6.4 years; placebo 5.9 years. IQ: not reported Baseline ABC-I or other behaviours of concern: RFRLRS (subscale3) 0.74 (secretin), 0.64 (placebo). Concomitant medications: 7/31 (secretin) were on either prozac (1), Adderall (2), guanfacine (2), methylphenidate (2). Placebo: either prozac, guanfacine or risperidone with 1 child taking prozac and guanfacine History of previous medications: not reported
Interventions	Intervention (single-dose secretin)with 6-week washout before placebo (or vice versa): single intravenous dose of human secretin (2 CU/kg). Initially, a test dose of 0.2 uh was given and if no reaction was noted after 1 min, the remaining dose of 2 CU/kg up to a maximum of 75 CU was injected slowly over 1 min Comparator (placebo): single intravenous dose of saline placebo (2 CU/kg)
Outcomes	Primary outcomes: irritability, measured using the RFRLRS Affectual Responses subscale (Freeman 1986); adverse effects although data were not reported for both groups and so could not be included.

Levy 2003 *(Continued)*

	Secondary outcomes: none reported Timing of outcome assessments: baseline, 2 and 4 weeks postinfusion
Notes	Study start date: not reported Study end date: not reported Source of funding: ChiRhoClin Corporation donated the human secretin used for the study. Otherwise, sponsorship was through research grants. Conflicts of interest: none declared Trial registry: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the 62 subjects were randomly assigned to two groups using a computerised randomisation assignment"
Allocation concealment (selection bias)	Unclear risk	Details were not provided on how the placebo was administered.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Each participant was separated from his or her parents during the infusion (since secretin may cause a transient skin rash—the presence of which may unblind the parent to the treatment condition).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All personnel involved in clinical and neurodevelopmental assessments were blinded to subject's allocation"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 participants did not complete both phases of the trial (1 in each group) however reasons were not provided and information not given if an ITT analysis was used or LOCF
Selective reporting (reporting bias)	Low risk	The outcome measures were the Global Behavior Rating Scale, Communication and Symbolic Behavior Scale and the Real Life Ritvo Behavior Scale. All outcomes were reported at baseline and at the end of each phase of the cross-over trial.
Other bias	Unclear risk	"ChiRhoClin Corporation donated the human synthetic secretin used for the study". Only a single dose of secretin was used

Lewis 2018

Study characteristics

Methods	3-week cross-over trial of nicotine versus placebo
Participants	Inclusion criteria: • aged 18-60 years • DSM-5 or DSM-4 diagnosis of autism or Asperger's syndrome or PDD-NOS • parent-reported symptoms of aggression, agitation or irritability

Lewis 2018 *(Continued)*

- ABC-I score of ≥ 16 at baseline
- on stable medication without changes during the study
- have a caregiver willing and able to complete behavioural scales
- BMI of > 17.5 and < 47

Exclusion criteria:

- current use of tobacco or nicotine products
- previous allergies to transdermal patches
- known cardiac abnormalities, or hypotension or hypertension

Location/ setting: Yale Child Study Center in New Haven, CT, USA

Sample size: 8 in total

Reason for dropouts: 1 participant did not complete the first phase of the trial because of a protocol violation.

Mean age: 21 years

Mean IQ: not reported

Gender: 7 male, 1 female

Baseline ABC-I or other BoC scale: 25.0 (8.0)

Concomitant medications: divalproex (3), risperidone (4), desipramine (1), methylphenidate (1), clonidine (2), lamotrigine (1), buspirone (1), olanzapine (1), aripiprazole (1), fluoxetine (1), clonazepam (1), propranol (1), gabapentin (1)

Previous medications: not reported

Interventions	Intervention: skin patches containing 7 mg of nicotine were applied for 7 days with a washout period of 7 days between each phase Comparator: skin patches containing 7 mg of placebo were applied for 7 days
Outcomes	Primary outcomes: ABC-I (Aman 1985) Secondary outcomes: none reported Timing of outcome assessments: baseline, completion of weeks 1 and 3
Notes	Study start date: May 2015 Study end date: November 2017 Funding: "This work was supported by Autism Speaks grant #9699, National Institutes of Health grants R01DA14241, R01MH077681, R25MH071584, T32MH019961, and T32MH14276, and the Yale Child Study Center Associates and the AACAP Pilot Award for General Psychiatry Residents". Conflicts of interest: "The authors declare no conflicts of interest". Trial registry: NCT02552147

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details on sequence generation beyond, "Randomization and preparation of patches was performed by the Yale Investigational Drug Service."

Lewis 2018 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details on allocation concealment beyond "Randomization and preparation of patches was performed by the Yale Investigational Drug Service"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details apart from double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details apart from double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Large % of people missing data for primary outcome
Selective reporting (reporting bias)	High risk	Doesn't report State-Trait Anxiety Inventory, State-Trait Anger Expression Inventory-2 etc
Other bias	Unclear risk	Early stoppage of trial before sample size reached

Loebel 2016

Study characteristics	
Methods	6-week, double-blind RCT, parallel trial of lurasidone (20 mg/day or 60 mg/day) versus placebo
Participants	Inclusion criteria: • children 6-17 years who met the DSM-4-TR criteria for a diagnosis of AS • a score of ≥ 18 on the ABC-I subscale and a score of ≥ 4 (moderate-or-greater severity) on the CGI-S Exclusion criteria: • a current diagnosis of bipolar disorder, schizophrenia, major depressive disorder, Fragile-X syndrome, or childhood disintegrative disorder • confirmed genetic disorder associated with cognitive and/or behavioural disturbance or profound intellectual disability • a history of seizures (unless seizure-free and off medication for 6 months or more) • use of any psychotropic medications Location/setting: not reported Sample size: 148 (lurasidone 60 mg/day 51, 20 mg/day lurasidone 48, placebo 49) Number of withdrawals/dropouts: placebo: lack of efficacy (1), AEs (4), lost to follow-up (1), withdrew consent (4); lurasidone 60 mg/day: lack of efficacy (1), AEs (2), miscellaneous (1); lurasidone 20 mg/day: AEs (2), lack of efficacy (1), lost to follow-up (2), withdrawal by participant (1) Gender: placebo 40/49 male, lurasidone 60 mg/day 43/51 male, lurasidone 20 mg/day 38/48 male Mean age: placebo 11 years, lurasidone 20 mg/day 10.5 years, lurasidone 60 mg/day 10.5 years IQ: not reported Baseline ABC-I or other BoC: irritability, placebo 29.0, lurasidone 60 mg/day 27.0 Concurrent medications: not reported

Loebel 2016 *(Continued)*

	History of previous medications: any antipsychotic: placebo 19/49, lurasidone 20 mg/day 17/48, lurasidone 60 mg/day 16/51. Any psychostimulant: placebo 18/49, lurasidone 20 mg/day 11/48, lurasidone 60 mg/day 16/51. Any antidepressant: placebo 6/49, lurasidone 60 mg/day 5/51
Interventions	Intervention 1 (lurasidone 60 mg/day) for 6 weeks: study participants randomised to the 60 mg/day arm received lurasidone 20 mg/day from days 1–3, 40 mg/day from days 4–6, and 60 mg/day from day 7 to week 6. If the participant was not able to tolerate the 60 mg/day dose, a one-time dose reduction to 40 mg/day was permitted (between days 8 and 29); the 40 mg/day dose was then maintained for the remainder of the study. Intervention 2 (lurasidone 20 mg/day) for 6 weeks: mean of 0.476 mg/kg/day Comparator (placebo) for 6 weeks: matching placebo
Outcomes	Primary outcomes: • irritability, measured with the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessments: weekly
Notes	Study start date: August 2013 Study end date: November 2014 Source of funding: researchers were employed by Sunovion Pharmaceuticals. Conflicts of interest: "Drs Loebel, Goldman, Silva, Hernandez, Mankoski, and Deng are employees of Sunovion Pharmaceuticals Inc. Dr Brams has been a speaker, consultant, and served on advisory boards for Novartis Pharmaceuticals Corp and Shire; and has received grant-research support from Novartis Pharmaceuticals Corp, Shire, and Eli Lilly. Dr Findling receives or has received research support, acted as a consultant and/or served on a speaker's bureau for Alcobra, American Academy of Child & Adolescent Psychiatry, American Physician Institute, American Psychiatric Press, AstraZeneca, Bracket, Bristol-Myers Squibb, CogCubed, Cognition Group, Coronado Biosciences, Dana Foundation, Elsevier, Forest, GlaxoSmithKline, Guilford Press, Johns Hopkins University Press Johnson and Johnson, Jubilant Clinsys, KemPharm, Lilly, Lundbeck, Merck, NIH, Neurim, Novartis, Noven, Otsuka, Oxford University Press, Pfizer, Physicians Postgraduate Press, Purdue, Rhodes Pharmaceuticals, Roche, Sage, Shire, Sunovion, Supernus Pharmaceuticals, Transcept Pharmaceuticals, Validus, and WebMD". Trial registry: NCT01911442

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised via an interactive voice/web response system
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinding although details not explicitly provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blinding although details not explicitly provided

Loebel 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	The ITT population consisted of randomised study participants who received at least 1 dose of study medication and had at least 1 postbaseline efficacy assessment.
Selective reporting (reporting bias)	Low risk	The trial was registered on clinicaltrials.gov and all outcomes were reported.
Other bias	High risk	"The sponsor was involved in the design, collection, and analysis of the data." "Drs. Loebel, Goldman, Silva, Hernandez, Mankoski, and Deng are employees of Sunovion Pharmaceuticals Inc."

Luby 2006

Study characteristics	
Methods	Parallel trial of risperidone versus placebo
Participants	Inclusion criteria: • aged 2.5-6.0 years • previously diagnosed with DSM-4 criteria for autism or PDD-NOS (American Psychiatric Association 1994) Exclusions: • other known significant central nervous system (CNS) disorders • significant medical problems or other psychiatric disorders requiring pharmacotherapy Location/setting: "psychiatric outpatient clinic at Washington University School of Medicine", USA Sample size: 23 (11 risperidone, 12 placebo) Number of withdrawals/dropouts: 1 exclusion from risperidone group as the "child did not meet the threshold for an ASD on the CARS or GARS [Gilliam Autism Rating Scale] at baseline, despite having been referred with a clinical diagnosis, and was excluded from analyses". 1 dropout from placebo group due to parent report of severe hyperactivity Gender: risperidone 9/11 male, placebo 8/12 male Mean age: risperidone 4.1 years, placebo 4 years IQ: not reported Baseline ABC-I or other BoC: not an outcome Concomitant medications: not reported History of previous medications: not reported.
Interventions	Intervention (risperidone) for 6 months: the majority of participants started risperidone at 0.5 mg once daily; mean starting dose was 0.03 mg/kg/day. 81.8% of risperidone participants took 1 mg (0.5 mg twice daily) after 4 weeks; 27.3% of risperidone participants were dispensed total daily doses of 1.5 mg after 8 weeks, whereas all others received total daily doses of 1 mg. The final risperidone mean dose was 0.05 mg/kg/day and mean daily final dose was 1.14 mg (SD 0.32). Comparator (placebo) for 6 months: placebo participants were dispensed 0.5 mg daily doses. Mean final daily dose was 1.38 mg (0.57), which was comparable to risperidone.
Outcomes	Primary outcomes: AEs

Luby 2006 *(Continued)*

	Secondary outcomes: none reported Timing of outcome assessments: at baseline visit, weekly visits during the 1st study month, biweekly visits during the 2nd month, followed by monthly visits for months 3–6
Notes	Study start date: November 1999 Study end date: November 2002 Source of funding: "this study was funded by Janssen Pharmaceutica as an investigator initiated project to Dr. Luby". Conflicts of interest: none disclosed Trial registry: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were consecutively assigned by an unblinded child psychiatrist (J.L) to risperidone or placebo treatment using a randomisation table obtained from the WUSM pharmacy and derived using a standard software package
Allocation concealment (selection bias)	High risk	Quote: "Patients were consecutively assigned by an unblinded child psychiatrist"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Parents and raters who conducted all standardized assessments were blind to treatment group"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Parents and raters who conducted all standardized assessments were blind to treatment group"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants, apart from one who did not meet the required baseline threshold for ASD on the CARS or Gilliam Autism Rating Scale, were included in the analysis. LTFU: 1 participant withdrew from placebo group due to staring spells. No other LTFU reported
Selective reporting (reporting bias)	High risk	All children were previously diagnosed and referred by a clinician. "the treating psychiatrist (J.L) was unblinded and conducted regular clinical assessments over the 6-month period". The unblinded child psychiatrist was also the lead investigator.
Other bias	High risk	All children were previously diagnosed and referred by a clinician. "the treating psychiatrist (J.L) was unblinded and conducted regular clinical assessments over the 6-month period". The unblinded child psychiatrist was also the lead investigator.

Mace 2001

Study characteristics

Mace 2001 *(Continued)*

Methods	Parallel trial of haloperidol versus placebo
Participants	Inclusion criteria: • admitted to an inpatient unit for the treatment of self-injurious behaviour (SIB) • aged 4.5-31.8 years • diagnosed with intellectual disabilities Exclusion criteria: • acute medical illness contributing to the SIB [self-injurious behaviour] • use of psychotropic medications during the trial Location/setting: inpatient unit in the USA Sample size: 7 in total who had autism Number of withdrawals/dropouts: none reported Gender: 3 male, 4 female Mean age: 11 years IQ: details not reported Baseline ABC-I or other BoC: self-injurious behaviour per hour at baseline, haloperidol 125; placebo 146.4 Concomitant medications: participants were not permitted to take psychotropic medications during the trial. History of previous medications: "participants were taking zero to three psychotropic medications upon admission to the inpatient unit. These medications were discontinued before completion of the functional analysis (except for Subjects 5 and 9), and individuals remained off these medications throughout the remainder of the study."
Interventions	Intervention: (haloperidol) for minimum 34 days: "started at 0.025 mg/kg/day for people weighing below 20 kg or 0.5 mg/day for those above 20 kg. The doses were titrated up to the maximum of the lower dose of 0.1 mg/kg/day or 4 mg/day, or until there was a 75% decrease in SIB or significant side effects to the medication. Individuals who did not have a positive response to haloperidol were weaned from the medication by decreasing the total daily dose by 0.25-0.5 mg every 3-5 days until the individual was off the medication. Once the haloperidol was stopped, a placebo was started and data reported for the placebo condition were collected after the individual was entirely off haloperidol for at least 14 days". Comparator (placebo) for minimum 34 days: matching placebo capsules
Outcomes	Primary outcomes: • rate of self-injurious behaviour, measured with a scale developed by the study authors for self-injurius behaviour • irritability, measured using the ABC-I subscale (Aman 1985) Secondary outcomes: none reported Timing of outcome assessments: not reported Trial registry: not reported
Notes	Study start date: not reported Study end date: not reported

Mace 2001 *(Continued)*

	Source of funding: supported, in part, by a grant from the National Institute of Mental Health (MH50358-8) Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All behaviour analysts, nurses, and inpatient unit staff were blind to the medication assignments. The physician was aware of the medication assignment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All behaviour analysts, nurses and inpatient unit staff were blind to the medication assignments". "To keep staff blinded to the different patterns of medication adjustment for behavioural treatment versus medication non-responders, the letters used to identify the medication could be changed by the physician even if the medication was not changed".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The data for the 15 participants were recorded in regards to response to behavioural treatment (% change in SIB), max dose haloperidol (mg/day), response to haloperidol (% change in SIB) and response to placebo (% change in SIB). ABC Irritability baseline and endpoint data were not provided for placebo despite being measured weekly. Other participants had placebo condition measured after 14 days off haloperidol; unclear whether there was any ITT analysis for these missing data.
Selective reporting (reporting bias)	High risk	ABC baseline and endpoint data were not provided for placebo at all.
Other bias	Low risk	None identified

Mahdavinasab 2019

Study characteristics

Methods	10-week parallel trial of baclofen versus placebo
Participants	Inclusion criteria: • children 4–12 years • meet the DSM-V criteria for diagnosis of ASD • have had irritability symptoms of at least moderate severity, defined as scores ≥ 12 on the ABC-I subscale Exclusion criteria: • children who were not deemed of sufficient severity to be treated with risperidone

Mahdavinasab 2019 *(Continued)*

- children who had had concomitant psychiatric disorders, (pre-existing medical or disease conditions especially epilepsy or seizure disorders)
- severe intellectual disability
- history of alcohol/drug abuse, tardive dyskinesia, or history of antipsychotic medication or behavior therapy within the 6 months prior to the trial trial

Location/setting: children's outpatient clinic at a tertiary hospital in Iran

Mean IQ: details not provided

Mean age: baclofen + risperidone 8.04 (SD = 2.33); placebo + risperidone 7.9 (SD = 2.0)

Gender: 46 male, 12 female

Sample size: baclofen (2); placebo (32).

Number analysed: baclofen (29); placebo (29)

Reasons for dropouts: baclofen (3), physician's choice (1), refusal of further therapy (2); placebo (3), refusal of further therapy (3)

Baseline ABC-I or other BoC scale: ABC-I baclofen + risperidone 22.76 (8.56); placebo + risperidone 22.62 (9.24)

Timing of outcome assessments: baseline, week 5, week 10

Concomitant medications: details not provided

Previous medications: excluded if history of antipsychotic medication within the past 6 months before enrolment.

Interventions	Baclofen + risperidone: initial dose of 0.5 mg and stepwise 0.5 mg weekly increases for the first 3 weeks + 0.6 mg kg; 1 baclofen 3 times/day Risperidone: initial dose of 0.5 mg and stepwise 0.5 mg weekly increases for the first 3 weeks + placebo
Outcomes	Primary outcomes: • irritability (Aman 1985) • AEs Secondary outcomes: tolerability
Notes	Study start date: April 2016 Study end date: August 2018 Funding: "This study was supported by a grant from Tehran University of Medical Sciences to Prof. Shahin Akhondzadeh (Grant No: 32601)". Conflicts of interest" "Authors declare no conflict of interest". Trial registry: IRCT201701131556N95

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization was performed by a randomization operator who was not otherwise involved in this trial."

Mahdavinasab 2019 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "Randomization codes were kept secure until data curation was completed."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. "Randomization codes were kept secure until data curation was completed... Participants and their parents were blinded to group allocations."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind. "Randomization codes were kept secure until data curation was completed... No specific details about outcome assessors."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition and all participants were accounted for
Selective reporting (reporting bias)	High risk	Trial reg lists additional primary outcome not reported: Childhood autism rating scale (CARS)
Other bias	High risk	• The contact author is also on the ethics committee at the university funding the study. • The contact author is a peer-reviewer for one of the journals in which some of their studies are published.

Malek 2020

Study characteristics	
Methods	12-week parallel trial of prednisolone versus placebo
Participants	Inclusion criteria: • clinical diagnosis of ASD according to DSM-5 criteria • children aged 3-12 years • regressive subtype according to ADI-R • presence of behavioral problems such as aggression, overactivity, or repetitive behaviors (indication of treatment with risperidone) Exclusion criteria: from those diagnosed with regressive ASD, • children who did not have any indication for risperidone therapy (i.e. overweight children; those with decreased white blood cell, blood volume, or blood pressure at baseline; those with heart, liver, or kidney problems) • presence of several medical problems (ie, uncontrolled epileptic activities, diabetes mellitus, peptic ulcer, gastrointestinal bleeding, hypertension, increased intracranial pressure, and cataract) • history or current diagnosis of concomitant psychiatric disorder, tardive dyskinesia, and diagnosis of neurologic syndromes accompanying by autistic characteristics (i.e. Fragile X syndrome, tuberous sclerosis, and mitochondrial disorders) • history of allergy to risperidone or prednisolone • history of taking any antipsychotic medication or behaviour therapy within the past 6 months before the start point of the trial. Location/setting: paediatric outpatient clinic at a hospital in Iran Sample size: prednisolone (n = 19); placebo (n = 18)

Malek 2020 *(Continued)*

	Reasons for dropouts: prednisolone (n = 6) 6 withdrawn consent; placebo (n = 5) 4 withdrawn consent, 1 dropped out due to severe irritability Mean IQ: details not provided Mean age: prednisolone 5.81 ± 2.5; placebo.34 ± 2.07 Gender: 25 male, 1 female Baseline ABC-I or other BoC scale: ABC-I prednisolone 30.15 (9.62); placebo 25.31 (10.46) Timing of outcome assessments: end of week 12 Concomitant medications: participants could not have taken any antipsychotic medication in past 6 months. Previous medications: details not outlined
Interventions	Intervention (prednisolone + risperidone) for 12 weeks: initial dose of risperidone was 0.5 mg/day during the first week of study and stepwise 0.5 mg weekly increases to maximum dose of 1 mg/d or 2 mg/day. Prednisolone given at 1 mg/kg/day Comparator (placebo + risperidone) for 12 weeks: initial dose of risperidone was 0.5 mg/day during the first week of study and stepwise 0.5 mg weekly increases to maximum dose of 1 mg/day or 2 mg/day. Placebo was administered in placebo pills.
Outcomes	Primary outcomes: irritability measured using the ABC-I (Aman 2017) Secondary outcomes: none reported Timing of outcome assessments: baseline, weeks 4, 8 and 12 (endpoint)
Notes	Study start date: January 2018 Study end date: February 2019 Funding: "This study was supported by a grant from Tehran University of Medical Sciences to Prof. Shahin Akhondzadeh (Grant Number: 36362)". Conflicts of interest - "The authors have no conflicts of interest to declare". Trial registry - IRCT20090117001556N102

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned to treatment groups by the permuted randomisation block method in a 1:1 ratio using a computer-generated code.
Allocation concealment (selection bias)	Low risk	"The participants were kept ignorant of either the groups to which they have been assigned. Prednisolone and placebo were identical in appearance"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind (only participants blinded)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Single-blind (only participants blinded)

Malek 2020 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition and all participants were accounted for
Selective reporting (reporting bias)	Low risk	All outcomes reported on clinical trials registry were reported in full
Other bias	High risk	• The contact author is also on the ethics committee at the university funding the study. • The contact author is a peer-reviewer for one of the journals in which some of their studies are published.

Malone 2001

Study characteristics	
Methods	Parallel trial of olanzapine versus haloperidol
Participants	Inclusion criteria: • children aged 5-17 years (mean age 7.8 +/- 2.1) • primary diagnosis of PDD (DSM-4 criteria) • at least moderate impairment on ≥ 2 of the first 28 items of the Children's Psychiatric Rating Scale at baseline Exclusion criteria: "major medical problems such as cardiac, liver, endocrine, or renal diseases, or seizure disorders or gross neurological deficit, treatment with concomitant psychotropic medication, or a history of previous treatment with haloperidol or olanzapine". Location/setting: not reported Sample size: 12 Number of withdrawals/dropouts: none reported Gender: olanzapine 4/6 male both groups Mean age: 7.8 years IQ: 2/6 and 3/6 (olanzapine and haloperidol) had severe intellectual disability, 3 and 2 had moderate intellectual disability, 1 in haloperidol had mild intellectual disability, and 1 in olanzapine had normal cognitive functioning. Baseline ABC-I or other BoC: not an outcome Concomitant medications: psychotropic drug use during trial was not permitted History of previous medications: 4 participants had no history of prior psychotropic drug use
Interventions	Intervention (olanzapine) for 6 weeks: the starting dosage of olanzapine was 2.5 mg every other day for participants who weighed ≤ 40 kg and 2.5 mg/day for participants who weighed > 40 kg. In general, dosages could be increased in 2.5-mg increments up to 5 mg a week, as needed. The maximum dosage for olanzapine permitted by the study protocol was 20 mg/day. Comparator (haloperidol) for 6 weeks: the starting dosage of haloperidol was 0.25 mg/day for participants who weighed ≤ 40 kg and 0.5 mg for participants who weighed > 40 kg. In general, dosages could be increased as clinically indicated in 0.5-mg increments up to 1 mg a week, as needed. The maximum

Malone 2001 *(Continued)*

	dosage for haloperidol permitted by the study protocol was 5 mg/day. Mean daily dose 1.4 mg/day (+/-0.7)
Outcomes	Primary outcomes: AEs Secondary outcomes: none reported Timing of outcome assessments: baseline and endpoint
Notes	Study start date: not reported Study end date: not reported Source of funding: supported, in part, by a grant from Lilly Research Laboratories (Investigator-Initiated Study) Conflicts of interest: none disclosed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed by use of a computer-generated list"
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	13 were originally enrolled in the study and 1 withdrew consent before beginning study medication. 12 were included in the analysis.
Selective reporting (reporting bias)	Low risk	The CGI and the Children's Psychiatric Rating Scale were the primary outcomes and were reported for both groups.
Other bias	Low risk	Treatment groups did not differ significantly on demographic variables such as age, race, gender, socioeconomic status, severity of illness, or level of cognitive functioning.

Marcus 2009

Study characteristics

Methods	8-week RCT, double-blind, placebo-controlled trial of aripiprazole versus placebo
Participants	Inclusion criteria: • aged 6 -17 years • weigh at least 15 kg

Marcus 2009 *(Continued)*

- meet DSM-4-TR criteria for autistic disorder
- demonstrated behaviours such as irritability, agitation, self-injurious behaviour
- CGI-S score ≥ 4
- ABC-I subscale score of ≥ 18 at screening

Exclusion criteria:

- current diagnosis of bipolar disorder, psychosis, schizophrenia or major depression, fragile X syndrome, or another disorder on the autism spectrum including PDD-NOS, Asperger's disorder, Rett disorder, or childhood disintegrative disorder
- history of neuroleptic malignant syndrome
- significant risk for committing suicide
- seizure in the past year
- history of severe head trauma or stroke
- history or current evidence of unstable medical conditions
- clinically significant laboratory test result or ECG
- resistant to neuroleptic medication
- allergy/hypersensitivity to aripiprazole

Location/setting: 35 independent research centres and research centres with a hospital affiliation

Sample size: 218 children in total; placebo (52); 5 mg aripiprazole (53), 10 mg aripiprazole (59) and 15 mg aripiprazole (54)

Number of withdrawals/dropouts: placebo (14), 5 mg aripiprazole (17), 10 mg aripiprazole (10) and 15 mg aripiprazole (7)

Gender: placebo 48/52 male, 5 mg aripiprazole 47/53 male, 10 mg aripiprazole 50/59 male and 15 mg aripiprazole 50/54 male

Mean age: placebo 10.2 years, 5 mg aripiprazole 9.0 years, 10 mg aripiprazole 10.0 years and 15 mg aripiprazole 9.5 years

IQ: not reported

Baseline ABC-I or other BoC: placebo 28.0, 5 mg aripiprazole 28.6, 10 mg aripiprazole 28.2 and 15 mg aripiprazole 28.9

Concurrent medications: "psychotropic medications including antipsychotics, antidepressants, anxiolytics, mood stabilisers and neuroleptics were prohibited during the study".

History of previous medications: aripiprazole 5 mg/day 24/52 had taken any nervous system medications, 9/52 had taken antipsychotics with 1 of those taking aripiprazole, 8/52 had taken anxiolytics, 8/52 had taken antidepressants, and 3/52 had taken psychostimulants previously. Placebo: 22/51 had taken any nervous system medications, 11/51 had taken antipsychotic and 3 of those had taken aripiprazole previously, 8/51 had taken anxiolytics, 3/51 had taken antidepressants, and 5/51 had taken psychostimulants

Interventions	All participants randomised to aripiprazole started on 2 mg/day for the 1st week, which was increased to 5 mg/day for the 2nd week. Aripiprazole 5 mg/day for 8 weeks: 5 mg tablet once daily for 8 weeks (mean 0.129 mg/kg/day) Aripiprazole 10 mg/day for 8 weeks: weekly 5 mg increments until 10 mg/day was reached. 10 mg tablets once daily for 8 weeks (mean 0.223 mg/kg/day) Aripiprazole 15 mg/day for 8 weeks: weekly 5 mg increments until 15 mg/day was reached. 15 mg tablet once daily for 8 weeks (mean 0.354 mg/kg/day) Placebo for 8 weeks: equivalent placebo
Outcomes	Primary outcomes:

Marcus 2009 *(Continued)*

- irritability (change from baseline), measured with the ABC-Irritability subscale (Aman 1985)
- AEs.

Secondary outcomes:

- quality of life, measured using the PedsQL scale (WHO 1998)
- improvement (> 25% improvement from baseline to endpoint in ABC-I and CGI (Guy 1976) score of 1 or 2 at endpoint)

Timing of outcome assessments: baseline, weeks 1, 2, 3, 4, 5, 6 and 8

Notes	Study start date: June 2006 Study end date: June 2008 Source of funding: "This study was supported by Bristol-Myers Squibb (Princeton, NJ) and Otsuka Pharmaceutical Co, Ltd (Tokyo, Japan). Editorial support for the preparation of this article was provided by Ogilvy Healthworld Medical Education." Conflicts of interest: "this study was supported by Bristol-Myers Squibb (Princeton, NJ) and Otsuka Pharmaceutical Co., Ltd. (Tokyo, Japan). Editorial support for the preparation of this article was provided by Ogilvy Healthworld Medical Education". "Drs Marcus, Owen, Kamen, and Manos are with Bristol-Myers Squibb; Drs McQuade and Carson are with Otsuka Pharmaceutical Developmental and Commercialization and Dr Aman is with Ohio State University". Trial registry" not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided, only that double-blinding occurred
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not provided, only that double-blinding occurred
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for and details recorded on www.clinicaltrials.gov Analyses were based on LOCF. LTFU 5 mg/day aripiprazole: AE (5), withdrew consent (2), LTFU (1), poor/ noncompliance (1)
Selective reporting (reporting bias)	High risk	Response defined as a ≥ 25% reduction from baseline to endpoint in the ABC-I Subscale score, and a CGI-I score of 1 or 2 at endpoint was not reported
Other bias	Unclear risk	The proportion of participants who were moderately ill (compared to, markedly, severely and extremely) was 25% lower in the aripiprazole 10 mg/day group compared to the placebo group.

McCracken 2002

Study characteristics	
Methods	Parallel trial of risperidone versus placebo
Participants	Inclusion criteria: • age 5-17 years • weight ≥ 15 kg • a mental age of ≥ 18 months • diagnosis of ASD according to the DSM-4 criteria with 1 or a combination of tantrums, aggression or self-injurious behaviour • no seizures for at least 6 months prior to the trial • withdrawn from ineffective psychotropic medication for the treatment of aggression, tantrums, or self-injurious behaviour 7-28 days prior to enrolment • free of all psychotropic drugs at least 2 weeks prior to randomisation (4 weeks for antipsychotics and fluoxetine) • ABC-I score of ≥ 18 at baseline Exclusion criteria: • any serious medical disorders or other psychiatric disorders requiring medications • receiving psychotropic drugs that were considered effective for the treatment of aggression, tantrums or self-injurious behaviour. Location/setting: University of California at Los Angeles, Ohio State University, Indiana University, Yale University, and the Kennedy Krieger Institute at Johns Hopkins University, USA Sample size: 101: 49 risperidone group, 51 placebo Number of withdrawals/dropouts: risperidone 3/49; placebo 18/52 (risperidone: 3 lack of efficacy; placebo: severe headache and seizure (1); withdrawal of consent (1); LTFU (3); non-compliance (1); lack of efficacy (12)). Gender: 82 boys, 19 girls Mean age: 8.6 years IQ: 13/101 had profound intellectual disability, 18/101 had severe intellectual disability, 18/101 had a moderate intellectual disability, 25/101 had a mild intellectual disability Baseline ABC-I or other BoC: ABC-I risperidone 26.2, placebo 25.5 Concomitant medications: participants had to be free of all psychotropic drugs at least 2 weeks prior to randomisation (4 weeks for antipsychotics and fluoxetine). History of previous medications: antipsychotics 5/101, SSRIs 16/101, stimulant 21/101, alpha-2-agonist 16/101
Interventions	Risperidone for 8 weeks: children who weigh 20-45 kg commenced on 0.5 mg at bedtime, increased to 0.5 mg twice daily on day 4. The dose was gradually increased in 0.5 mg increments of 2.5 mg/day (1.0 mg in the morning and 1.5 mg at bedtime) by day 29. Children weighing > 45 kg had a maximum dose of 1.5 mg in the morning and 2.0 mg at bedtime. Children weighing < 20 kg were given an initial dose of 0.25 mg/ day. Dose increases could be delayed because of adverse effects or significant improvement on lower doses. No dose increases after day 29. Mean daily dose of 1.8 mg/day or maximum daily dose of 2.5 mg/day children < 45 kg or 3.5 mg/day children > 45 kg Placebo for 8 weeks: placebo equivalent of 2.4 ± 0.6 mg/day
Outcomes	Primary outcomes

McCracken 2002 *(Continued)*

- Irritability (ABC-I) (Aman 1985)
- Improvement in irritability (defined as a minimum 25% improvement in ABC-Irritability scores)
- Relapse in Irritability (defined as a minimum 25% increase, or deterioration in ABC-Irritability scores)
- AEs

Secondary outcomes: none reported

Timing of outcome assessments: weekly for 8 weeks

Notes	Study start date: June 1999 Study end date: April 2001 Source of funding: "supported by contracts from the National Institute of Mental Health (N01MH70009), to Dr Scahill; N01MH70010 to Dr McCracken; N01MH70001 to Dr McDougle ; and N01MH80011 to Dr Aman, General Clinical Research Centre grants from the National Institute of Health (M01 RR00750 to Indiana University; M01 RR00052 to Johns Hopkins University; M01 RR00034 to Ohio State University; and M01 RR06022 to Yale University, and a grant from the Korczak Foundation to Dr Scahill". Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details
Allocation concealment (selection bias)	Unclear risk	Insufficient details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Each child was seen weekly by two clinicians who were unaware of the treatment assignment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Each child was seen weekly by two clinicians who were unaware of the treatment assignment: a primary clinician, who reviewed side effects and adjusted the dose of medication, and a clinical evaluator, who assessed the response to treatment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	LTFU risperidone: treatment ineffective (3) 46 of original 49 in risperidone group completed trial (3 withdrew "because the study was not effective") 18 children in placebo group withdrew: severe headaches and a seizure (1); withdrawal of consent (1); nonadherence (1); LTFU (3) and lack of efficacy (12) 4 were identified as having an ABC-I that fell below the ABC-I score of 18 and were included in theITT analysis. Authors noted that zero participants withdrew from study due to AEs. An ITT analysis was used, and all participants were included in the analysis.
Selective reporting (reporting bias)	High risk	Sedation not reported as an AE
Other bias	Low risk	No concerns

McDougle 1996

Study characteristics	
Methods	Parallel trial of fluvoxamine versus placebo
Participants	Inclusion criteria: • ASD diagnosis based on DSM-III and ICD-10 • "moderate" symptoms as defined by global severity of illness on CGI • psychotropic drug-free for at least 6 weeks before the start of the trial Exclusion criteria: • met DSM-III-R criteria for schizophrenia or had psychotic symptoms • abused illicit substances within the previous 6 months • notable medical condition, including seizure disorder • women with positive serum pregnancy test results Location/setting: a neuroscience research centre at the Connecticut Mental Health Center, New Haven, and the Adult Pervasive Developmental Disorders Clinic at the same neuroscience research centre, USA Sample size: fluvoxamine 15; placebo 15 Number of withdrawals/dropouts: none reported Gender: 27 men, 3 women Mean age: 30.1 years IQ: not reported Baseline ABC-I or other BoC: aggression (Brown Aggression Scale; Brown 1979) fluvoxamine 9.3, placebo 12.3 Concomitant medications: participants were required to be psychotropic drug-free before the trial History of previous medications: not reported
Interventions	Intervention (fluvoxamine for 12 weeks): started at 50 mg every night. "The dosage could then be increased by 50 mg daily every 3 or 4 days to a maximum dosage of 300 mg/day, as tolerated, if maximal clinical response was not obtained. Thus, the maximum dosage of fluvoxamine was attained within 3 weeks, and patients received this dose for at least 9 weeks." maximum 300 mg/day Comparator (placebo for 12 weeks): equivalent placebo, "lactose in identical-looking tablets"
Outcomes	Primary outcomes: • AEs • aggression (measured using the Brown Aggression Scale (Brown 1979)) Secondary outcomes: none reported Timing of outcome assessments: baseline, 4, 8 and 12 weeks
Notes	Study start date: September 1990 Study end date: December 1993 Source of funding: "this work was supported by a National Alliance for Research on Schizophrenia and Depression Young Investigator Award (Dr McDougle), the State of Connecticut Department of Mental Health and Addiction Services, The Korczak Foundation for Autism and Related Disorders, and

McDougle 1996 *(Continued)*

grants MOI RR06022-33, P50 MH30929-18, HD 0300827, and POI MH25642from the National Institutes of Health, Bethesda, Md. Fluvoxamine and financial support were provided by Solvay Pharmaceuticals, Marietta, Ga".

Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The prescribing psychiatrist (C.J.M.), the nurse (S.T.N.) who performed the behavioral ratings, the patients, and all family and other members of the patients' treatment teams were unaware of drug assignment"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The prescribing psychiatrist (C.J.M.), the nurse (S.T.N.) who performed the behavioral ratings, the patients, and all family and other members of the patients' treatment teams were unaware of drug assignment.". Apart from that it was not described how the outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for and included in the analysis. Quote: "All patients who complete at least two weeks of drug treatment will be included in the analysis. The final rating scores of any patient who terminates the study prematurely will be carried forward to the end of the study."
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	Unclear risk	No significant differences were seen in age, sex distribution, Autism Behavior Checklist scores, or full-scale IQ scores between the 2 groups.

McDougle 1998

Study characteristics

Methods	Parallel trial of risperidone versus placebo
Participants	Inclusion criteria: • met DSM-4 criteria for PDD NOS or autistic disorder (autism) • aged 18-43 years • at least a "moderate" rating of symptoms according to CGI Scale; "a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) compulsion (repetitive behaviour) subscale score of greater than 10, a Self-injurious Behavior Questionnaire (SIB-Q) (Gualtieri 2002) score of 25 or greater, or a Ritvo-Freeman Real-life Rating Scale overall score of 0.20 or greater". • "Had not taken any psychotropic drugs for at least 4 weeks before the start of the trial". Exclusion criteria: • met "criteria for other DSM-4 Axis I or Axis II disorder other than mental retardation [intellectual disabilities]"

McDougle 1998 *(Continued)*

- "met DSM-4 criteria for schizophrenia or had psychotic symptoms or if a significant acute medical condition was identified"
- positive serum pregnancy test

Location/setting: all participants were evaluated and treated within the outpatient (24) and inpatient (7) divisions of the neuroscience research centre at the Connecticut Mental Health Centre, New Haven, USA

Sample size: risperidone 15, placebo 16

Number of withdrawals/dropouts: 7 withdrew: 3 from risperidone group (1 withdrew after 1 week due to "notable agitation"; 1 developed an "abnormal gait" after 4 weeks; and 1 withdrew "because of a lack of significant improvement in symptoms"); 4 from placebo group withdrew: 2 with PDD and 2 with autism withdrew "because of interfering agitation after 4 weeks"

Gender: risperidone 13 male, 2 female; placebo 9 male, 7 female

Mean age: 26.4 years

IQ: risperidone mean 55.5; placebo 52.9

Baseline ABC-I or other BoC: irritability (using the RFRLRS subscale 3) risperidone 1.02, placebo 0.78; SIB (Self-Injurious Behaviour Questionnaire) risperidone 47.8, placebo 24.2

Concomitant medications: participants could not have taken any psychotropic drugs for at least 4 weeks before the start of the trial.

History of previous medications: 24 had received psychotropic medications previously

Interventions	Risperidone for 12 weeks: risperidone was started at 1 mg every night. The dosage was then increased by 1 mg daily every 3-4 days to a maximum dosage of 10 mg/day. Patients received the maximum dose (based on tolerability) for at least 7 weeks. Mean dose of 2.9 mg/day Placebo for 12 weeks: placebo started at 1 mg every night. The dosage was then increased by 1 mg daily every 3-4 days to a maximum dosage of 10 mg/day. Patients received the maximum dose (based on tolerability) for at least 7 weeks.
Outcomes	Primary outcomes: • irritability, measured using the RFRLRS (Aman 1985) • self-injurious behaviour, measured using the Self-Injurious Behaviour Questionnaire (Gualtieri 2002) • adverse effects Secondary outcomes: none reported Timing of outcome assessments: baseline, weeks 4, 8 and 12
Notes	Study start date: June 1994 Study end date: February 1997 Source of funding: grants MH-30929 and HD-03008 from the Public Health Service, Bethesda Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly allocated according to a computer-generated list.

McDougle 1998 *(Continued)*

Allocation concealment (selection bias)	Low risk	Risperidone or placebo (lactose) in identical-appearing capsules
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The prescribing psychiatrist, the research nurse clinician who performed the behavioural ratings, the patients, and all family and other members of the patients' treatment teams were unaware of the drug assignment (blind).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The research nurse clinician who performed the behavioural ratings...were unaware of the drug assignment (blind)
Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF and ITT analysis used LTFU: risperidone (3), AEs (agitation) (1); developed abnormal gait (1); lack of efficacy (1)
Selective reporting (reporting bias)	Low risk	The measures were the CGI, the RFRLRS, Yale-Brown Obsessive Compulsive Scale and the Self-Injurious Behaviour Questionnaire. All scales were reported at both baseline and endpoint for both risperidone and placebo group. Sedation not reported as an AE
Other bias	Low risk	No concerns

Minshawi 2016

Study characteristics	
Methods	Parallel trial of D-cycloserine versus placebo
Participants	Inclusion criteria: • diagnosis of ASD through administration of of the ADI-R and clinical interview using the DSM-4 criteria for ASD, Asperger's disorder, or PDD-NOS • Participants with ASD were required to have an IQ > 7 on the Stanford-Binet 5th edition and a communication standard score > 70 on the Vineland Adaptive Behavior Scale 2nd edition. • Triad Social Skills Assessment (TSSA) score of ≤ 70% on both parent questionnaire and child assessment • significant social impairment as measured by a T score of ≥ 60 on the Social Responsiveness Scale (SRS) and CGI-S of at least four (moderately ill). • required to remain on stable psychotropic medication dosing targeting symptoms associated with ASD for a minimum of 2 weeks prior to randomisation Exclusion criteria: • participants with diagnoses of Rett's disorder or childhood integrative disorder • anyone who has recently had a significant change in their psychosocial interventions will not be eligible until this intervention has been stable for 90 days • participants exhibiting significant disruptive, aggressive, self-injurious, or sexually inappropriate behaviour • the presence of current DSM-4-TR psychiatric disorders that require alternative pharmacotherapy or different treatment such as psychotic disorders, or major affective disorders • participants with significant cardiac, hepatic, or renal disease, uncontrolled epilepsy or seizure disorders (seizures within the past 6 months) • pregnant women, or female patients of child-bearing age who do not agree to take birth control during the trial

Minshawi 2016 *(Continued)*

	Location/setting: "Indiana University School of Medicine and Cincinnati Children's Hospital Medical Center". Sample size: D-cycloserine 34; placebo 33 Number of withdrawals/dropouts: no dropouts postrandomisation Gender: D-cycloserine 28/34 male; placebo 27/33 male Mean age: D-cycloserine 8.4 years; placebo 8.3 years IQ: D-cycloserine 92.4; placebo 87.3 Baseline ABC-I or other BoC: treatment: ABC-I 11.06; placebo 12.67 Concomitant medications: antipsychotics 8/34, 8/33 placebo, alpha-2 agonist 6/34, 8/33, stimulants 14/34 and 11/33, sleep aids 9/34 and 7/33, mood stabilisers 1 and 2, glutamatergic modulators 1 in D-cycloserine group, other 3 and 1 History of previous medications: not reported
Interventions	D-cycloserine for 10 weeks: given at a 50 mg dose 30 min prior to weekly group social skills training over 10 weeks Placebo for 10 weeks: placebo pill (sugar pill) administered 30 min prior to each of the 10 social skills training sessions
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessments: baseline, week 6 and week 10 (endpoint)
Notes	Study start date: March 2010 Study end date: January 2014 Source of funding: "funding for this study was provided by the United States Department of Defense Award Number W81XWH-09-1-0091." Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Children with ASD were randomised to receive 10 weeks (10 doses) of D-cycloserine or placebo in a 1:1 ratio
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided
Blinding of outcome assessment (detection bias)	Unclear risk	No details on parents and teachers completing ABC questionnaire

Minshawi 2016 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts were reported and all 67 were included in the analysis.
Selective reporting (reporting bias)	Low risk	Baseline and endpoint data reported for all outcomes mentioned
Other bias	Low risk	No significant group differences, or pharmaceutical company funding

Miral 2008

Study characteristics	
Methods	Parallel trial of risperidone versus haloperidol
Participants	Inclusion criteria: • meet DSM-4 criteria for ASD • age 8–18 years • have parents' informed consent • agree to be followed-up • antianalgesics, antipyretics, decongestants and antibiotics were allowed during the trial • participants with extrapyramidal symptoms could use anticholinergics, but prophylactic use was discouraged Exclusion criteria: • epilepsy • had a concomitant neuropsychiatric illness (such as ADHD, Tourette's syndrome etc), or demonstrated a psychotic disorder or symptoms, or had other PDDs • benzodiazapines and other sedatives were not allowed Location/setting: Turkey Sample size: 30 (15 in each group) Number of withdrawals/dropouts: 2 in risperidone group excluded from final analysis from the week 12 evaluation because of the lack of efficacy data Gender: risperidone 11/15 male; haloperidol 13/15 male Mean age: risperidone 10 years, haloperidol 10.9 years IQ: not reported Baseline ABC-I or other BoC: irritability (using the RFRLRS) risperidone 1.09, haloperidol 1.05 Concomitant medications: details not provided History of previous medications: details not provided
Interventions	Intervention (risperidone) for 12 weeks: risperidone was initiated at a dosage of 0.01 mg/kg/day and the dosage was increased to 0.04 mg/kg/day until the end of the 2nd week. If tolerated, then it was increased to a maximum dosage of 0.08 mg/kg/day. Mean daily dose 2.6 mg/day or maximum 0.08 mg/kg; haloperidol mean dose 2.6 mg/day

Miral 2008 *(Continued)*

	Comparator (haloperidol) for 12 weeks: haloperidol was initiated at a dosage of 0.01 mg/kg/day and the dosage was increased to 0.04 mg/kg/day until the end of the 2nd week. If tolerated, then it was increased to a maximum dosage of 0.08 mg/kg/day.
Outcomes	Primary outcomes: • irritability, measured using the RFRLRS - Affectual Responses scale (Freeman 1986) • AEs Secondary outcomes: none reported Timing of outcome assessments: baseline, weeks 2, 4, 8 and 12
Notes	Study start date: not reported Study end date: not reported Source of funding: "this research was supported in part by Janssen and Cilag Drug company". Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding not discussed Quote: "two experienced clinicians performed all of the measures"
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "two subjects who were being administered risperidone were excluded from our final analysis from the week 12 evaluation because of lack of efficacy data" LTFU: 2 in risperidone group were excluded from analysis due to lack of efficacy data ITT analysis or LOCF not noted by study authors
Selective reporting (reporting bias)	High risk	RFRLRS subscores and weight were outlined for both baseline and endpoint, as well as other outcomes reported in the paper. However, the CGI baseline scores were not reported despite being a primary outcome measure.
Other bias	Unclear risk	The research was supported in part by Janssen and Cilag Drug Company.

Moazen-Zadeh 2018

Study characteristics

Moazen-Zadeh 2018 *(Continued)*

Methods	10-week parallel trial of simvastatin versus placebo
Participants	Inclusion criteria: • male and female • aged 4-12 years • diagnosis of AD based on the DSM-4-TR criteria • ABC-I subscale score of at least 12 Exclusion criteria: • concomitant DSM-4 axis I or II disorders • active medical conditions • severe intellectual disability making the diagnosis inconclusive based on prior records and clinical judgement • seizure disorders • history of alcohol/drug abuse • tardive dyskinesia, history of antipsychotic medication or behaviour therapy within the past 6 months before the trial. Location/setting: speciality outpatient autism clinic at Roozbeh Psychiatry Hospital, Iran Sample size: 35 in each group Number of withdrawals/dropouts: 2 from each group (simvastatin: 1 no longer met criteria, 1 withdrew consent; placebo: 2 withdrew consent) Gender: 53 male, 13 female Mean age: simvastatin 7.06 years (2.33); placebo 7.61 (2.74) years IQ: details not provided Baseline ABC-I or other BoC: ABC-I simvastatin 20.97 (5.37); placebo 19.97 (7.24) Concomitant medications: children did not have a history of psychotropic drug use History of previous medications: children did not have a history of psychotropic drug use
Interventions	Intervention (simvastatin + risperidone): risperidone (Risperdal; Janssen Pharmaceuticals, Belgium) plus simvastatin (Osveh, Iran) for 10 weeks. Risperidone starting dose was 0.5 mg/day in 0.5 mg tablets, and in the absence of clinically significant AEs it was increased by 0.5 mg per week to the target dose of 1 mg/day for children weighing < 20 kg and 2 mg/day for those weighing at least 20 kg. Simvastatin was administered in the form of a 20 mg tablet/day for children < 10 years of age and a 40 mg tablet per day for those at least 10 years of age. Comparator (placebo + risperidone): risperidone (Risperdal; Janssen Pharmaceuticals, Belgium) plus placebo for 10 weeks. Risperidone starting dose was 0.5 mg/day in 0.5 mg tablets, and in the absence of clinically significant AEs it was increased by 0.5 mg/week to the target dose of 1 mg/day for children weighing < 20 kg and 2 mg/day for those weighing at least 20 kg. Placebo was administered in the form of a 20 mg tablet/day for children < 10 years of age and a 40 mg tablet per day for those at least 10 years of age.
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: tolerability Timing of outcome assessments: baseline, weeks 5 and 10 (endpoint)

Moazen-Zadeh 2018 *(Continued)*

Notes	Study start date: February 2016 Study end date: December 2016 Funding: "This study was supported by a grant to Prof. Shahin Akhondzadeh (Grant number 30327) from Tehran University of Medical Sciences (TUMS)" Conflicts of interest: "No competing financial interests exist" Trial registry: IRCT201602041556N86

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised random number generator
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Simvastatin and placebo tablets were identical in shape, size, texture, colour, and taste, and they were dispensed in identical containers by an investigational drug pharmacist. Quote: "During the trial, the physicians, other healthcare personnel, participants, and parents were blinded to treatment assignments."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "During the trial, the physicians, other healthcare personnel, participants, and parents were blinded to treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No further statistical methods such as data imputation or ITT analysis were conducted for participants who were lost to follow-up or dropped out.
Selective reporting (reporting bias)	Low risk	All outcomes on the trial registry were reported in the paper.
Other bias	High risk	• The contact author is also on the ethics committee at the university funding the study. • The contact author is a peer-reviewer for one of the journals in which some of their studies are published.

Mohammadi 2013

Study characteristics

Methods	Parallel trial of amantadine + risperidone versus placebo + risperidone
Participants	Inclusion criteria: • outpatients aged 4-12 years • diagnosis of autism based on DSM-4, score of ≥ 12 ABC-I subscale at screening/baseline, • "presenting with chief complaint of severely disruptive symptoms related to autistic disorder so that risperidone was indicated as a medical intervention". Exclusion criteria:

Mohammadi 2013 *(Continued)*

- other diagnoses on Axis I or II except for intellectual disability, severe intellectual disability, which makes the diagnosis of autism inconclusive (based on clinical judgement of the child psychiatrist)
- any significant active medical problem including hepatic diseases as well as history of seizure and allergy to amantadine or risperidone
- received any psychotropic medication within 6 weeks before enrolment

Location/setting: a psychiatric academic hospital affiliated with Tehran University of Medical Sciences, Iran

Sample size: 40 (20 in each group)

Number of withdrawals/dropouts: 1 participant in the risperidone plus placebo group discontinued after week 5.

Gender: amantadine 16/20 boys; placebo 17/20 boys

Mean age: amantadine 6.4 years; placebo 7.1 years

IQ: not reported

Baseline ABC-I or other BoC: ABC-I amantadine group 20; ABC-I placebo 20.9

Concomitant medications: not reported

History of previous medications: not reported

Interventions	Amantadine + risperidone for 10 weeks: amantadine was given twice a day at 100 mg/d for children < 30 kg, and 150 mg/d for those ≥ 30 kg. Risperidone was started at 0.5 mg/day, and titrated up to 2.0 mg/day in a 0.5 mg/week rate if there were no complications. Placebo + risperidone for 10 weeks: risperidone was started at 0.5 mg/day, and titrated up to 2.0 mg/day in a 0.5 mg/week rate if there were no complications. Placebo was identical in appearance (shape, size, colour, and taste) and dispensed by investigational drug pharmacist, alongside risperidone, which started at 0.5 mg/day, and was titrated up to 2.0 mg/day in a 0.5 mg/week rate if there were no complications.
Outcomes	Primary outcomes: • irritability, measured using the ABC-Irritability subscale (Aman 1985) • AEs Secondary outcomes: not reported Timing of outcome assessments: baseline, 5 weeks, 10 weeks (endpoint)
Notes	Study start date: June 2011 Study end date: May 2012 Source of funding: supported by a grant from Tehran University of Medical Sciences (grant 10797) Conflicts of interest: "no conflict of interest exists for any of the authors associated with the manuscript and there was no source of extra-institutional commercial funding".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was accomplished using a computerised random number generator in a 1:1 ratio and blocks of 4

Mohammadi 2013 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "treatment allocation was concealed from the patients and the rating psychiatrists using sequentially numbered, opaque, sealed, and stapled envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Separate persons were responsible for random allocation and rating of the patients. The patients, the psychiatrists who referred them, the clinician who assessed the patients and prescribed the drugs, and the statistician were blind to the allocations."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The patients, the psychiatrists who referred them, the clinician who assessed the patients and prescribed the drugs, and the statistician were blind to the allocations."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All analyses were based on the ITT sample and were performed using LOCF procedure on participants with at least 1 post-baseline visit.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the trial protocol on the Iranian Registry of Clinical trials were reported in the paper.
Other bias	High risk	• The contact author is also on the ethics committee at the university funding the study. • The contact author is a peer-reviewer for one of the journals in which some of their studies are published.

Montazmenesh 2020

Study characteristics	
Methods	10-week parallel trial of sulforaphane versus placebo
Participants	Inclusion criteria: • children aged 4–12 years • probable autistic signs and symptoms and meeting the DSM-5 criteria • 2 expert paediatric psychiatrists confirmed the diagnosis of ASD based on the children's behavioural examination and semi-structured interviews with the caregivers Exclusion criteria: • presentation at baseline not severe enough to be considered for risperidone treatment • concurrent prominent psychiatric disorder • pre-existing medical conditions (in particular epileptic disorders and febrile seizures) • intellectual disability (IQ < 70) • history of drug or alcohol abuse • history of tardive dyskinesia • history of taking antipsychotic medication within 6 months prior to enrollment • drug-free for less than 6 months Location/setting: autism clinic in the children's outpatient clinic of Roozbeh Hospital (Iran) Sample size: sulforaphane group (34), placebo group (34) Number of withdrawals/dropouts: sulforaphane group (4), 4 discontinued intervention; placebo group (4), 4 discontinued intervention

Montazmenesh 2020 *(Continued)*

	Mean age: sulforaphane 6.87 years (2.06), placebo 7.67 (2.35) Gender: 40 male, 20 female IQ: details not provided Baseline ABC-I or other BoC: sulforaphane ABC-I 22.50 (4.89); placebo 21.30 (6.13) Concomitant medications: only children who had been drug-free for at least 6 months were included. No other concomitant intervention or medication was permitted during the trial History of previous medications: details not provided
Interventions	Sulforaphane + risperidone: participants in both groups received risperidone in a similar manner. The starting daily dose of risperidone was 0.25 mg in children weighing < 20 kg and 0.5 mg in children weighing ≥ 20 kg. The dosage was increased stepwise by 0.5 mg weekly up to a maximum dose of 1 mg for children weighing < 20 kg, 2.5 mg for those weighing 20–45 kg, and 3.5 mg for those weighing > 45 kg. Sulforaphane (1-isothiocyanato-4-methylsulfinylbutane; ACER, Tehran, Iran) was prescribed at 50 µmol and 100 µmol (approximately 10 mg and 20 mg) per day for children weighing < 45 kg and 45–90 kg, respectively. Placebo + risperidone: participants in both groups received risperidone in a similar manner. The starting daily dose of risperidone was 0.25 mg in children weighing < 20 kg and 0.5 mg in children weighing ≥ 20 kg. The dosage was increased stepwise by 0.5 mg weekly up to a maximum dose of 1 mg for children weighing < 20 kg, 2.5 mg for those weighing 20–45 kg, and 3.5 mg for those weighing > 45 kg. The placebo group received placebo capsule.
Outcomes	Primary outcomes: • irritability measured using the ABC-Irritability (Aman 1985) • AEs Secondary outcomes: tolerability
Notes	Study start date: April 2018 Study end date: November 2019 Funding: "This study was funded by Tehran University of Medical Sciences and Health Services (Grant number 37048)" Conflicts of interest: "The authors declare no conflict of interest" Trial registry: IRCT20090117001556N107

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation of the treatment groups using block randomisation (with blocks of size 4)
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes were unveiled at the study end-point for statistical analysis.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Sealed opaque envelopes were unveiled at the study end-point for statistical analysis. "Randomizations, drug administration, rating, data entry, and statistical analysis were implemented by separate individuals."

Montazmenesh 2020 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Randomizations, drug administration, rating, data entry, and statistical analysis were implemented by separate individuals. Placebo capsules were identical to sulforaphane based on shape, size, color, and taste."
Incomplete outcome data (attrition bias) All outcomes	Low risk	~12% attrition
Selective reporting (reporting bias)	High risk	CARS is a primary outcome in trial registration but not in paper
Other bias	High risk	• The contact author is also on the ethics committee at the university funding the study. • The contact author is a peer-reviewer for one of the journals in which some of their studies are published.

Mouti 2014

Study characteristics	
Methods	Parallel study of fluoxetine versus placebo
Participants	Inclusion criteria: • aged 7.5-18 years • met criteria for an ASD based on the DSM-4 or the ICD-10 criteria • a score of ≥ 6 on the total score of the CYBOCS at the time of screening. Exclusion criteria: • any psychotropic medication (including typical and atypical anti-psychotics, mood stabilisers, anti-depressants, anti-anxiolytics and stimulant medication including atomoxetine, monoamine oxidase inhibitor or pimozide, and St John's wort) or any use of such medication in the 3 months prior to the commencement of the trial • concomitant administration of drugs that interact with the metabolism of fluoxetine (e.g. phenytoin and carbamazepine) • co-morbid significant medical conditions (e.g. unstable seizure disorder, cardiac disease, liver failure or renal failure) • female participants of childbearing potential require a urine pregnancy test to exclude pregnancy Location/setting: 3 tertiary hospitals in Australia Sample size: 146 participants Number of withdrawals/dropouts: 31 in fluoxetine, 21 in placebo dropped out or did not complete treatment. Mean age: 11.2 years Gender: 124 boys, 22 girls IQ: 46/146 had an intellectual disability Baseline ABC-I or other BoC: fluoxetine ABC-I 18.57; placebo 17.87 Concomitant medications: 62/146 were on concurrent medications and a further 2 were receiving stimulant medications

Mouti 2014 *(Continued)*

	History of previous medications:details not provided
Interventions	Fluoxetine for 16 weeks: commenced at 4 or 8 mg/day for the first week depending on weight and then titrated to a maximum of 20 mg/day for children weighing < 40 kg or 30 mg/day if ≥ 40 kg Placebo for 16 weeks: equivalent placebo
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • self-injurious behavior, measured using the Repetitive Behavior Scale (Bodfish 2000) • AEs Secondary outcomes: none reported Timing of outcome assessments: AEs assessed weekly and other primary outcomes at baseline and endpoint
Notes	Study start date: November 2010 Study end date: August 2017 Source of funding: "Drs Reddihough and Lee and Ms Orsini report receiving grants from NHMRC and the Royal Children's Hospital Foundation during the conduct of the study. Dr Hazell reports that his employer has received payment from Shire for speaker's fees. Dr Whitehouse reports receiving grants from NHMRC during the conduct of the study." Conflicts of interest: none declared Comment: Study authors were contacted for further information and they emailed a separate published paper providing all the details (Reddinhough).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Low risk	Quote: "The randomization schedule was provided to the clinical trials pharmacist at each site, who arranged a sequential stock of trial medication for each stratum, labeled with only the study number, strata, and instructions for use"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "This schedule remained confidential throughout the study. The independent statistician retained a copy of the master randomization schedule to check for any discrepancies. Participants and their families, clinicians, and the research team assessing outcomes remained blind to the randomization schedule throughout the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "This schedule remained confidential throughout the study. The independent statistician retained a copy of the master randomization schedule to check for any discrepancies. Participants and their families, clinicians, and the research team assessing outcomes remained blind to the randomization schedule throughout the study."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	A large number from each group withdrew from the trial (31 fluoxetine and 21 placebo) and "Twenty-five percent of the participants did not provide data on the primary outcome (n = 21 and n = 16 in the fluoxetine and placebo groups, respectively) however where outcome data was reported at least once an ITT analysis was used. There was a chance baseline imbalance in some of the key

Mouti 2014 *(Continued)*

		behavioral measures of ASDs, indicating that the placebo group had a comparatively more severe behavioral phenotype than the fluoxetine group". LTFU fluoxetine group: 31 discontinued (20 parent or caregiver withdrew consent; 5 AEs; 2 clinician decisions to discontinue; 1 used other ineligible drugs; and 3 others withdrew for personal reasons) LTFU placebo group: 21 discontinued (12 parent or caregiver withdrew; 4 AEs; 2 clinician decisions to discontinue; 3 others withdrew for personal reasons)
Selective reporting (reporting bias)	Unclear risk	All scales mentioned in the protocol were reported in the final paper, however the subscales of the Repetitive Behaviour Scale were not reported, only the total score however, more information was provided by the study authors.
Other bias	High risk	Quote: "The active and placebo medication will be produced by Richard Stenlake Chemists (Bondi Junction, Australia)". "PH and MK have received payment from Eli Lilly (the manufacturer of fluoxetine) for participation in consultancies, advisory boards, speaker's bureau, and the conduct of clinical trials"

Munesue 2016

Study characteristics	
Methods	Cross-over trial of oxytocin versus placebo
Participants	Inclusion criteria: • ASD diagnosis based on DSM-4 criteria • male or female outpatients aged 15-45 years • CGI–S ≥ 4 (moderately ill) • on stable pharmacologic and nonpharmacologic treatments for at least 3 months • normal physical examination • full-scale IQ > 70 • sexually active women had to be on 2 barrier methods of contraception and no hormonal birth control Exclusion criteria: • prematurity • primary axis 1 disorders such as bipolar disorder, psychosis, post-traumatic stress disorder, schizophrenia, or major depressive disorder/anxiety disorder • history of significant neurological disease including, but not limited to, unstable epilepsy disorder, known genetic syndromes, or known abnormal brain magnetic resonance imaging, or history of malignancy or any significant haematological, endocrine, cardiovascular (including any rhythm disorder), respiratory, renal, hepatic, or gastrointestinal disease • unable to tolerate venipuncture procedures Location/setting: outpatient setting of the Department of Child and Adolescent Psychiatry of Kanazawa University Hospital in Kanazawa, Japan Sample size: 29, 15 oxytocin-placebo; 14 placebo-oxytocin Number of withdrawals/dropouts: none reported Gender: all participants were male Mean age: range 15-40 years IQ: oxytocin first: 24.9; placebo first: 37.5

Munesue 2016 *(Continued)*

	Baseline ABC-I or other BoC: ABC-I oxytocin first: 11.9; placebo first: 17.4 Concomitant medications: not reported History of previous medications: 22 participants (75.9%) received psychotropic medications at stable doses during the 3 weeks prior to randomisation.
Interventions	Intervention (oxytocin) for 6 weeks: oxytocin dosage was 8 IU twice-daily for 6 weeks (16 IU per day). Comparator (placebo) for 6 weeks: equivalent placebo
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: WHOQOL (WHO 1998) Timing of outcome assessments: every 2 weeks
Notes	Study start date: February 2012 Study end date: October 2013 Source of funding: "this work was supported by the Strategic Research Program for Brain Sciences from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (MEXT) and from the Japan Agency for Medical Research and Development and also by the Industry-Academia Collaborative R&D Programs [Center of Innovation (COI) Program] from MEXT." Conflicts of interest: none declared Trial registry: UMIN000007250

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a computer generated randomization table was created by the research pharmacist and used to randomise participants"
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All efficacy assessments were carried out by an independent evaluator who was blinded to both side effects and group assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were analysed using an ITT analysis and baseline and endpoint QoL scores were recorded.
Selective reporting (reporting bias)	Low risk	The primary and secondary outcomes of interest were recorded on clinicaltrials.gov and all results were provided.

Munesue 2016 *(Continued)*

Other bias	Unclear risk	No significant differences in gender, race, age. Perhaps a slight difference in IQ - oxytocin group 99 (22) and placebo 118 (19) however, several study authors are connected to many pharmaceutical companies

NCT00183339

Study characteristics	
Methods	12-month parallel trial of fluoxetine versus placebo
Participants	Inclusion criteria: diagnosis of autism Exclusion criteria: • diagnosis of Asperger's Syndrome, Rett Syndrome, Childhood Disintegrative Disorder, or PDDNOS' • if SSRIs are not medically advisable, taking ongoing medications (except for diphenhydramine, clonidine, or melatonin for sleep) • use of stimulants within the 5 days prior to enrolment • recent use of psychotropic medications in the 14 days prior to commencing the trial • recent commencement of behavioural, dietary or other treatment for autism in the month prior to commencing the trial Location/setting: details not provided on clinical registry Sample size: 18 Number of withdrawals/dropouts: 4/8; 6/10 (reasons not provided) Mean age: 44 months Gender: details not provided IQ: details not provided Baseline ABC-I or other BoC: baseline ABC-I not provided Concomitant medications: details not provided History of previous medications: details not provided
Interventions	Fluoxetine: "between 2 mg per day and 20 mg per day of liquid fluoxetine will be given in the morning using a flexible dosing strategy, following a 36-week dose titration schedule" Placebo: "between 0.5ml per day and 5ml per day of liquid placebo will be given in the morning using a flexible dosing strategy, following a 36-week dose titration schedule"
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: tolerability
Notes	Study start date: September 2005 Study end date: March 2014 Funding: details not provided

NCT00183339 *(Continued)*

	Conflicts of interest: details not provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided apart from, "Masking: quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not provided apart from, "Masking: quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)"
Incomplete outcome data (attrition bias) All outcomes	High risk	This study primarily aimed to look at rate of attrition and recruitment but doesn't provide data on reason for dropout.
Selective reporting (reporting bias)	Unclear risk	Primary outcome is rate of recruitment however without a protocol we can't be sure.
Other bias	Unclear risk	Paper has not been published as yet, so greater details have not been provided.

NCT00198107

Study characteristics	
Methods	48-week parallel trial of aripiprazole versus placebo
Participants	Inclusion criteria: • aged 5-17 years • weight ≥ 15 kg • meet the DSM-4 criteria for autism • free of psychotropic medications for at least 2 weeks prior to baseline • ABC-I of at least 18 at baseline • CGI-S score of at least 4 • mental age of at least 18 months Exclusion criteria: • Asperger's syndrome, Rett's disorder, childhood disintegrative disorder, Fragile X, tuberous sclerosis, any other PDD, schizophrenia, psychotic disorder, or bipolar disorder • any other significant medical condition such as heart, kidney, liver or lung disease, or seizure disorders • pregnant • previous treatment with aripiprazole or hypersensitivity to aripiprazole

NCT00198107 *(Continued)*

	Location/setting: USA (Riley Hospital for Children, Christian Sarkine Autism Treatment Center, Indiana University School of Medicine) Sample size: 81 randomised, 40 aripiprazole, 41 placebo Mean IQ: details not provided Mean age: details not provided Gender: 4/38 female in aripiprazole group, 7/40 female in placebo group Reasons for dropouts: 6 from placebo group discontinued, AE (1), lack of efficacy (2), LTFU (2), doctor decision (1); 3 from aripiprazole group discontinued, AE (1), LTFU (1), withdrawal by participant (1) Baseline ABC-I or other BoC scale: details not provided Concomitant medications: details not provided Previous medications: details not provided
Interventions	Intervention (aripiprazole) for 8 weeks: participants ≤ 49 kg will receive maximum dose of 10 mg/day of aripiprazole over 8 weeks. Participants weighing ≥ 50 kg will receive a maximum dose of 15 mg/day aripiprazole over 8 weeks. Comparator (placebo) for 8 weeks: matching placebo pill for 8 weeks
Outcomes	Primary outcomes: • ABC-Irritability (Aman 1985) • AEs Secondary outcomes: tolerability Timing of outcome assessments: ABC-I measured in weeks 1, 2, 3, 4, 6, and 8 (endpoint)
Notes	Study start date: September 2005 Study end date: April 2019 Funding: details not provided Conflicts of interest: details not provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Only details provided were on the trials registry, "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Only details provided were on the trials registry, "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)"

NCT00198107 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout < 15%, reasons reported
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	Not stated

NCT00468130

Study characteristics	
Methods	8-week parallel trial of aripiprazole versus placebo
Participants	Inclusion criteria: • meets DSM-4 for ASD • is an outpatient • 5-17 years of age • parents consent to participate in the trial Exclusion criteria: • diagnosed with a psychotic disorder • history of prior treatment of aripiprazole ≥ 5 mg/day • history of diabetes • significant medical conditions • at risk of self-injury • pregnant or breastfeeding Setting/location: the USA Sample size: 15 in total Number and reason for dropouts: 2 in each group dropped out, 3 due to AEs and 1 withdrew Mean age: 12.4 years Gender: 2 female, 11 male Mean IQ: details not provided Previous or current medications: details not provided
Interventions	Intervention (aripiprazole): participants weighing < 40 kg will receive a maximum of 10 mg/day of aripiprazole, and a maximum of 20 mg/day for children ≥ 40 kg for 8 weeks Comparator (placebo): equivalent placebo (sugar pills) for 8 weeks
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessments: every second week

NCT00468130 *(Continued)*

Notes	Source of funding: University of Medicine and Dentistry of New Jersey Conflicts of interest: unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Apart from, "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)", no other details provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Apart from "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)", no other details provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	8-week data appear to be reported for all participants, but study authors note 2 dropouts due to AEs in treatment group (i.e. nearly 30% dropout). Unclear if outcome data are really complete.
Selective reporting (reporting bias)	Unclear risk	Protocol is available and all prespecified outcomes of interest reported in the prespecified way
Other bias	High risk	The baseline ABC-I scores were twice that in the intervention group compared to placebo.

NCT00498173

Study characteristics

Methods	8-week parallel trial of atomoxetine versus placebo
Participants	Inclusion criteria: • 5-15 years of age • diagnosis of ASD • significant hyperactivity, inattention, or impulsivity as determined by a score on an investigator-administered ADHD Rating Scale (ADHDRS)-Home Version that is at least 1.5 standard deviations above the mean for age and sex • parent/caregiver's primary complaint about the child is inattention, hyperactivity, and/or impulsivity ("ADHD" symptoms) • symptoms present for 6 months prior to study entry • psychotropic drug-free for at least 2 weeks prior to starting study medication (or 5 weeks for fluoxetine (Prozac)) Exclusion criteria: • weighs < 15 kg

NCT00498173 *(Continued)*

- any another psychiatric disorder that may require a different treatment, including psychotic disorders, major affective disorders, obsessive compulsive disorder, panic disorder, or substance-related disorders
- clinical diagnosis of Rett's disorder or childhood disintegrative disorder
- presence of extreme aggression or self-injury
- currently taking an effective psychotropic drug
- currently using other medications that may be unsafe to take with atomoxetine (e.g. potent CYP 2D6 inhibitors, intravenous albuterol, monoamine oxidase inhibitors)
- inability to swallow study medication
- presence of a medical condition that would make treatment with atomoxetine unsafe (e.g. unstable hypertension or cardiac disease, asthma requiring frequent treatment with albuterol, narrow angle glaucoma, pregnancy, etc.)
- mental age of < 18 months
- previous adequate trial of atomoxetine
- previous evidence of hypersensitivity or an allergic reaction to atomoxetine
- clinically significant abnormalities in laboratory measures indicating an undiagnosed medical condition as determined by the study physician in discussion with the participant's primary care physician
- clinically significant abnormalities on ECG as determined by a pediatric cardiologist
- pregnant
- initiation of a new psychosocial intervention within 90 days prior to starting study medication. Participants who have recently had a significant change in their psychosocial interventions will not be eligible until this intervention has been stable for 90 days in order to avoid confounding results of the study. Stable interventions (e.g. speech and occupational therapy) will be allowed to continue during the course of the study. Minor changes in ongoing treatment (e.g., missed therapy sessions due to holiday/vacation planned break in therapy due to school holidays) will not be considered significant

Location/setting: details not described

Mean IQ: details not described

Mean age: atomoxetine 9.3 years, placebo 8.4 years

Gender: 54 male, 6 female

Sample size: 60

Reasons for dropouts: no postbaseline ratings for 2 people in atomoxetine group and 1 in placebo group

Baseline ABC-I or other BoC scale: PedsQL atomoxetine 56.3 (18.8); placebo 60.5 (19.6)

Concomitant medications: atomoxetine (34.5%) were taking concomitant medications; placebo 41.9% were taking concomitant medications

Previous medications: details not provided

Interventions	Intervention (atomoxetine) for 8 weeks: available tablet strengths of atomoxetine: 5 mg, 10 mg, 25 mg, 40 mg. Week 1, participant takes 0.5 mg/kg/day; week 2, 0.8 mg/kg/day; week 3, 1.2 mg/kg/day. Potential exists for dose increase at week 4 to 1.8 mg/kg/day based on CGI improvement rating at week 4. Comparator (placebo) for 8 weeks: participants will receive blinded, matched placebo for 8 weeks. Dosage can be increased over the first 4 weeks of study participation and will then be held constant for the remainder of the 8-week trial. Placebo tablets dosages: 5 mg, 10 mg, 25 mg, 40 mg
Outcomes	Primary outcomes: • irritability using the ABC-I (Aman 1985) • AEs Secondary outcomes:

NCT00498173 *(Continued)*

	• acceptability/tolerability • QoL using PedsQL (WHO 1998) Timing of outcome assessments: details not described
Notes	Study start date: July 2007 Study end date: August 2017 Source of funding: details not provided Conflicts of interest: details not provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Sequential Assignment"
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Only details provided were on the trial registry, "Masking: triple (participant, care provider, investigator)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Only details provided were on the trial registry, "Masking: triple (participant, care provider, investigator)"
Incomplete outcome data (attrition bias) All outcomes	High risk	3 participants were not included in the analysis all due to "no post-baseline ratings"
Selective reporting (reporting bias)	Unclear risk	Only relying on Clinical trials reg
Other bias	Unclear risk	Difficult to know without a published paper and protocol

NCT01337687

Study characteristics

Methods	6-week parallel trial of oxytocin versus placebo
Participants	Inclusion criteria: • male or female • 18-55 years • meet DSM-4, ADOS, and ADI-R standards for ASD or Asperger's Syndrome • have a high, normal or near normal IQ • speak and understand English fluently Exclusion criteria:

NCT01337687 *(Continued)*

- born prior to 35 weeks' gestational age
- any psychiatric diagnosis apart from autism
- any neurological disorders
- known MRI/structural lesion of the brain
- pregnant
- taking psychoactive medication
- evidence or history of a significant haematological, endocrine, cardiovascular, respiratory, renal, hepatic or gastrointestinal disease
- planning to initiate or change medications during the trial
- unable to tolerate blood sampling

Location/setting: Montefiore Medical Center, USA

Mean IQ: not reported

Mean age: 33.2 years

Gender: 16 male, 3 female

Sample size: 19 in total

Reasons for dropouts/withdrawals: none reported

Baseline ABC-I or other BoC scale: not reported

Concomitant medications: details not provided

Previous medications: details not provided

Interventions	Intervention (oxytocin) for 6 weeks: administered intranasally twice a day via 1 x 12 unit puff to each nostril, totalling 48 IU a day Comparator (saline) for 6 weeks: administered intranasally twice a day via 1 puff per nostril, totalling 48 IU a day
Outcomes	Primary outcomes: AEs Secondary outcomes: none reported Timing of outcome assessments: baseline and 6 weeks (endpoint)
Notes	Study start date: April 2011 Study end date: February 2020 Funding: details not provided Conflicts of interest: details not provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided

NCT01337687 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Only details provided were on the trial registry, "Masking: quadruple (participant, care provider, investigator, outcomes assessor)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Only details provided were on the trial registry, "Masking: quadruple (participant, care provider, investigator, outcomes assessor)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout reported
Selective reporting (reporting bias)	Unclear risk	No peer-reviewed paper
Other bias	Low risk	No other sources of bias identified

NCT01624675

Study characteristics	
Methods	8-week parallel trial of risperidone versus placebo
Participants	Inclusion criteria: • 5-17 years of age • diagnosis of autism • CGI-S score of ≥ 4 and an ABC-I score of ≥ 18 • mental age > 18 months • participants must have parent or caregiver willing and able to observe and rate their behaviour • weigh ≥ 15 kg at time of screening Exclusion criteria: • patients with current or previous psychotic disorders, or "endocrine, metabolic, cardiac, hepatic, renal, or pulmonary disorder, or hypertension" • "Patients with known hypersensitivity to risperidone or paliperidone" Location/setting: 18 study centres in Japan Mean IQ: not reported Mean age: not reported Gender: not reported Sample size 39: risperidone (21); placebo (18) Reasons for dropouts/withdrawals: no dropouts reported Baseline ABC-I or other BoC scale: ABC-I risperidone 28.2 (6.36); placebo 27.5 (5.26) Concomitant medications: not reported Previous medications: not reported

NCT01624675 *(Continued)*

Interventions	Intervention (risperidone) for 8 weeks: participants weighing < 20 kg received risperidone 0.25 mg/day up to day 4. On day 4, dose was titrated in increments of 0.25 mg/day (up to a daily dose of 1.0 mg) at the regular study visit thereafter until week 8. Participants weighing ≥ 20 kg received risperidone 0.5 mg/day up to day 4. On day 4, dose was titrated in increments of 0.5 mg/day (up to a daily dose of 2.5 mg) at the regular visit thereafter until week 8. The maximum daily dose for participants weighing ≥ 45 kg was 3.0 mg. Comparator (placebo) for 8 weeks: matching placebo
Outcomes	Primary outcomes: • ABC-I (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessments: unclear
Notes	Study start date: June 2012 Study end date: October 2015 Funding: details not provided Conflicts of interest: details not provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information beyond double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information beyond double-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data available for all participants
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Outcomes matched those on clinical trials registry

NCT01908205

Study characteristics

NCT01908205 *(Continued)*

Methods	12-week trial of oxytocin versus placebo
Participants	Inclusion criteria: • Male or female outpatients, 10-17 years of age inclusive • Meet DSM-4, ADOS-2 and ADI-R 4 criteria for ASD • CGI-S score ≥ 4 (moderately ill) at screening • Verbal and Performance scale IQ ≥ 70 (both subtests of the Wechsler Abbreviated Scale of Intelligence (WASI-I or WASI-II ≥ 70) • if already receiving stable concomitant medications affecting behaviour, have continuous participation for 1 month prior to screening (6 weeks for fluoxetine) - no changes to existing or new medication during the study • if already receiving stable non-pharmacologic educational, behavioral, and/or dietary interventions, have continuous participation during the preceding 3 months prior to screening - no changes to existing or new medication during the study • normal physical examination and laboratory test results at screening. • able to speak and understand English • participant or parents/legal guardian provides written informed consent Exclusion criteria: • born prior to 35 weeks' gestational age • primary psychiatric diagnosis other than ASD • medical history of neurological disease, including, but not limited to, epilepsy/seizure disorder (except simple febrile seizures), movement disorder, tuberous sclerosis, fragile X, and any other known genetic syndromes, or known abnormal brain MRI/structural lesion • pregnant; if sexually active, female patients not on hormonal birth control or using at least two types of non-hormonal birth control • evidence or history of malignancy or any significant haematological, endocrine, cardiovascular (including any rhythm disorder), respiratory, renal, hepatic, or gastrointestinal disease • one or more of the following: HIV, Hepatitis B virus, Hepatitis C virus, haemophilia (bleeding problems, recent nose and brain injuries), abnormal blood pressure (hypotension or hypertension), drug abuse, immunity disorder or severe depression • currently taking oxytocin or have taken intranasal oxytocin in the past with no response • sensitivity to oxytocin or any components of its formulation • unable to tolerate venipuncture procedures for blood sampling • in foster care for whom the province/state is defined as a legal guardian Location/setting: Canada Mean IQ: not stated Mean age: all under 18 years Gender: 47 male, 7 female Sample size: 60 Reasons for dropouts/withdrawals: oxytocin 5, placebo 1 (2 LTFU, 4 withdrew) Baseline ABC-I or other BoC scale: not an outcome Concomitant medications: details not provided Previous medications: details not provided
Interventions	Intervention (oxytocin) for 12 weeks: the proposed dosing schedule is 0.4 IU/kg oxytocin, taken twice daily, for a maximum of 24 IUs per dose for 12 weeks

NCT01908205 *(Continued)*

	Comparator (placebo) for 12 weeks: the proposed dosing schedule is 0.4 IU/kg, taken twice daily, for a maximum of 24 IUs per dose for 12 weeks
Outcomes	Primary outcomes: AEs Secondary outcomes: • QoL (measured using the PedsQL) (WHO 1998) • tolerability Timing of outcome assessments: baseline and 12 weeks (endpoint)
Notes	Study start date: July 2013 Study end date: November 2020 Funding: details not provided Conflicts of interest: details not provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information. Quote: "Allocation: Randomized\"
Allocation concealment (selection bias)	Unclear risk	Insufficient information. Quote: "Allocation: Randomized"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Only details provided were on the trials registry Quote: "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Only details provided were on the trials registry Quote: "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)"
Incomplete outcome data (attrition bias) All outcomes	High risk	2 LTFU, and 4 withdrew - no further information
Selective reporting (reporting bias)	Unclear risk	Without a published paper or protocol it is difficult to know if all outcomes were reported
Other bias	Low risk	No other sources of bias identified

NCT01972074

Study characteristics

Methods	12-week trial of memantine versus placebo
Participants	Inclusion criteria: • children aged 8-17 years • diagnosis of ASD according to DSM-5 criteria,

NCT01972074 *(Continued)*

- at least moderate severity of social impairment, as measured by a total raw score of ≥ 85 on the parent/guardian-completed Social Responsiveness Scale, Second Edition (SRS-2) and a score of ≥ 4 on the clinician-administered ASD CGI-S scale

Exclusion criteria:

- IQ ≤ 70
- Current treatment with lamotrigine, amantadine, N-acetylcysteine, or D-cycloserine
- Current treatment with a psychotropic medication, not listed above, on a dose that has not been stable for at least 4 weeks prior to study baseline
- Participants with a history of or a current liver or kidney disease
- Clinically unstable psychiatric conditions or judged to be at serious suicidal risk
- Serious, stable or unstable chronic disease such as hepatic, renal, gastroenterological, respiratory, cardiovascular (including ischaemic heart disease), endocrinologic, neurologic, immunologic, or haneidematologic disease

Location/setting: Massachusetts General Hospital. USA

Mean IQ: details not provided

Mean age: details not provided

Gender: details not provided

Sample size: memantine, 22 randomised; placebo, 21 randomised

Reasons for dropouts/withdrawals: memantine, 6 did not complete (4 due to AEs, 1 lack of efficacy, and 1 withdrawal by participant); placebo, 4 did not complete (1 due to AEs, 1 LTFU, 1 lack of efficacy, and 1 withdrawal by participant).

Baseline ABC-I or other BoC scale: not an outcome

Concomitant medications: details not provided

Previous medications: details not provided

Interventions	Intervention (memantine) for 12 weeks: given in capsule form twice daily. It will be administered twice daily for 12 weeks (including a 4-week titration phase to a maximum dose of 20 mg/day). Participants will undergo neuroimaging before and after the 12-week treatment phase. Comparator (placebo) for 12 weeks: no active ingredients; given in capsule form twice daily. It will be administered twice daily for 12 weeks. Participants will undergo neuroimaging before and after the 12-week treatment phase.
Outcomes	Primary outcomes: AEs Secondary outcomes: tolerability Timing of outcome assessments: unclear
Notes	Study start date: October 2013 Study end date: September 2019 Funding: details not provided Conflicts of interest: details not provided

Risk of bias

Bias	Authors' judgement	Support for judgement

NCT01972074 *(Continued)*

Random sequence generation (selection bias)	Low risk	"ASD subjects will be randomized to either active memantine or placebo in a 1:1 ratio after they have been determined to meet all eligibility criteria. Randomization lists stratified by gender and racial/ethnic minority status (minority vs Caucasian) will be generated by the statistician and passed to the investigational pharmacy for assignment".
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Only details provided were on the trials registry Quote: "Masking: quadruple (participant, care provider, Investigator, outcomes assessor)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Only details provided were on the trials registry Quote: "Masking: quadruple (participant, care provider, Investigator, outcomes assessor)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants included in analyses
Selective reporting (reporting bias)	Unclear risk	It is difficult to know without a protocol
Other bias	Low risk	No other sources identified

NCT02940574

Study characteristics	
Methods	4-week trial of oxytocin versus placebo
Participants	Inclusion criteria: • clinical diagnosis of ASD, Asperger's Syndrome or Autism • male • aged 18-40 years Exclusion criteria: • associated neuro(psycho)logical disorder (i.e. epilepsy, concussion, stroke), eyesight worse than + or - 7, Genetic syndrome, colour blindness • any contraindication to neuroimaging research as assessed with the MRI screening list: pacemaker, implanted defibrillator, ear implant/a cochlear implant, insulin or implanted pump, a neurostimulator or ventriculoperitoneal shunt, any metallic object in the eyes (metallic fragments). Location/setting: Belgium Mean IQ: details not provided Mean age: 18-40 year olds Gender: all participants were male. Sample size: 40 (oxytocin 22, placebo 18)

NCT02940574 *(Continued)*

	Reasons for dropouts/withdrawals: 1 in oxytocin group withdrew from the study, 1 from placebo not included in analysis due to "excessive in-scanner head motion" Baseline ABC-I or other BoC scale: not an outcome Concomitant medications: details not provided Previous medications: details not provided
Interventions	Intervention (oxytocin) for 4 weeks: single dose of 24 IU oxytocin (Syntocinon) nasal spray (3 puffs of 4 IU per nostril), followed by 4 weeks of a daily single dose (24 IU; 3 puffs of 4 IU per nostril) of nasal spray. Comparator (placebo) for 4 weeks: placebo (physiological water (solution of sodium chloride (NaCl) in water)) administered via nasal spray. A single dose (24 IU) of nasal spray (3 puffs of 4 IU per nostril), followed by 4 weeks of a daily single dose (24 IU; 3 puffs of 4 IU per nostril) of nasal spray.
Outcomes	Primary outcomes: AEs Secondary outcomes: • QoL, measured using the WHO-QoL (WHO 1998) (higher scores indicate a more positive response) • tolerability Timing of outcome assessments: baseline and 4 weeks (endpoint)
Notes	Study start date: October 2016 Study end date: February 2020 Funding: details not provided Conflicts of interest: details not provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail: "allocation: randomized"
Allocation concealment (selection bias)	Unclear risk	Insufficient detail. Quote: "allocation: randomised"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Only details provided were on the trials registry Quote: "masking: quadruple (participant, care provider, investigator, outcomes assessor)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Only details provided were on the trials registry Quote: "masking: quadruple (participant, care provider, investigator, outcomes assessor)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "1 subject lost in Syntocinon group due to subject withdrawal. 1 subject lost in placebo group due to low data quality (excessive in-scanner head motion)"
Selective reporting (reporting bias)	Unclear risk	Difficult to know without a protocol

NCT02940574 *(Continued)*

Other bias	Low risk	No other apparent sources of bias

NCT03242772

Study characteristics	
Methods	11-week parallel trial of amphetamine plus parent training versus placebo plus parent training
Participants	Inclusion criteria: • children 3-10 years • parent or legal guardian consents and is willing to comply with all study procedures and is available for the duration of the study • diagnosed with both ASD and ADHD based consensus diagnosis informed by results of the ADOS-2, ADI-R, and a Standardized ADHD Diagnostic Interview and the MINI psychiatric diagnostic interview • in good general health as evidenced by medical history and physical exam and review of safety labs and ECG Exclusion criteria: • recent use of prohibited psychoactive medication in close proximity of baseline assessments • known allergic reactions to amphetamines • known history of or personal history of sudden non-ischaemic cardiac death in a first or second degree family member (sibling, parent, aunt, uncle, cousin or grandparent) or significant cardiac abnormalities or disease • inability of the caregiver participating in P-ESDM and responding to questionnaires to fluently speak English • presence of any psychiatric conditions or psychiatric symptoms in addition to ASD and ADHD History of epilepsy or seizure disorder (except for history of simple febrile seizures or if the child is seizure free (regardless of seizure type) for the past year) Location/setting: Duke Center for Autism and Brain Development, USA Number of withdrawals/dropouts: amphetamine group 3 dropped out (2. LTFU, 1 withdrew); placebo group 1 dropped out due to "physician decision" Gender*:* 12 male, 6 female Mean age: intervention group 86.83 (SD20.80) months; placebo group 103.00 (18.88) months IQ: not reported Baseline ABC-I scores or other BoC: not an outcome Concomitant medications:details not provided History of previous medications*:* details not provided
Interventions	Intervention: • amphetamine: administered in the morning. Treatment initiated at 1 tablet = 3.1 mg or 0 mg of mixed amphetamine. Doses flexibly titrated upward and "may be decreased or stopped at any time." • Parent training: all participants receive 8 weekly parent-child therapy sessions. Sessions delivered by a therapist trained in parent coaching and Early Start Denver Model principles and strategies, and utilising a therapy manual (includes coaching for behaviour management and handouts) Comparator:

NCT03242772 *(Continued)*

- placebo: matched placebo tablets administered in the morning and provided for 11 weeks. Tablets "titrated in the same way as the active drug and may be stopped at any time."
- Parent training: all participants receive 8 weekly parent-child therapy sessions. Sessions delivered by a therapist trained in parent coaching and Early Start Denver Model principles and strategies, and utilising a therapy manual (includes coaching for behaviour management and handouts)

Outcomes	Primary outcomes: adverse effects Secondary outcomes: none reported Timing of outcome assessments: 11 weeks (endpoint)
Notes	Study start date: December 2018 Study end date: results submitted online December 2021 Funding: Duke University Conflicts of interest: details not provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only information "Allocation: Randomized"
Allocation concealment (selection bias)	Unclear risk	Only information "Allocation: Randomized"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information apart from, "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information apart from, "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)"
Incomplete outcome data (attrition bias) All outcomes	High risk	Primary outcome data not reported. "This variable required behavioral coding of videotaped caregiver-child interactions collected at two time points. This coding were not conducted due to the fact that the study was terminated and time 2 data were not collected for participants due to safety concerns related to Covid-19."
Selective reporting (reporting bias)	High risk	Primary outcome data not reported. "This variable required behavioral coding of videotaped caregiver-child interactions collected at two time points. This coding were not conducted due to the fact that the study was terminated and time 2 data were not collected for participants due to safety concerns related to Covid-19."
Other bias	Low risk	"Principal Investigators are NOT employed by the organization sponsoring the study." "There is NOT an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed."

Niederhofer 2002

Study characteristics	
Methods	Cross-over trial of lofexidine versus placebo
Participants	Inclusion criteria: • met ICD-10 criteria for ASD • no history of identified medical or neurological illnesses • off medications for at least 1 month before the study Exclusion criteria: details not provided Location/setting: Austria Sample size: 12 in total (cross-over) Number of withdrawals/dropouts: details not provided Gender: all participants were male. Mean age: lofexidine group 7.3 years; placebo group 9.2 years Mean IQ: lofexidine 59; placebo 48 Baseline ABC-I or other BoC: details not provided Concomitant medications: participants had been off medications for at least 1 month prior to the study. History of previous medications: details not provided
Interventions	Intervention (lofexidine) for 13 weeks: lofexidine was started at 0.4 mg/day, and tapered up over 2 weeks to 0.8-1.2 mg/day in 3 doses. Comparator (placebo) for 13 weeks: identical placebo tablets were given.
Outcomes	Primary outcomes: • irritability, measured using the ABC-Irritability subscale (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessments: ABC- I and AEs assessed weekly
Notes	Study start date: not reported Study end date: not reported Source of funding: not reported Conflicts of interest: none declared

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Quote: "Tablets for each subject were placed in sealed envelopes designated for each day of the study"

Niederhofer 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All raters (parents, teachers, and clinicians) were blind to drug order until ratings were completed"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details on how clinicians were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No baseline data reported. Not clear how many included in the analysis
Selective reporting (reporting bias)	Unclear risk	Unclear outcomes for 2 arms of active treatment (10 mg and 20 mg doses)
Other bias	Unclear risk	Funding and author affiliations unknown

Niederhofer 2003

Study characteristics	
Methods	Cross-over trial of tianeptine versus placebo
Participants	Inclusion criteria: • met "ICD-10 criteria for autistic disorder" • no history of identified medical or neurological illnesses • free of medication for at least 4 weeks (12 weeks for a single subject who had been taking fenfluramine) before beginning the study Exclusion criteria: • history of medical or neurological illnesses • taking regular medications in the month prior to the study Sample size: 7 in tianeptine group, 6 placebo (13 in total) Reason for withdrawals/dropouts: "a thirteenth subject entered the study but was dropped because of noncompliance with medication" Location/setting: Italy Mean age: 7.3 years Gender: all participants were male. Mean IQ: ranged from 35-84 Baseline ABC-I or other BoC: tianeptine ABC-I 13.9; placebo 14.1 Concomitant medications: participants had been off medication for at least 1 month before the study. History of previous medications: "all these children had been treated with either methylphenidate, neuroleptics or desipramine before entry into the study. In each case, these medications had either not been effective or caused intolerable side effects."
Interventions	Intervention (tianeptine) for 12 weeks: 37.5 mg/day dose for 12 weeks

Niederhofer 2003 *(Continued)*

	Comparator (placebo) for 12 weeks: identical placebo tablets
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessments: weekly ABC ratings and AEs
Notes	Study start date: 2002 Study end date: not reported Source of funding: not reported Conflicts of interest: none disclosed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "subjects were randomly assigned by a nonrating clinician to begin tianeptine or placebo."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	All raters were blind to drug order until ratings were completed. However, the authors note of "possible unblinding of parents and teachers because of side effects"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details about participation and dropouts
Selective reporting (reporting bias)	Unclear risk	Adverse effects not reported. Without a trial protocol it is difficult to know if any outcomes were measured but not reported.
Other bias	Unclear risk	Details not provided

Nikoo 2015

Study characteristics

Methods	Parallel trial of N-acetylcysteine versus placebo
Participants	Inclusion criteria: • children aged 4-12 years of age • meet the diagnostic criteria for autism according to the DSM-4-TR

Nikoo 2015 *(Continued)*

	• score > 6 in the DSM-4 criteria • baseline ABC-I subscale score of ≥ 12 Exclusion criteria: • history of psychotropic drug treatment within 6 weeks of enrolment • tardive dyskinesia • known adverse reaction to N-acetylcysteine or risperidone • taking concomitant medications with glutamatergic effects (e.g. dextromethorphan, D-cycloserine, amantadine, memantine, lamotrigine, riluzole) • other DSM-IX axis I or II disorders • any significant active medical problem • severe intellectual disability that interfered with diagnosis of autism • participation in any psychosocial intervention or concomitant drug during course of trial Location/setting: Tehran, Iran Sample size: 20 in N-acetylcysteine + risperidone, 20 placebo + risperidone (40 in total) Number of withdrawals/dropouts: no reported dropouts after first post-baseline measurements Gender: 33 male, 7 female Mean age: 7.5 years (N-acetylcysteine), 7.6 years (placebo) IQ: not reported Baseline ABC-I or other BoC: ABC-I NAC 21.2, placebo 19.7 Concomitant medications: concomitant drug during course of trial not allowed History of previous medications: details not provided
Interventions	Intervention (N-acetylcysteine) for 10 weeks: administered at 200 mg 3 times/day for children weighing < 20 kg. For children weighing ≥ 20 kg, N-acetylcysteine was given at 300 mg 3 times/day. Risperidone was also started at 0.5 mg and titrated weekly by 0.5 mg to a maximum of 1.0 mg/day for children weighing < 20 kg. For children weighing ≥ 20 kg, risperidone was given at the same starting dose and titration rate, but to a maximum of 2.0 mg/day. Comparator (placebo) for 10 weeks: equivalent placebo
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessments: baseline, week 5, week 10
Notes	Study start date: November 2011 Study end date: November 2013 Source of funding: "this study was supported by a grant from Tehran University of Medical Sciences to Shahin Akhondzadeh, PhD, (grant no. 15155)." Conflicts of interest: none disclosed
Risk of bias	

Nikoo 2015 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation of the patients into 2 groups in a 1:1 ratio with the help of computer-generated codes
Allocation concealment (selection bias)	Low risk	Quote: "the assignments were kept in consecutively numbered, confidential, and sealed envelopes until the statistical analysis step"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided except double-blinding used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "during the study, separate persons held the responsibility of randomisation and rating of the patients. Resultant data were also entered in a database by a person not involved in other parts of the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears to have been no LTFU
Selective reporting (reporting bias)	Low risk	The trial was registered on http://irct.ir/trial/879 and all outcomes reported in the protocol were reported.
Other bias	High risk	• The contact author is also on the ethics committee at the university funding the study. • The contact author is a peer-reviewer for one of the journals in which some of their studies are published.

Nikvarz 2017

Study characteristics	
Methods	8-week parallel trial of risperidone versus memantine
Participants	Inclusion criteria: • children 4-17 years • diagnosis of autism based on the DSM-4-TR • unsatisfactory response to previous drugs • participants with epilepsy allowed but only if seizure-free within the month prior to study start. Exclusion criteria: • currently receive drugs that satisfactorily treat symptoms of autism • patients with epilepsy and one or more seizures in the month prior to the study commencing • other neurological conditions • "a history of substance abuse, neuroleptic malignant syndrome, severe allergic reactions to risperidone or memantine, any cardiac disease, hematologic malignancy, acute kidney or liver failure, consumed stimulant drugs" • pregnant Setting/location: Roozbeh Psychiatric Hospital, Iran Sample size: 34, memantine (18 participants), risperidone (16 participants)

Nikvarz 2017 *(Continued)*

	Number of dropouts/withdrawals: 1 participant in the risperidone group did not complete the trial due to a change in psychiatrist. 3 participants in the memantine group did not complete the trial - all reportedly due to a lack of therapeutic response in first 2 weeks of trial. Mean age: 6.7 years IQ: details not provided Gender: memantine 13/15 male; risperidone 10/15 male Baseline ABC-I scores: 21.8 Concomitant medications: details not provided Previous medications: risperidone: 2 in risperidone group and 4 in memantine group had previously taken risperidone; aripiprazole: 2/15 in memantine group and zero from risperidone group had previously taken aripiprazole.
Interventions	Intervention (memantine) for 8 weeks: started at a once-daily dose of 0.2 mg/kg/day then increased to 0.3 mg/kg/day in the 2nd week and ultimately to 0.4 mg/kg/day in the 3rd week. The maximum daily dose of memantine was 20 mg/day. Comparator (risperidone) for 8 weeks: "Risperidone was started at 0.02 mg/kg/day then increased to 0.04 mg/kg/day at week 2" up to a maximum of "0.06mg/kg/day at the third week." The maximum daily dose of risperidone was 3mg/day.
Outcomes	Primary outcomes: • ABC-I (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessments: baseline, week 4 and week 8 (endpoint)
Notes	Study start date: April 2012 Study end date: March 2013 Funding: "This study was supported by Tehran University of Medical Sciences (TUMS) (Grant number: 91-01-33-16991)." Conflicts of interest: "The authors declare no conflict of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sample size was 30. Patients were randomly allocated to receive risperidone or memantine based on simple, balanced, blocked randomisation.
Allocation concealment (selection bias)	Unclear risk	Although referred to as "simple balanced blocked randomisation", no information on how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information beyond it being "open label", so assume unblinded

Nikvarz 2017 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Data not imputed for participants who discontinued
Selective reporting (reporting bias)	Unclear risk	Difficult to know for certain without seeing study protocol
Other bias	Low risk	No other sources of bias identified

Owen 2009

Study characteristics	
Methods	Parallel trial of aripiprazole versus placebo
Participants	Inclusion criteria: • children and adolescents (aged 617 years) • met DSM-4-TR criteria for ASD • demonstrated behaviours such as tantrums, aggression, self-injurious behaviour or a combination of these • weighed ≥ 15 kg • CGI-S score > 4 and ABC-I score of > 18 Exclusion criteria: • current diagnosis of bipolar disorder, psychosis, schizophrenia or major depression; fragile X syndrome or a diagnosis of another disorder on the autism spectrum including PDDNOS, Asperger syndrome, Rett syndrome, or childhood disintegrative disorder Location/setting: USA Sample size: 98 participants were randomised (aripiprazole 47; placebo 51) Number of withdrawals/dropouts: placebo group discontinued (15): lack of efficacy (6), AEs (3), withdrew consent (2), LTFU (4). Aripiprazole group discontinued (8): lack of efficacy (1), AEs (5), withdrew consent (1), LTFU (1) Gender: 44/51 and 42/47 were male Mean age: placebo 8.8 years, aripiprazole 9.7 years IQ: not reported Baseline ABC-I or other BoC: placebo ABC-I 30.2; aripiprazole 29.6 Concomitant medications: not reported History of previous medications: 50% had previously received psychotropic medications. The most commonly received medications were antipsychotic agents (placebo: 30.0%; aripiprazole: 17.0%), psychostimulant agents (placebo: 26.0%; aripiprazole: 17.0%), anxiolytic agents (placebo: 16.0%; aripiprazole: 17.0%), and antidepressant agents (placebo: 10.0%; aripiprazole: 6.4%)
Interventions	Intervention (aripiprazole) for 8 weeks: approximately 7.5 mg/day or 0.172 mg/kg/day Comparator (placebo) for 8 weeks: equivalent to 5, 10, or 15 mg/day doses
Outcomes	Primary outcomes:

Owen 2009 *(Continued)*

	• Irritability (mean change from baseline), measured using the parent-rated ABC-I subscale (Aman 1985) • AEs Secondary outcomes: QoL, measured using the PedsQL (WHO 1998) Timing of outcome assessments: baseline, weeks 1, 2, 3, 4, 5, 6 and 8, with telephone call in week 7
Notes	Study start date: June 2006 Study end date: February 2008 Source of funding: "Drs Owen, Corey-Lisle, Manos, and Marcus are employees of Bristol-Myers Squibb. This study was supported by Bristol- Myers Squibb (Princeton, NJ) and Otsuka Pharmaceutical Co, Ltd (Tokyo, Japan). Editorial support for the preparation of this manuscript was provided by Ogilvy Health-world Medical Education; funding was provided by Bristol-Myers Squibb." Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Computer-generated randomisation schedule prepared by Bristol Myers Squibb using a permuted block design
Allocation concealment (selection bias)	Low risk	Investigational sites accessed a call-in interactive voice response system. The system assigned a medication bottle number to each participant.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF LTFU aripiprazole: discontinued (8); lack of efficacy (1); AEs (5); withdrew consent (1); LTFU (1) LTFU placebo: discontinued (15); lack of efficacy (6); AEs (3); withdrew consent (2); LTFU (4)
Selective reporting (reporting bias)	Low risk	The trial was registered on clinicaltrials.gov and the outcomes registered were reported
Other bias	Unclear risk	No differences in age, gender, ethnicity, weight or baseline scores but previous antipsychotic use (51% across groups) was not reported by group

Owley 2001

Study characteristics

Methods	Cross-over trial of porcine secretin versus placebo
Participants	Inclusion criteria:

Owley 2001 *(Continued)*

	• met the criteria for ASD by both the ADI-R and the ADOS Exclusion criteria: • any history of allergy to porcine products • significant medical illness (excluding autism) including nonfebrile seizures Location/setting: University of Chicago, University of California-Irvine, University of Utah, USA Sample size: 56 in total (28 to secretin-placebo, 28 to placebo-secretin) Number of withdrawals/dropouts: none reported Gender: 48 boys, 8 girls Mean age: 6.7 years IQ: mental age ≥ 24 months Baseline ABC-I or other BoC: ABC-I placebo-secretiin 10.1. secretin-placebo 11.6 Concomitant medications: 14 participants were taking a total of 15 psychotropic medications (at stable doses) during the study, including SSRIs (3), atypical neuroleptics (3), α-adrenergic agonist (1), and psychostimulants (8) History of previous medications: participants on stable doses of psychotropic medications were included but they were asked not to change the dosages of these medications for the duration of the trial.
Interventions	Intervention (secretin) for 4 weeks: secretin was administered at 2 CU/kg/day Comparator (placebo) for 4 weeks: placebo (infused saline) that was indistinguishable from the active treatment
Outcomes	Primary outcomes: irritability, measured using the ABC-Irritability subscale (Aman 1985) Secondary outcomes: none reported Timing of outcome assessments: baseline and then at the end of weeks 2, 4, 6 and 8
Notes	Study start date: not reported Study end date: not reported Source of funding: "this work was supported in part by the University of California at Davis Medical Investigation of Neurodevelopmental Disorders Institute (WM, EHC, PAF). Additional support was provided by grants from the NIMH (R01 MH52223, K02 MH01389, EC), the Jean Young and Walden W. Shaw Foundation (BLL), and the Irving B. Harris Foundation (BLL). This work was conducted as part of the NICHD/NIDCD Collaborative Network on the Neurobiology and Genetics of Autism." Conflicts of interest: none disclosed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomisation was done by the investigational pharmacy at each site". Unclear as to the method and whether the same method was used across all sites.
Allocation concealment (selection bias)	Unclear risk	Details not provided

Owley 2001 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All patients, their parents, all members of the assessment team were blind to drug assignments until all subjects at that site had completed the trial."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Members of the assessment team were blind to drug assignments until all subjects at that site had completed the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for and where particular assessments were missed, the number of participants who were analysed were indicated in brackets ().
Selective reporting (reporting bias)	Low risk	All outcomes reported at cross-over endpoints
Other bias	High risk	Only a single dose of secretin was used.

Parker 2017

Study characteristics	
Methods	4-week parallel trial of oxytocin versus placebo
Participants	Inclusion criteria: • children aged 6-12 years • met diagnostic criteria for ASD • medically healthy outpatients • IQ > 40 (as determined by the Stanford-Binet Intelligence Scales, fifth edition) • CGI-S rating of ≥ 4 • had a care provider who could reliably bring them to clinic visits, provide trustworthy ratings, and interact with the participant on a regular basis • on stable medications for at least 4 weeks • no planned changes in psychosocial interventions during the trial • willing to provide blood samples Exclusion criteria: • prior or current use of oxytocin • DSM-4-TR or DSM-5 diagnosis of schizophrenia, schizoaffective disorder, or psychotic disorder • regular nasal obstruction or nosebleeds • active medical problems (unstable seizures or significant physical illness e.g. serious liver, renal, or cardiac pathology) • sensitivity to preservatives (e.g. chlorobutanol hemihydrate) • evidence of a genetic mutation known to cause ASD (e.g., fragile X Syndrome) • significant hearing or vision impairments • habitual consumption of large volumes of water • pregnant, breastfeeding, or childbirth within the last 6 months • sexually active female participants not using a reliable method of contraception Location/setting: study was conducted in the Autism and Developmental Disabilities Clinic in the Division of Child and Adolescent Psychiatry at Stanford University, USA Sample size: 32

Parker 2017 *(Continued)*

	Number of withdrawals/dropouts: 2/16; 0/18 (1 LTFU, 1 withdrew) Gender: 27 male, 5 female Mean age: 6-12 years IQ: approx 35-90 Baseline ABC-I or other BoC: baseline scores not reported Concomitant medications: participants were allowed to take concurrent psychotropic medications provided they do not interact with oxytocin, were on a stable dose before study entry and medication use did not differ between groups. History of previous medications: details not provided
Interventions	Intervention (oxytocin): twice-daily each participant will have 3 puffs per nostril of 4 IU/puff (24 IU twice daily) for 4 weeks Comparator (placebo): placebo nasal spray 3 puffs per nostril of 4 IU/puff (24 IU twice daily) for 4 weeks
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: tolerability Timing of outcome assessments: baseline, week 4 (endpoint)
Notes	Study start date: June 2012 Study end date: April 2016 Funding: "K.J.P. and A.Y.H. provided funding for the research" Conflicts of interest: "The authors declare no conflict of interest" Trial registry: NCT01624194

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed by an IDS pharmacist using www.randomization.com, which allocates each participant to an intervention by using the method of randomly permuted blocks"
Allocation concealment (selection bias)	Low risk	"Randomization was performed by an IDS pharmacist using www.randomization.com, which allocates each participant to an intervention by using the method of randomly permuted blocks"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Quote: "the research team to remain blinded throughout the trial's duration"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"This practice allowed the research team to remain blinded throughout the trial's duration... A technician blinded to treatment condition performed sample preparation and OXT quantification following established procedures"

Parker 2017 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for.
Selective reporting (reporting bias)	High risk	Some outcomes from clinicaltrials.gov not reported in the peer-reviewed paper
Other bias	Low risk	No other sources of bias identified

Parker 2019

Study characteristics	
Methods	4-week trial of vasopressin versus placebo
Participants	Inclusion criteria: • met diagnostic criteria for ASD • medically healthy outpatients • aged 6-12.9 years • IQ ≥ 50 as determined by the Stanford Binet 5th Edition • CGI-S scale rating of ≥ 4 • care provider who can reliably bring participant to clinic visits, provides trustworthy ratings, and interacts with the participant on a regular basis • stable concomitant medications for at least 4 weeks • no planned changes in psychosocial interventions during the trial • willing and able to provide blood samples and undergo ECGs Exclusion criteria: • previous or current use of vasopressin • abnormal chemistry result • ECG abnormality as determined by the study pediatric cardiologist • DSM-IV-TR diagnosis of schizophrenia, schizoaffective disorder, or psychotic disorder • regular nasal obstruction or nosebleeds • active medical problems: uncontrolled seizures and physical illness (e.g. serious liver, renal, or cardiac pathology) • sensitivity to preservatives (e.g. chlorobutanol) • evidence of a genetic mutation known to cause ASD (e.g., fragile X syndrome) • hearing or vision impairments • habitually drinks large volumes of water • pregnant, breastfeeding, or childbirth within the last 6 months • sexually active girls not using a reliable method of contraception; negative urine pregnancy test required for girls who'd started menstruating. Location/setting: autism disorders clinic, USA Sample size: 30 Number of withdrawals/dropouts: none reported Gender: 25 male, 5 female Mean age: 6-12.9 years of age (outpatients) IQ: approximately 77-98

Parker 2019 *(Continued)*

	Baseline ABC-I or other BoC: baseline ABC-I 8.29 (7.4); baseline QoL 64.53 (13.86) Concomitant medications: details not provided History of previous medications: details not provided
Interventions	Intervention (vasopressin nasal spray): 4 IU twice daily of vasopressin during week 1 and 8 IU twice daily of vasopressin during week 2. Participants aged 6-9.5 years then received 12 IU twice daily of vasopressin during weeks 3 and 4, whereas participants aged 9.6-12.9 years received 16 IU twice daily of vasopressin during weeks 3 and 4. Comparator (placebo nasal spray): matching placebo for 4 weeks
Outcomes	Primary outcomes: • ABC-I (Aman 1985) • AEs Secondary outcomes: • QoL, measured with parent-rated PedsQL (WHO 1998) • tolerability Timing of outcome assessments: ABC-I and QoL were measured at baseline and week 4 (endpoint). Participants underwent weekly safety/tolerability assessments in the clinic to monitor for AEs.
Notes	Study start date: December 2013 Study end date: May 2017 Funding: various grants to the researchers Conflicts of interest: financial compensation by pharmaceutical companies and other involvement with pharmaceutical companies Trial registry: NCT01962870

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by an unblinded investigator using a machine-generated treatment schedule, which allocated each participant to an intervention.
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Research team, parents/legal guardians, and child participants remained blind throughout the trial's duration.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Research team, parents/legal guardians, and child participants remained blind throughout the trial's duration.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts reported and all were included in the analysis.

Parker 2019 *(Continued)*

Selective reporting (reporting bias)	High risk	PedsQL and ABC not reported in peer-reviewed paper. The Overt Aggression Scale was mentioned as an outcome but not reported.
Other bias	Low risk	No other sources identified

Pearson 2013

Study characteristics	
Methods	1-week cross-over trial of methylphenidate (3 doses) versus placebo
Participants	Inclusion criteria: • children who met DSM-4-TR criteria for an ASD on the ADI-R and ADOS • significant symptoms of ADHD Exclusion criteria: • serious neurological disorders (e.g. stroke, seizures) • Down syndrome, Fragile X syndrome, Tourette syndrome, psychosis, and mood disorders Location/ setting: University of Texas Medical School at Houston, USA Sample size: 24 Number of withdrawals/dropouts: none reported Gender: details not provided Mean age: 8.8 years (1.7) IQ: 85.0 (16.8) Baseline ABC-I or other BoC: not reported Concomitant medications: 7 children were stable on long-term (> 3 months) medications that they continued (at a constant dose) during the trial: risperidone (n = 3), aripiprazole (n = 1), sertraline (n = 1), bupropion (n = 1), and trazodone (n = 1). History of previous medications: 13 children had previously taken stimulant medication, which was discontinued 1 week prior to entry into the trial.
Interventions	Intervention (methylphenidate): each child received 1 week each of the four MPH dosing regimens (placebo, low-dose methylphenidate, medium-dose methylphenidate, and high-dose methylphenidate). The children received Ritalin long-acting (LA; extended-release methylphenidate) at breakfast and immediate-release methylphenidate in the afternoon, with dosing based on body weight. The mean immediate-release methylphenidate per dose equivalents of the Ritalin LA (given in the morning) were 0.21 mg/kg methylphenidate in the low-dose, 0.35 mg/kg in medium-dose, and 0.48 mg/kg in the high-dose. The immediate-release methylphenidate dose (given in the afternoon) was approximately half of each single-dose equivalent of the morning's Ritalin LA. Comparator: not described apart from "Participants will take a placebo for 1 full week of the randomized drug trial. They will take one capsule in the morning and one capsule in the afternoon."
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • AEs

Pearson 2013 *(Continued)*

	Secondary outcomes: none reported
Notes	Study start date: September 2005 Study end date: May 2013 Funding: "This study was funded by grant number MH072263 from the National Institute of Mental Health (NIMH)." Conflicts of interest: "Dr. Pearson and Ms. Mansour have received travel reimbursement and research support from the Forest Research Institute and Curemark LLC." Trial registry: NCT00178503

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study personnel were unblinded to placebo.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Study personnel were unblinded to placebo.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reported no dropouts, however 5 of the 24 children discontinued the afternoon immediate-release methylphenidate dose because of behaviour concerns in late afternoon/evening - unclear if ITT
Selective reporting (reporting bias)	High risk	Primary outcome in trial reg not reported - Mean Continuous Performance Test (CPT)-Commission Errors by Dose
Other bias	Low risk	No other sources of bias identified

Posey 2005

Study characteristics

Methods	Cross-over trial of methylphenidate versus placebo
Participants	Inclusion criteria: • children aged 5-14 years • diagnosis of autistic disorder, Asperger disorder, or PDD-NOS based on the criteria in the DSM-4 • interfering symptoms of hyperactivity and/or impulsiveness present for at least 6 months and commenced prior to 7 years of age • mental age of at least 18 months Exclusion criteria:

Posey 2005 *(Continued)*

- concurrent psychotropic medications
- other neuropsychiatric disorders that might require alternative medical management
- significant medical conditions such as heart or liver disease
- seizures in the past 6 months
- hypertension
- treatment with methylphenidate hydrochloride within the past 2 years
- history of severe adverse response to methylphenidate

Location/setting: 5 centres, Indiana University (Indianapolis), the Kennedy Krieger Institute at John Hokins University (Baltimore), The Ohio State University (Columbus), the University of California (Los Angeles), Yale University (New Haven), USA

Sample size: 66

Number of withdrawals/dropouts: 8 exited cross-over phase, 7 due to AEs (3 from high dose, 3 medium dose and 1 low dose), 1 due to other reasons, withdrawing consent prior to receiving treatment.

Gender: 59/66 male

Mean age: 7.5 years

IQ: mental age of at least 18 months

Baseline ABC-I or other BoC: ABC-I 16.5

Concomitant medications: no concurrent psychotropic medications for at least 1-3 weeks (1 week for stimulants and clonidine hydrochloride; 2 weeks for antidepressants except fluoxetine and citalopram hydrobromide; 3 weeks for fluoxetine, citalopram hydrobromide, or antipsychotics) prior to baseline visit.

History of previous medications: not described

Interventions	Intervention (methylphenidate) for 4 weeks: dosage levels were varied depending on the weight of the child. The low-dosage level approximate 0.125 mg/kg per dose. The medium-dosage level approximate 0.250 mg/kg per dose. The high-dosage level approximate 0.500 mg/kg per dose. Each participant received 1 week placebo and 1 week each of 3 different doses in random order (except high dose never followed placebo). Each dose was received 3 times daily (8 am, 12 pm, 4 pm). Comparator (placebo) for 4 weeks: equivalent placebo
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale; however, only baseline scores reported • AEs Secondary outcomes: none reported Timing of outcome assessments: details not provided
Notes	Study start date: November 2001 Study end date: September 2003 Source of funding: research supported by authors' contracts with National Institute of Mental Health, and grants with various universities, the General Clinical Research Centers, National Center for Research Resources, National Institutes of Health, Bethesda, and by the Korczak Foundation, Amsterdam Conflicts of interest: none declared Trial registry: NCT00025779

Risk of bias

Posey 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation lists were generated centrally and were held by an investigational pharmacist at each site.
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Clinicians, the patient, and the caregiver were blind to treatment assignment during this phase.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The rating clinician was also kept blinded to any information about AEs or changes in vital signs or weight.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Consistent with ITT principles, all of the data from participants receiving 2 medium doses (owing to the inability to tolerate a high dose) were analysed. No significant differences were found between these 2 weeks of receiving the medium dose, so the data were combined. LTFU unclear as they did not report for intervention and placebo groups.
Selective reporting (reporting bias)	High risk	ABC-I was reported in baseline scores however it was not reported in the endpoint scores (only ABC hyperactivity).
Other bias	Low risk	None identified

Quintana 1995

Study characteristics	
Methods	Cross-over trial of methylphenidate versus placebo
Participants	Inclusion criteria: • participants recruited from the New York State Psychiatric Institute outpatient clinic • DSM-III-R criteria for autistic criteria for ASD • children off neuroleptics for a period of at least 1 month or if their parents would agree to have them off neuroleptics for 1 month prior to the start of the study. Exclusion criteria: • on methylphenidate at any time before entry into the study • history of seizure disorder or other major neurological or medical illness Location/setting: USA Sample size: 10 Number of withdrawals/dropouts: none reported Gender: 6 boys, 4 girls Mean age: 8.5 years IQ: mean Developmental Quotient was 64.3

Quintana 1995 *(Continued)*

	Baseline ABC-I or other BoC: ABC-I 11.8 Concomitant medications: participants were required to have been off neuroleptics for a period of at least 1 month prior to the study. History of previous medications: all the children had been on neuroleptic medications (haloperidole etc) at some point in their lives but had not been previously treated with methylphenidate
Interventions	Intervention (methylphenidate) for 2 weeks: started at 10 mg/kg twice a day for the 1st week, then 20 mg/kg twice a day in the 2nd week Placebo for 2 weeks: equivalent placebo
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessments: unclear
Notes	Study start date: not reported Study end date: not reported Source of funding: not reported Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No other comments apart from, "These investigators, the children, and the parents were blind to drug and drug dose."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10 total participants mentioned, without detail as to dosage allocation, completion of study and individual outcome measures LTFU was not mentioned
Selective reporting (reporting bias)	Low risk	All outcomes measured were reported at baseline and endpoint. Published baseline and endpoint data on all outcome measures
Other bias	Unclear risk	No mention of funding sources or conflicts of interest

Remington 2001

Study characteristics	
Methods	Cross-over trial of clomipramine versus placebo
Participants	Inclusion criteria: • children and adults 10-36 years • DSM-4 diagnosis of autism • recommendation, based on initial assessment, of pharmacotherapy • evidence that haloperidol or clomipramine had not been used previously or, if so, that an adequate therapeutic trial was not completed Exclusion criteria: with the exception of "antiparkinsonian medication in the form of benztropine...no other psychotropic medications were permitted during the study." Location/setting: "recruited from the Autism and Pervasive Developmental Disorder Clinic at the Centre for Addiction and Mental Health, Clarke Division, a teaching hospital associated with the University of Toronto." (Canada) Sample size: 36 (phase 1) Number of withdrawals/dropouts: 5 withdrew from placebo group because of behaviour; 5 withdrew from clomipramine group, 2 because of behaviour and AEs, and 3 because of AEs alone Gender: 31/36 male Mean age: 16.3 years IQ: not reported Baseline ABC-I or other BoC: ABC-I 19.0 Concomitant medications: 13/36 were taking other medications such as trifluoperazine, methylphenidate, fluvoxamine or carbamazepine History of previous medications: not reported
Interventions	Intervention 1 (clomipramine) for 7 weeks: 25 mg at bedtime for 2 days, 25 mg twice a day for 2 days, 25 mg 3 times/day for 2 days, and 50 mg twice a day Intervention 2 (haloperidol): 0.25 mg at bedtime for 2 days, 0.25 mg twice a day for 2 days, 0.25 mg 3 times/day for 2 days, and 0.5 mg twice a day Comparator (placebo) for 7 weeks: placebo equivalent
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessments: not reported
Notes	Study start date: not reported Study end date: not reported Source of funding: grant from the Ontario Mental Health Foundation Conflicts of interest: none declared

Remington 2001 *(Continued)*

Trial registry: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned to one of three treatment groups as part of a Latin square design (clomipramine-placebo-haloperidol, placebo-haloperidol-clomipramine, and haloperidol-clomipramine-placebo)
Allocation concealment (selection bias)	Unclear risk	Quote: "Medications and placebo were packaged in similar capsules to maintain the double-blind component"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	LTFU clomipramine: 20 in total withdrew: • Trial one, 5 withdrew, 2 because of behaviour and AEs, and 3 because of AEs alone. • Trial 2: 9 withdrew from clomipramine group; 4 due to behaviour, 1 due to AEs and behaviour, 4 due to AEs alone • Trial 3: 6 withdrew from clomipramine group (3 due to behaviour and 3 due to AEs) LTFU haloperidol: 10 in total withdrew from haloperidol group. • Trial 1: 3 withdrew, 2 because of AEs and 1 because of behaviour and AEs • Trial 2: 4 due to AEs, and 2 due to behaviour • Trial 3: 1 due to behaviour and 2 due to AEs LTFU placebo: 10 in total withdrew • Trial 1: 5 because of behaviour • Trial 2: 4 due to behaviour • Trial 3: 1 due to behaviour
Selective reporting (reporting bias)	High risk	Outcomes including ABC subscales measured every 2 weeks, however these results were not reported.
Other bias	Low risk	No other sources identified

Research Units 2005

Study characteristics

Methods	8-week discontinuation phase of McCracken 2002 study
Participants	Inclusion criteria:

Research Units 2005 *(Continued)*

- participants who showed a positive response to risperidone in the previous 8-week controlled trial (McCracken 2002) and 4-month open-label trial.
- Positive response defined as being a 25% reduction on the ABC-I subscale and a rating of much improved or very much improved on the CGI improvement scale.

Exclusion criteria: no concomitant treatment with psychotropic medication was allowed during any phase of the study, except anticonvulsant treatment for seizure control if the child had been taking a stable dose for 4 weeks and had been free of seizures for 6 months.

Location/setting: the 5 clinical sites included the University of California Los Angeles, Ohio State University, Indiana University, Yale University, and Kennedy Krieger Institute (Johns Hopkins University), USA

Sample size: 38 participants

Number analysed: 32 (16 from each group)

Number of withdrawals/dropouts: 2 not included in the analyses however reasons were not provided

Gender: 81% were male in the original McCracken study.

Mean age: 8.6 years

IQ: 73% of participants had a mild to profound intellectual disabilities

Baseline ABC-I or other BoC: following McCracken study ABC-I was 11.3

Concomitant medications: participants had to be free of all psychotropic drugs at least 2 weeks prior to randomisation (4 weeks for antipsychotics and fluoxetine).

History of previous medications: details not reported

Interventions	Risperidone for 8 weeks: the maintenance risperidone dose was reduced by 25% each week until only placebo in the fourth week Placebo for 8 weeks: equivalent placebo
Outcomes	Primary outcomes: relapse rates, measured in % Secondary outcomes: none reported. Apart from relapse rates, no other outcomes or new data were provided. Timing of outcome assessments: all participants were seen weekly for a total of 8 weeks in the discontinuation phase.
Notes	Study start date: not reported Study end date: not reported Source of funding: "NIMH contracts to principal investigators Dr McCracken (grant N01 MH-70010), Dr Scahill (N01 MH-70009), Dr McDougle (N01 MH-70001) and Dr Aman (N01 MH-80011); NIH Division of Research Resources General Clinical Research Center grants to Indiana University (M01 RR00750), Johns Hopkins University (M01 RR-00052), Ohio State University (M01 RR-00034) and to Yale University (M01 RR-06022). Funding was also received by Dr Scahill from the Korczak Foundation and study medications were donated by Janssen Pharmaceutica." Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement

Research Units 2005 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided about outcome assessors or clinicians
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "subjects were randomly assigned again, this time either to continued risperidone at the same dose or to gradual placebo substitution, in a double-blind fashion"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not provided
Selective reporting (reporting bias)	Unclear risk	Only relapse reported
Other bias	Unclear risk	Details not provided

Rezaei 2010

Study characteristics	
Methods	Parallel trial of topiramate + risperidone versus placebo + risperidone
Participants	Inclusion criteria: • children 3-12 years of age • a score of ≥ 6 on DSM-4-TR criteria for diagnosis of autism • an ABC-C Irritability subscale score of ≥ 12 at screening and baseline Exclusion criteria: • concomitant schizophrenia, psychotic disorders and epilepsy • history of drug or alcohol abuse • history of tardive dyskinesia • any significant medical condition • severe or profound intellectual disabilities in whom a definitive diagnosis of autism could not be made Location/setting: paediatric outpatient clinic in Iran Sample size: 40 (20 to each group) Number of withdrawals/dropouts: none reported Gender: 27 boys, 13 girls Mean age: topiramate + risperidone: 8.17 years; placebo + risperidone: 7.85 years IQ: not reported Baseline ABC-I or other BoC: topiramate + risperidone: 17.25; placebo + risperidone: 16.80

Rezaei 2010 *(Continued)*

	Concomitant medications: not reported History of previous medications: not reported
Interventions	Topiramate + risperidone for 8 weeks: maximum topiramate dose of 100 mg/day for children < 30 kg or 3-6 years of age. Maximum of 200 mg/day for children 7-12 years or ≥ 30 kg. Maximum risperidone dose of 2 mg/day for children 10-40 kg or 3 mg/day for children > 40 kg Risperidone + placebo for 8 weeks: maximum risperidone of 2 mg/day for children 10-40 kg or 3 mg/day for children > 40 kg
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessment: AEs recorded at weeks 1, 2, 4, 6 and 8
Notes	Study start date: April 2008 Study end date: January 2010 Source of funding: grant from Tehran University of Medical Sciences to Prof Shahin Akhondzadeh (Grant No: 6550) Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised to receive topiramate or placebo in a 1:1 ratio using a computer-generated code.
Allocation concealment (selection bias)	Low risk	The assignments were kept in sealed, opaque envelopes until data analysis.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Throughout the study, the person who administered the medications, the rater and the patients were blind to assignments"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Throughout the study, the person who administered the medications, the rater and the patients were blind to assignments"
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Patients will be randomly allocated to topiramate + risperidone (Group A) or placebo + risperidone (Group B) for a 10-week, double-blind, placebo-controlled study" only 8-weeks of the trial was reported in the paper LTFU: none reported
Selective reporting (reporting bias)	High risk	The ABC and the 5 subscales were the primary outcome measure and were reported, however it is unexplained why the Iranian clinical trials website and the paper are different in terms of length of study. "Timepoint weeks 2-4-6-8-10 after beginning of trial".
Other bias	High risk	The Iranian clinical trial website says that timepoints are weeks 2-4-6-8-10 after beginning of trial, however, week 10 is not recorded in the paper and nei-

Rezaei 2010 *(Continued)*

	ther is a 2-week follow-up period. "Patients will be randomly allocated to topiramate + risperidone (Group A) or placebo + risperidone (Group B) for a 10-week, double-blind, placebo-controlled study. The contact author is also on the ethics committee at the university funding the study and is a peer-reviewer for one of the journals in which some of their studies are published.

Scahill 2015

Study characteristics	
Methods	8-week parallel trial of guanfacine versus placebo
Participants	Inclusion criteria: • aged 5-14 years • DSM-4 diagnosis of ASD, asperger's syndrome, or PDD-NOS • minimum score of 24 on the parent-rated ABC-hyperactivity subscale and CGI-S score of moderate or greater • Anticonvulsant medication for seizures was allowed if the dose was stable and the participant had been seizure-free for at least 6 months • IQ of 35 or mental age of ≥ 18 months Exclusion criteria: • children taking a psychotropic treatment deemed ineffective were required to be withdrawn from the medication for at least 1 week for stimulants or clonidine, 2 weeks for atomoxetine and most antidepressants, and 3 weeks for fluoxetine, citalopram, and antipsychotics • a significant medical condition by history, physical examination, or laboratory testing • a positive pregnancy test • lifetime diagnosis of psychosis or bipolar disorder or current diagnosis of major depression, obsessive-compulsive disorder, or substance abuse Setting/ location: University of California (Los Angeles), Emory University, Massachusets General Hospital, University of Washington at Seattle, and Yale University, USA Sample size: guanfacine 30; placebo 32 Number of withdrawals/dropouts: 4 from guanfacine group (2 lack of efficacy, 2 AEs); 4 from placebo group all due to lack of efficacy Gender: 26/30 male in guanfacine group; 27/32 male in placebo group Mean age: 8.4 years IQ: not reported Baseline ABC-I or other BoC: guanfacine ABC-I 20.3; placebo 18.06 Concomitant medication: not reported Previous medications: not reported
Interventions	Intervention (guanfacine) for 8 weeks: starting dose for all children was 1 mg/day. Children < 25kg remained on 1 mg/day until day 14 and then increased to 2 mg/day until day 28, and increased again to 3 mg/day for the remaining 4 weeks. Children 25 kg or more increased to 2 mg/day at day 7 up to a maximum of 4 mg/day by day 21 or 28 of the trial.

Scahill 2015 *(Continued)*

	Comparator (placebo) for 8 weeks: placebo administered for up to 8 weeks
Outcomes	Primary outcomes: • Irritability, measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessment: weekly for the first 4 weeks, then week 6 and week 8
Notes	Study start date: December 2011 Study end date: March 2014 Source of funding: "supported by NIMH grants to Dr. Scahill (R01MH083707), Dr. McDougle (RO1MH83739), Dr.McCracken (RO1MH083747), and Dr. King (R01MH86927); by a Yale Clinical and Transitional Science Award (UL1 RR024139) from the NIH National Center for Research Resources; and by Atlanta Clinical and Translational Science Institute, Emory University, which is supported by the NIH National Center for Advancing Translational Sciences under award UL1TR000454. Shire Pharmaceuticals provided active extended-release guanfacine and placebo." Conflicts of interest: none declared Trial registry: NCT01238575

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Quote: "Using permeated blocks to conceal allocation, eligible subjects were randomly assigned within site without stratification in a 1:1 ratio to extended-release guanfacine or placebo for 8 weeks."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Two blinded clinicians followed each subject: a treating clinician and an independent evaluator....To protect the blind, the independent evaluator did not discuss adverse effects or dosing".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The treatment mask was broken for subjects who did not show a positive response. The blind was broken by the treating clinician, and treatment status was not disclosed to independant evaluators"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Consort diagram was provided outlining numbers at each stage of the trial, including the number analysed and number that completed the trial. All randomly assigned participants were included in the ITT analyses.
Selective reporting (reporting bias)	Unclear risk	Although the ABC-hyperactivity was the primary outcome measure, other secondary measures such as the CGI were not reported.
Other bias	Unclear risk	Shire pharmaceuticals provided active extended-release guanfacine and placebo.

Shea 2004

Study characteristics	
Methods	Parallel trial of risperidone versus placebo
Participants	Inclusion criteria: • male and female outpatients aged 5-12 years • a diagnosis of ASD or PDD according to the DSM-4 • "a total score of 30 or more on the Childhood Autism Rating Scale (CARS)". Exclusion criteria: • schizophrenia • other psychotic disorders • clinically relevant non-neurologic disease • clinically significant laboratory abnormalities • seizure disorder for which participants were receiving > 1 anticonvulsants • seizure in the last 3 months Location/setting: 7 investigational sites in Canada Sample size: 79 participants Number of withdrawals/dropouts: risperidone (2 total), "1 withdrew because of an adverse event (the result of an accidental overdose on day 2) and 1 withdrew because of insufficient response". Placebo (5 total) "1 withdrew because of an adverse event (an accidental medication overdose on day 16), 2 withdrew because of insufficient response, and 2 withdrew consent." Gender: 29/40 boys (risperidone); 32/39 placebo Mean age: 7.6 years (risperidone, 7.3 years (placebo) IQ: 14 participants had IQ > 85; 10 had IQ 71-84, 20 had IQ 50-70, and 22 had IQ 35-49 Baseline ABC-I or other BoC: ABC-I 18.9 risperidone, 21.2 placebo Concurrent and previous medications: during the trial, anticholinergics could be initiated to treat emergent extrapyramidal symptoms after the Extrapyramidal Symptom Rating Scale (ESRS) had been completed. Prohibited medications included antipsychotics other than the study medication, antidepressants, lithium, _2-antagonists, clonidine, guanfacine, cholinesterase inhibitors, psychostimulants, and naltrexone. A single anticonvulsant and/or medications for sleep or anxiety were permitted only in the case in which the participant was already taking them at a stable dose for the 30 days before enrolment. Similar restrictions were placed on the use of behaviour intervention therapy. Medications for pre-existing organic disorders were allowed provided that the dose and schedule of administration were kept as constant as possible.
Interventions	Intervention (risperidone) for 8 weeks: "risperidone oral solution 1.0mg/mL was administered once daily in the morning at 0.01mg/kg/day on treatment days 1 and 2 and increased to 0.02mg/kg/day on day 3. The dose could be increased from day 8 by a maximal increment of 0.02mg/kg/day. After that, the dose could be adjusted at the investigator's discretion at weekly intervals by increments/ decrements not to exceed 0.02mg/kg/day. The maximal allowable dosage was 0.06mg/kg/day. (mean dose 0.06mg/day; mean 1.48mg/day)" Comparator (placebo) for 8 weeks: 1 mg/mL once daily increasing to 0.02 mg/kg/day
Outcomes	Primary outcomes • Irritability, measured using the ABC-I subscale (Aman 1985) • aggression, measured using the Nisonger Child Behavior Rating Form-Conduct Problem subscale • AEs

Shea 2004 *(Continued)*

	Secondary outcomes: none reported Timing of outcome assessments: baseline, and weeks 1, 2, 3, 5, 7 and 8
Notes	Study start date: not reported Study end date: not reported Source of funding: Janssen-Ortho Inc, Canada, and Johnson & Johnson Pharmaceutical Research and Development Conflicts of interest: none declared Trial registry: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Inadequate details
Allocation concealment (selection bias)	Unclear risk	Inadequate details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details
Incomplete outcome data (attrition bias) All outcomes	High risk	Used an ITT analysis (participants who had received at least 1 dose of study medication) LTFU: 2 in treatment group withdrew because of AE and 1 withdrew due to insufficient response
Selective reporting (reporting bias)	High risk	Sedation not reported as an AE
Other bias	High risk	Study authors note that measurements were made 7 times throughout the study however only baseline and endpoint data were reported.

Sikich 2013

Study characteristics

Methods	Parallel trial of oxytocin versus placebo
Participants	Inclusion criteria: • ASD diagnosis based on DSM-4 criteria • male or female outpatients • aged 18-60 years • CGI–S score ≥ 4 (moderately ill)

Sikich 2013 *(Continued)*

- on stable pharmacologic and nonpharmacologic treatments for at least 3 months
- normal physical examination
- full-scale IQ > 70
- sexually active women had to be on two barrier methods of contraception and no hormonal birth control

Exclusion criteria:

- prematurity
- primary axis 1 disorders such as bipolar disorder, psychosis, post-traumatic stress disorder, schizophrenia, or major depressive disorder/ anxiety disorder
- history of significant neurological disease including, but not limited to, unstable epilepsy disorder, known genetic syndromes, or known abnormal brain magnetic resonance imaging, or history of malignancy or any significant haematological, endocrine, cardiovascular (including any rhythm disorder), respiratory, renal, hepatic, or gastrointestinal disease
- unable to tolerate venipuncture procedures

Location/setting: not stated

Sample size: 25 (12 in oxytocin/oxytocin sequence; 13 in placebo/oxytocin)

Number of withdrawals/dropouts: 1 in oxytocin/oxytocin group due to AEs

Gender: oxytocin 12/12 were male; placebo 11/13 were male

Mean age: oxytocin 10.6 years; placebo 10.0 years

IQ: oxytocin: 4/12 had IQ < 70; placebo 10/13 had IQ < 70

Baseline ABC-I or other BoC: not reported

Concurrent medications: details not provided

History of previous medications: details not provided

Interventions	Intervention (oxytocin) for 6 weeks: oxytocin (Syntocinon; NOVARTIS) dosage was up to 32 IU (8 intranasal spray puffs) twice-daily for 6 weeks. Participants aged 3-10 years titrated up to a maximum dose of 24 IU. Participants aged 11-17 years titrated up to a maximum dose of 32 IU Comparator (placebo) for 6 weeks: placebo nasal spray
Outcomes	Primary outcomes: AEs Secondary outcomes: none reported Timing of outcome assessments: not reported
Notes	Study start date: March 2011 Study end date: April 2013 Source of funding: University of North Carolina, Chapel Hill Autism Speaks, USA Conflicts of interest: none declared Trial registry: NCT01944046

Risk of bias

Bias	Authors' judgement	Support for judgement

Sikich 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "a computer generated randomization table was created by the research pharmacist and used to randomise participants"
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All efficacy assessments were carried out by an independent evaluator who was blinded to both side effects and group assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were analysed using an ITT analysis and baseline and endpoint QoL scores were recorded.
Selective reporting (reporting bias)	Low risk	The primary and secondary outcomes of interest were recorded on clinicaltrials.gov and all results were provided.
Other bias	Unclear risk	No significant differences in gender, race, age. Perhaps a slight difference in IQ - oxytocin group 99 (22) and placebo 118 (19) however, several study authors are connected to many pharmaceutical companies.

Sikich 2021

Study characteristics	
Methods	24-week parallel trial of oxytocin versus placebo
Participants	Inclusion criteria: • aged 3 years-17 years 11 months • diagnosed ASD, Asperger's syndrome, or PDD-NOS using DSM-5-TR criteria • clinical diagnosis of ASD confirmed using the ADOS and ADI-R; must be within 1 point of autism criteria on both social and communication domains of the ADI or meet autism criteria in one of these ADI domains and come within 2 points of autism criteria in the other • guardian or participant able to provide informed consent Exclusion criteria: • Participants could not have received a diagnosis of the Rett syndrome or childhood disintegrative disorder, deafness or blindness, active cardiovascular or renal disease, or uncontrolled epilepsy or be pregnant, lactating, or sexually active without contraception • Previous daily treatment with intranasal oxytocin for more than 30 days • Changes in neuropsychiatric medications were not allowed within 1 month before randomisation; changes in nonmedication therapies for autism spectrum disorder were not allowed within 2 months before randomisation Location/setting: USA Sample size: oxytocin 146; placebo 144 Reasons for withdraws/dropouts: oxytocin 21 (AEs (5), clinical worsening (3), LTFU (3), participant withdrew (2), physician decision (1), did not have baseline ABC-SW (2), did not have a postbaseline ABC SW

Sikich 2021 *(Continued)*

	(5)); placebo 19 (AEs (2), clinical worsening (2), LTFU (3), participant withdrew (4), physician decision (2), did not have a postbaseline ABC SW (6)) Gender: 242 male, 35 female Mean age: approximately 10.5 years across both groups IQ: details not provided Baseline ABC-I or other BoC scale (mean and SD): oxytocin ABC-Irritability 10.9 (SD7.83); placebo 12.6 (8.94) Concomitant medications: participants must be on stable psychotropic medication in the month prior to and during the study. Anticonvulsants and stimulants were allowed. Previous medications: details not provided
Interventions	Intervention (oxytocin) for 24 weeks: "Each insufflation will deliver 8 IU or 24 IU of oxytocin. A maximum of 3 insufflations at a time will be required. Dosing will be flexible between 8 IU/day and 80 IU/day, typically in two divided doses delivered in the morning and in the afternoon. Doses will typically increase by 8 IU twice daily (BID) at week 2 and weeks 4 and 8 until achieving the target dose of 24 IU BID at week 8. Subsequently doses may be increased in 8 IU BID increments ONLY at each visit until a maximum dose of 40 IU BID is achieved.Each bottle's label will have its own unique nonsequential randomly assigned number and not a lot number to facilitate masking". Comparator (placebo) for 24 weeks: "This nasal spray will contain all of the ingredients that are in the active oxytocin spray in the same quantities, except oxytocin will NOT be added to the solution. It will be packaged using the same container system as the active oxytocin nasal spray. Each bottle's label will have its own unique nonsequential randomly assigned number and not a lot number to facilitate masking. Dose titration will occur using exactly the same criteria and procedures as for active study drug."
Outcomes	Primary outcomes: • irritability (measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessments: endpoint (24 weeks)
Notes	Study start date: August 2014 Study end date: June 2017 Funding: “Supported by a grant (U01HD073984) from the Eunice Ken[1]nedy Shriver National Institute of Child Health and Human Development through the Autism Centers of Excellence Program and the Department of Psychiatry and Behavioral Sciences at Duke University. The data and safety monitoring board was funded by a grant (UL1TR002489) from the National Center for Advancing Translational Sciences.” Conflicts of interest: details not provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned in a 1:1 ratio, by means of a centralised randomisation table
Allocation concealment (selection bias)	Unclear risk	Participants were randomly assigned in a 1:1 ratio, by means of a centralised randomisation table

Sikich 2021 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; "the trial physician, who was unaware of the participant's trial-group assignment, completed a physical examination, systematically elicited a history of adverse events, verified concomitant treatments, and, at visits after the baseline visit, assessed current symptoms of autism spectrum disorder using the Clinical Global Impressions" "Scale of Improvement. Parents or guardians completed the Aberrant Behavior Checklist (ABC) and the Pervasive Developmental Disorders Behavior Inventory–Screening Version (PDDBI-SV) at each visit..."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind; "the trial physician, who was unaware of the participant's trial-group assignment, completed a physical examination, systematically elicited a history of adverse events, verified concomitant treatments, and, at visits after the baseline visit, assessed current symptoms of autism spectrum disorder using the Clinical Global Impressions" "Scale of Improvement. Parents or guardians completed the Aberrant Behavior Checklist (ABC) and the Pervasive Developmental Disorders Behavior Inventory–Screening Version (PDDBI-SV) at each visit..."
Incomplete outcome data (attrition bias) All outcomes	High risk	Several exclusions for "not having data" e.g. "2 Had no baseline ABC-mSW data"
Selective reporting (reporting bias)	High risk	At least one of the outcomes on trials registry was not reported in the paper (CGI)
Other bias	Low risk	Nothing else identified

Soorya 2021

Study characteristics	
Methods	6-month parallel trial of memantine versus placebo
Participants	Inclusion criteria: • verbal outpatients aged 6-12 years • clinical diagnosis of PDD based on the DSM-4 criteria, or a diagnosis of ASD based on the DSM-5 criteria • required to have difficulty with motor skills as per caregiver report during the psychiatric intake interview. • stable on all nonpharmacologic treatments for 3 months before randomisation and stable on up to 2 concomitant psychotropic medications 30 days before randomisation • CGI-S score of ≥ 4 (i.e. moderately ill) • ABC-I subscale score of < 17 Exclusion criteria: • born prior to 35 weeks' gestational age • any primary psychiatric diagnosis other than autism at screening • history of ADHD, bipolar disorder, psychosis, post-traumatic stress disorder, schizophrenia, or major depressive disorder • medical history of neurological disease, including, but not limited to, epilepsy/seizure disorder (except simple febrile seizures), movement disorder, tuberous sclerosis, fragile X, and any other known genetic syndromes, or known abnormal MRI/structural lesion of the brain

Soorya 2021 *(Continued)*

- a medical condition that might interfere with the conduct of the study, confound interpretation of the study results, or endanger their own well-being
- evidence or history of malignancy or any significant haematological, endocrine, cardiovascular (including any rhythm disorder), respiratory, renal, hepatic, or gastrointestinal disease
- planning to initiate or change pharmacological or nonpharmacologic interventions during the course of the study
- on d-cycloserine or riluzole
- on agents that alkalinise the urine (acetazolamide, potassium citrate, and sodium bicarbonate),
- received treatment with memantine in the past with no response
- history of hypersensitivity reaction to dextromethorphan, amantadine, or any other NMDA receptor antagonists
- unable to tolerate venipuncture procedures for blood sampling
- might not be suitable for the study in the Investigator's opinion
- weigh < 20 kg (to meet FDA approvals)
- positive pregnancy test

Location/setting: 2 outpatient clinics in the USA

Sample size: 23 in total (memantine (12); placebo (11))

Reasons for withdrawals/dropouts: 5 in memantine group discontinued (AEs (1), time constraints (1), lack of efficacy (2), LTFU (1)); 3 in placebo group discontinued (time constraints (1), AEs (2))

Gender: 20 male, 3 female

Mean age: approximately 9.5 years across both groups

IQ: approximately 77 across both groups

Baseline ABC-I or other BoC scale: ABC-I was < 17 at baseline

Concomitant medications: "stable on up to two concomitant psychotropic medications 30 days before randomization"

Previous medications: details not provided

Interventions	Intervention (memantine) for 6 months: "memantine will be initiated at 3 mg. The dose will be increased every week by 3 mg for a maximum of 12mg for subjects weighing ≥ 60kg, 9mg for subjects weighing ≥ 40 kg but <60 kg, and 6 mg for subjects weighing ≥ 20 kg but < 40kg." Comparator (placebo): equivalent placebo for 6 months
Outcomes	Primary outcomes: AEs Secondary outcomes: tolerability Timing of outcome assessments: every 2 weeks
Notes	Study start date: December 2011 Study end date: October 2015 Funding:"No funding was received for this article." Conflicts of interest: study medication was provided through an in-kind contribution from Forest Pharmaceuticals. Most of the study authors received consultation fees or other support from pharmaceutical companies.

Risk of bias

Bias	Authors' judgement	Support for judgement

Soorya 2021 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No information on how the sequence was generated. Quote: "Participants (n = 23), ages 6–12, were randomized at a 1:1 ratio to treatment with memantine or placebo by the study pharmacist at the Icahn School of Medicine at Mount Sinai (original coordinating site)."
Allocation concealment (selection bias)	Unclear risk	Randomisation process unclear, pharmacist may have known the next allocation Quote: "Participants (n = 23), ages 6–12, were randomized at a 1:1 ratio to treatment with memantine or placebo by the study pharmacist at the Icahn School of Medicine at Mount Sinai "
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants and investigators were blind to group assignment until the blind was broken by the study statistician at the end of the study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All participants and investigators were blind to group assignment until the blind was broken by the study statistician at the end of the study.
Incomplete outcome data (attrition bias) All outcomes	High risk	Large attrition from treatment group (near 50%), denominator unclear for outcomes reported
Selective reporting (reporting bias)	Low risk	Appears to match registry
Other bias	High risk	Study medication was provided through an in-kind contribution from Forest Pharmaceuticals.

Sprengers 2021

Study characteristics	
Methods	13-week parallel trial of bumetanide versus placebo
Participants	Inclusion criteria: • children 7-15 years of age • clinical diagnosis of autism • IQ of at least 55 Exclusion criteria: • IQ < 55 • psychoactive medication use < 8 weeks prior to screening visit (except chronic melatonin treatment) • start of any new therapy for developmental disorder problems (e.g. cognitive behavioral therapy) • comorbid neurological disorders, chronic renal disease, unstable serious illness • use of nonsteroidal anti-inflammatory drugs • documented history of hyper-sensitivity reaction to sulphonamide derivatives Location/setting: a tertiary hospital in the Netherlands Mean age: 10.5 years Mean IQ: 101

Sprengers 2021 *(Continued)*

	Gender: bumetanide 68% male; placebo 69% male Sample size: 47 randomised to bumetanide group, 45 randomised to placebo group Reasons for dropouts: 4 participants (2 from each group) discontinued prior to collecting the first outcome data. "One participant in the placebo arm stopped because of nonspecific somatic complaints and another because of intractable resistance to venipunctures. The two discontinued treatments in the bumetanide arm were because of inability to adhere to potassium supplementation and one because of a school crisis requiring immediate psychiatric intervention." Baseline ABC-Irritability scores: bumetanide 14.3 (8.2); placebo 14.5 (7.9) Concomitant medications: details not provided Previous medications: 30% had received stimulants and 6% antipsychotics in the bumetanide group while 24% and 11% from the placebo group had received stimulants and antipsychotics respectively.
Interventions	Intervention (bumetanide) for 13 weeks: twice daily bumetanide liquid with a concentration of 0.5 mg/mL for 91 days (13 weeks). The mean dose of bumetanide was 0.0482 mg/kg/day. Comparator (placebo) for 13 weeks: twice daily placebo liquid with a concentration of 0.5 mg/mL
Outcomes	Primary outcomes: • ABC-I (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessments: baseline, day 4, day 7, day 14, day 28, day 56, day 91 (endpoint)
Notes	Study start date: June 2016 Study end date: December 2018 Funding: "The study was funded by the Netherlands Organisation for Health Research and Development (ZonMw; GGG - #836041015)" Conflicts of interest: some study authors received grants for other studies. Trial registry: details not provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The sequence was generated with restricted randomisation using permuted block design with block sizes randomly varying from 2 to 4 to 6 participants
Allocation concealment (selection bias)	Low risk	Undistinguishable medication kits were numbered accordingly by Neurochlore, the company who provided the study medication, and were shipped to the local trial pharmacy where a sealed copy of the randomisation sequence was stored for emergency unmasking.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, parents, healthcare providers, and outcome assessors were masked for randomisation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	To secure masking of the outcome assessors for possible (diuretic) side effects of bumetanide, medical checks and handling of AEs during the treatment and wash-out phase were performed by a team at the paediatric nephrology de-

Sprengers 2021 *(Continued)*

		partment of the nearby Wilhelmina Children's Hospital who were also masked for randomisation.
Incomplete outcome data (attrition bias) All outcomes	High risk	Modified ITT with a high (relative) number of dubious exclusions. Quote: "Outcome measures of six participants had to be excluded from analysis. One participant appeared to have started extensive dyslexia training during the medication phase. The outcomes of the other five participants were excluded because parents explicitly mentioned unreliable reporting on outcome measures due to stress of, for example, pending divorce lawsuits or conflicts to obtain access to health care provisions."
Selective reporting (reporting bias)	Low risk	Prespecified primary outcomes reported (Social Responsiveness Scale-2 at 91 days)
Other bias	Low risk	No obvious other sources of bias

Squassante 2018

Study characteristics	
Methods	12-week parallel trial of balovaptan versus placebo
Participants	Inclusion criteria: • men 18-45 years of age • met the criteria for ASD based on both the DSM-5 and ICD-10 • CGI-S score ≥ 4, Social Responsiveness Scale-2 T score ≥ 66 • IQ ≥ 70 • language, hearing, and vision capabilities compatible with completion of study measurements, as judged by the investigator • have lived with or have had substantial periods of contact with a caregiver willing and able to attend on-site assessments, oversee participant compliance, and report on participant status via completion of study assessments Exclusion criteria: • alcohol and/or substance abuse/dependence during the last 12 months • significant risk for suicidal behaviour, in the opinion of the investigator • systolic blood pressure > 140 or < 90 mm Hg, and diastolic blood pressure > 90 or < 50 mm Hg; resting pulse rate > 90 or < 40 beats per minute • use of prohibited medications (including oxytocin and carbamazepine) or herbal remedies within 2 weeks prior to randomisation, or 5 half-lives (whichever is longer) • initiation of a new major change in psychological intervention within 4 weeks prior to randomisation • participation in an investigational drug or device study within 60 days prior to randomisation Location/setting: 26 sites across USA Sample size: placebo (5), balovaptan 1.5 mg (32), balovaptan 4 mg (77), balovaptan 10 mg (39) Number of withdrawals/dropouts: missing postbaseline efficacy assessment placebo (3), balovaptan 1.5 mg (2), balovaptan 4 mg (4), balovaptan 10 mg (1) Gender: all paticipants were male Mean age: placebo 24.7 (6.3); balovaptan 1.5 mg 28.2 (7.8); balovaptan 4.0 mg 24.5 (6.6); balovaptan 10 mg 23.9 (5.0) IQ: details not provided

Squassante 2018 *(Continued)*

	Baseline ABC-I or other BoC: baseline scores not reported Concomitant medications: "before enrollment and throughout the study, 81 to 86% of participants across treatment groups were on concomitant pharmacological treatments, with the most common being selective serotonin reuptake inhibitors (28 to 35% across groups). Antipsychotic agents were taken by 15 to 28% of participants across treatment groups, and central nervous system stimulants were taken by 13 to 26% of participants. There were no imbalances in the percentage of participants taking psychotropic drugs across the treatment arms." Previous medications: details not provided
Interventions	Intervention (balovaptan) for 12 weeks: 1.5 mg, 4.0 mg, or 10 mg: balovaptan or placebo was administered orally daily for 12 weeks, with the first dose on day 1 after predose and baseline assessments, with a 6- to 7-week follow-up period after the last dose. Study medication was provided as balovaptan 0.5-, 4-, and 5-mg hard capsules or matching placebo capsules. Comparator (placebo) for 12 weeks: matching placebo
Outcomes	Primary outcomes: • irritability (change from baseline), measured using the ABC-Irritability subscale (Aman 1985) • AEs Secondary outcomes: QoL, measured using the PedsQL (WHO 1998) Timing of outcome assessments: baseline and week 12 (endpoint)
Notes	Study start date: February 2013 Study end date: February 2017 Funding: "Funding was provided by F. Hoffmann-La Roche Ltd. for the study and third-party writing assistance, which was provided by Dinakar Sambandan, PhD, of Envision Pharma Group". Conflicts of interest: the majority of the study authors were employees of the funder (F.Hoffmann-La Roche Ltd.). Trial registry: NCT01793441

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, site personnel, and the sponsor were blinded to treatment assignments, with the exception of the individual responsible for pharmacokinetic data analysis and the internal monitoring committee/scientific oversight committee for specified data reviews.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, site personnel, and the sponsor were blinded to treatment assignments, with the exception of the individual responsible for pharmacokinetic data analysis and the internal monitoring committee/scientific oversight committee for specified data reviews.
Incomplete outcome data (attrition bias)	Low risk	Low attrition

Squassante 2018 *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	Percentage of participants with suicidality, as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS) was a primary outcome on trial reg (NCT01793441) but is not reported. Doesn't report PedsQL at baseline.
Other bias	High risk	Pharma company funded the study and was involved in the analysis. 'F. Hoffmann–La Roche AG, Basel, Switzerland provided support for the study and participated in the study design, conducted the study, undertook data collection, management, and interpretation as well as preparation, review, and approval of the manuscript. Funding was provided by F. Hoffmann–La Roche Ltd. for the study and third-party writing assistance, which was provided by K. H. Condon of Envision Pharma Group'

Takamitsu 2015a

Study characteristics	
Methods	6-week cross-over trial of oxytocin versus placebo
Participants	Inclusion criteria: • diagnosis of ASD • male • full-scale IQ (480) • aged 18–55 years Exclusion criteria: • any history of allergic responses to oxytocin, seizures, traumatic brain injury with any known cognitive consequences, loss of consciousness for more than 5 min, and substance abuse or addiction. • current instability of comorbid psychiatric symptoms and contraindications on MRI scanning Location/setting: outpatient clinic of The University of Tokyo Hospital, Japan Sample size: oxytocin-placebo (10), placebo-oxytocin (10) Number of withdrawals/dropouts: oxytocin-placebo (1), placebo-oxytocin (1) - both due to self-termination Gender: all participants were male Mean age: oxytocin-placebo = 35.1, placebo-oxytocin = 29.3 IQ: details not provided Baseline ABC-I or other BoC: oxytocin-placebo QoL 3.25 (0.65); placebo-oxytocin 2.68 (0.82) Concomitant medications: details not provided History of previous medications: "moreover, a comparable effect size was also seen in psychotropic-free participants after excluding one participant with continual medication of serotonin-norepinephrine reuptake inhibitors for his recurrent major depression (d = 0.74)."
Interventions	Intervention (oxytocin) for 6 weeks: the participants received oxytocin (24 IU, Syntocinon-Spray; Novartis) in the morning and afternoon over 6 consecutive weeks (i.e. 48 IU/day).

Takamitsu 2015a *(Continued)*

	Comparator (placebo) for 6 weeks: in the same way (24 IU placebo Syntocinon-Spray; Novartis) in the morning and afternoon over 6 consecutive weeks (i.e. 48 IU/day).
Outcomes	Primary outcomes: none reported Secondary outcomes: QoL (WHO-QoL) (WHO 1998)
Notes	Study start date: March 2012 Study end date: April 2013 Funding: "A part of this study is a result of the 'Development of biomarker candidates for social behaviour' project under the Strategic Research Program for Brain Sciences by the MEXT (K.K. and H.Y.) and the Centre of Innovation Program from Japan Science and Technology Agency (HY)". Conflicts of interest: "The authors declare no conflict of interests". Trial registry: UMIN000007122

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomised order
Allocation concealment (selection bias)	Unclear risk	Quote: "The manager completely covered the bottle labels to keep drug types unknown to all participants, their families, experimenters, clinicians and assessors including ADOS administrators and assessors"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Details not provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for and included in the analysis.
Selective reporting (reporting bias)	Low risk	Primary outcome measures reported per trial reg - https://rctportal.niph.go.jp/en/detail?trial_id=UMIN000007122
Other bias	Low risk	No other sources of bias identified

Troost 2005

Study characteristics

Methods	Parallel discontinuation trial of risperidone versus placebo
Participants	Inclusion criteria: • aged 5-17 years • weighed at least 15 kg

Troost 2005 *(Continued)*

- mental age of at least 18 months
- required to demonstrate clinically significant tantrums, aggression, self-injurious behaviour, or a combination
- ineffective medications were gradually withdrawn in a 7-28-day wash-out period. In the case of comorbid ADHD, stimulants were allowed to be continued, provided that no changes in dose during the study would occur.

Exclusion criteria: on effective psychotropic drug treatment for disruptive behaviour

Location/setting: "study participants were recruited from Groningen and Utrecht University Child and Adolescent Psychiatry Centres", the Netherlands

Sample size: 24

Number of withdrawals/dropouts:

Gender: 22/24 were male

Mean age: risperidone 9 years; placebo 8 years

IQ: mental age of ≥ 18 months

Baseline ABC-I or other BoC: ABC-I risperidone 11.1, placebo 12.7

Concomitant medications: provided that no changes in dose during the study would occur. Anticonvulsants used for the treatment of a seizure disorder were permitted if the dose had been stable for at least 4 weeks and the patient was seizure-free for at least 6 months. 20/24 were not taking any medications concurrently. 3 were on stimulants and 1 was on stimulants and anticonvulsants.

History of previous medications: 19/24 had not received any prior psychotropic drugs, 3 had been on stimulants, 1 on antipsychotics and 1 on a stimulant and anticonvulsant.

Interventions	Intervention (risperidone) for 8 weeks: risperidone mean daily dose of 1.8 mg/day or maximum daily dose of 2.5 mg (children weighing < 45 kg) or 3.5 mg (children ≥ 45 kg) Comparator (placebo) for 8 weeks: "for the placebo group, entry doses were reduce by 25% per week for 3 consecutive weeks. After full placebo substitution, the placebo group remained on placebo for 8 weeks."
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • rate of relapse (defined as 25% increase in ABC-I scores), measured in % Secondary outcomes: none reported Timing of outcome assessments: weekly during the discontinuation phase
Notes	Study start date: details not reported Study end date: details not reported Source of funding: "Korczak Foundation" - EBMH publication Conflicts of interest: "Dr. Buitelaar is a paid consultant to or has received support from Janssen Cilag BV, Abbott, VCB, Shire, Medice, and Eli Lilly; Dr. Minderaa is a paid consultant to Eli Lilly and Janssen Cilag BV; and Dr. Scahill is a paid consultant to Janssen Pharmaceutica Inc., Bristol-Myers Squibb, and Pfizer."Study medications were donated by Janssen Cilag BV." Trial registry: not reported.

Risk of bias

Troost 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation sequence was generated by an outside vendor and was stratified by investigational site.
Allocation concealment (selection bias)	Low risk	Risperidone and placebo were supplied by the pharmacist at each site as matching capsules in identical packages.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients, parents and evaluators all were unaware of assignment to placebo or risperidone.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients, parents and evaluators all were unaware of assignment to placebo or risperidone.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Sedation was not reported as an AE. No LTFU reported by the study authors. ITT analysis: an ITT analysis was used for all participants enroled by using the LOCF for all measures.
Selective reporting (reporting bias)	High risk	The ABC-I scores were reported in full for both the open-label and discontinuation phases of the trial. However, the CGI scores were only reported at baseline.
Other bias	High risk	Dr. Buitelaar is a paid consultant to or has received support from Janssen Cilag BV, Abbott, VCB, Shire, Medice, and Eli Lilly; Dr. Minderaa is a paid consultant to Eli Lilly and Janssen Cilag BV; and Dr. Scahill is a paid consultant to Janssen Pharmaceutica Inc., Bristol-Myers Squibb, and Pfizer. Only 8/24 with autism were in discontinuation phase despite title mentioning ASD. Baseline ABC-I was relatively low.

Umbricht 2017

Study characteristics	
Methods	Cross-over study of vasopressin versus placebo
Participants	Inclusion criteria: • men • aged 18–45 years • diagnosis of autistic disorder (DSM-4-TR) • IQ > 70 • ABC-I subscale score ≤ 13 • existing medication regimens should be stable for 4 weeks, with the intent to remain stable throughout the study • a reliable caregiver, able and willing to provide information regarding the participant's behaviour and symptoms Exclusion criteria:

Umbricht 2017 *(Continued)*

	• positive urine test for drugs of abuse or alcohol and/or substance abuse/dependence during the last 12 months • significant risk of suicidal behaviour • disruptive, aggressive or self-injurious, or sexually inappropriate behaviour during the last 3 months • uncontrolled or any unstable medical condition other than ASD (e.g. diabetes) that might interfere with the study, or endanger the participant's well-being • treatment with prohibited medications and not willing to cease treatment for the minimum time period before randomisation. Location/setting: multicenter (3 sites, universities in the USA) Sample size: first phase vasopressin followed by placebo, 9 were randomised first phase; placebo followed by RG7713, 10 were randomised. 1 participant was excluded from the vasopressin analysis. Number of withdrawals/dropouts: none reported Gender: all participants were male Mean age: 23.4 years (5.1) IQ: 100 (14.5) Baseline ABC-I or other BoC: intervention ABC-I 3.0 (3.9); placebo 3.0 (3.9) Concomitant medications: prohibited medications included all medications except those for ongoing treatment of symptoms of irritability, mood disorders, anxiety and hypertension, and paracetamol/acetaminophen for treatment of AEs. CYP3A4 inhibitors and inducers, or P-gp substrates must not be taken ≤ 4 weeks before the study. History of previous medications: details not provided
Interventions	Vasopressin-placebo: sequence 1. Participants received a single dose of 20 mg vasopressin during treatment visit 1 followed by placebo during treatment visit 2. "A single 20 mg dose of vasopressin or placebo was administered intravenously as a 2-h infusion to each subject on two different days (treatment visits 1 and 2) separated by a 7–14- day washout period." Placebo-vasopressin: sequence 2. Participants received a single dose of placebo followed by vasopressin.
Outcomes	Primary outcomes: AEs Secondary outcomes: Timing of outcome assessments: baseline and at the end of each phase of cross-over study
Notes	Study start date: December 2011 Study end date: March 2013 Source of funding: the study was funded by a pharmaceutical company (F. Hoffmann-La Roche) and the drug was also supplied by this company. Conflicts of interest: none declared Trial registry: NCT01474278

Risk of bias

Bias	Authors' judgement	Support for judgement

Umbricht 2017 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Subjects were randomized to sequence 1 or 2 using a randomized treatment schedule that was developed by the study sponsor for each site and incorporated into double-blind (investigator and subject) treatment labelling"
Allocation concealment (selection bias)	Low risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Subjects were randomized to sequence 1 or 2 using a randomized treatment schedule that was developed by the study sponsor for each site and incorporated into double-blind (investigator and subject) treatment labeling."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Subjects were randomized to sequence 1 or 2 using a randomized treatment schedule that was developed by the study sponsor for each site and incorporated into double-blind (investigator and subject) treatment labeling."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All were included in the analysis
Selective reporting (reporting bias)	Unclear risk	ABC-I was reported at baseline but only total ABC was reported at endpoint.
Other bias	High risk	The study was funded by pharma companies and the drug was also supplied by them.

Unis 2002

Study characteristics	
Methods	4-week parallel study of secretin versus placebo
Participants	Inclusion criteria: • children aged 3-12 years • DSM-4 diagnosis of autism or PDD-NOS • non-verbal IQ of > 55 Exclusion criteria: • any other medical condition "for which autism was considered symptomatic (for example Fragile X, or tuberous sclerosis)" • previously been in receipt of secretin • been on psychotropic drug treatments within the past 6 months • children with any known pork allergies Setting: not described Sample size: 85 Number of dropouts: 4 participants discontinued, the infusion was not given (2), decided against the infusion (1), did not return for follow-up assessment (1). Another child developed illness and a fever after infusion and did not complete the study. Mean age: 6.5 years Gender: details not provided

Unis 2002 *(Continued)*

	IQ: mean IQ of 55 Baseline ABC-I or other BoC: scores were > 57 at baseline Concomitant medications: psychotropic medications were not permitted during the study or in the 6 months prior to the study except for "occasional symptomatic use for sleep, etc" Previous medications: details not provided
Interventions	Intervention (secretin): single infusion of 0.4 ug/kg synthetic secretin given intravenously over a 2-minute period, or single infusion of 2 CU/kg biologic secretin given intravenously over a 2-minute period Comparator (placebo): single infusion of placebo intravenously over a 2-minute period
Outcomes	Primary outcomes: ABC-I (change from baseline) (Aman 1985) Secondary outcomes: none reported Timing of outcome assessments: baseline and week 4 (endpoint)
Notes	Study start date: June 1999 Study end date: May 2000 Funding: "Unis, Munson, Abbott, and Dawson were supported by a grant from the NICHD and the NIDCD (PO1HD34565). Dr. Rogers was supported by a grant from the NICHD (PO1HD35468). Drs. Rogers, Gabriels, and Goldson were also supported by ADD grant 90dd041401 and MCH grant MCJ08941301. Dr. Goldson was also supported by a grant from the NCRR (MO1-RR00069)". Conflicts of interest: none declared Trial registry: NCT00065962

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Children were then randomly assigned to treatment group"
Allocation concealment (selection bias)	Unclear risk	Quote: "Children were then randomly assigned to treatment group"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "parents, teachers and investigators were all blind to treatment (allocation)"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "parents, teachers and investigators were all blind to treatment (allocation)"
Incomplete outcome data (attrition bias) All outcomes	High risk	5 participants were reported to have not completed the study however only 77/85 results were reported for ABC-I. Up to 40% missing data (see table 1) for teacher-reported ABC-I
Selective reporting (reporting bias)	Low risk	Outcome measures included in trials registry reported
Other bias	High risk	All participants were responders to secretin from previous open-label trial

VanAndel 2022

Study characteristics	
Methods	13-week parallel trial of bumetanide versus placebo
Participants	Inclusion criteria: • current ASD, ADHD (according to DSM-4-TR or DSM-5 criteria), and/or epilepsy diagnosis • aged 5–15 years • IQ ≥ 55 • diagnosis accompanied by altered sensory reactivity, defined as a deviant score (> 1 SD deviant) on the Sensory Profile for parents or teachers (SP-NL or SP-SC) • use of concomitant psychoactive and antiepileptic drugs (AED) was allowed, when being taken on an unadjusted dosage at least 2 months prior to baseline measures Exclusion criteria: • renal or liver insufficiency • serious unstable illnesses (including gastroenterological, respiratory, cardiovascular, endocrinologic, immunologic, haematologic disease, dehydration or hypotension, electrolyte disturbances) • treatment with nonsteroidal anti-inflammatory drugs, aminoglycosides, digitalis, antihypertensive agents, indomethacin, probenecid, acetazolamide, lithium, other diuretics, stimulants (like methylphenidate and dexamphetamine, due to it assumed diametrical effects), and drugs known to have a nephrotoxic potentia • children were allowed to receive care as usual when it was initiated minimally 2 months prior to baseline measures Location/setting: The Netherlands Sample size: 38 (19 to each group) Reasons for withdrawals/dropouts: 4 in each group dropped out (bumetanide: discontinued treatment (3), excluded due to incomplete parent reports (1); placebo group discontinued treatment (2), excluded due to incomplete or unreliable parent reports (2)) Gender: 22 male, 8 female Mean age: bumetanide group 10.9 years, placebo group 8.7 years IQ: approx 99 in both groups Baseline ABC-I or other BoC scale: bumetanide group 13.1, placebo group 17.1 Diagnoses: 22/30 participants had an ASD diagnosis, of whom 15 only had an ASD diagnosis (another 6 had ASD and ADHD, and 1 participant had ASD and epilepsy) Concomitant medications: during the trial 68.4% in both groups did not receive any other medications. Of those who were taking other medications 15.8% in bumetanide group and 5.3% in placebo group were taking antipsychotics; 5.3% in placebo group were taking a benzodiazepine in addition to an antipsychotic; 15.8% in the placebo group were taking an anticonvulsant; 10.5% in the bumetanide group were taking an SSRI; and 5.3% in both groups were taking an SSRI in addition to an antipsychotic. Previous medications: 47.4% in both groups did not take medications prior to the trial. Of those who took medications 21.1% in bumetanide group and 10.5 in placebo group were taking antipsychotics; 5.3% in the placebo group were taking a benzodiazepine; 5.3% and 31.6% in the bumetanide and placebo groups respectively were taking an anticonvulsant; 10.5% and 5.3% in the bumetanide and placebo groups respectively were taking an SSRI; 31.6% and 26.3% in the bumetanide and placebo groups respectively were taking stimulants; 5.3% and 10.5% in the bumetanide and placebo groups respectively were taking an alpha adrenergic agonist.

VanAndel 2022 *(Continued)*

Interventions	Intervention (bumetanide) for 13 weeks: maximum of 1 mg bumetanide twice daily followed by a 28-day washout period Comparator (placebo) for 13 weeks: equivalent placebo twice daily followed by a 28-day washout period
Outcomes	Primary outcomes: • irritability (measured using the ABC-I subscale) (Aman 1985) • AEs • self injurious behaviour (measured using the Repetitive Behaviour Scale self-injury subscale) (Bodfish 2000) Secondary outcomes: none reported Timing of outcome assessments: AEs were monitored on days 4, 7, 14, 28, 56, 91, and 119; other outcomes were measured at day 91 (endpoint) and day 119 following washout
Notes	Study start date: June 2017 Study end date: June 2019 Funding: "This study was supported by a grant from Dutch Brain Foundation (Hersenstichting #HA2015-01-04)." Conflicts of interest: HB (the contact author) has reported being a shareholder of Aspect Neuroprofiles BV, which provides EEG-analysis services for clinical trials. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Sequence generation, concealment, and treatment allocation was overseen by a third-party not involved in the study (i.e., Julius Center, a consultant support agency for clinical research and trials located in the UMC Utrecht). Restricted randomization was used with permuted block design randomly varying between two, four, and six participants. Treatment allocation was done automatically using minimization with a probability of 0.75 on the participant factors active epilepsy (y/n), IQ (55–75; 76–110; >110) and study center (UMC/Jonx)"
Allocation concealment (selection bias)	Low risk	"Sequence generation, concealment, and treatment allocation was overseen by a third-party not involved in the study"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, parents, healthcare providers, and outcome assessors were blinded for randomisation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, parents, healthcare providers, and outcome assessors were blinded for randomisation
Incomplete outcome data (attrition bias) All outcomes	High risk	> 25% dropout, "one participant was excluded from analyses as questionnaires were not reliable"

VanAndel 2022 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Can't find outcomes on either trial reg (EudraCT trial registry (2016-002875-81) and Dutch trial registry (NL6178)
Other bias	Low risk	Funder had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript

Veenstra-VanderWeele 2017

Study characteristics	
Methods	12-week parallel trial of arbaclofen versus placebo
Participants	Inclusion criteria: • current diagnosis of ASD • CGI-S score of moderate or higher at time of screening and baseline before randomisation • stable medications for at least 4 weeks prior to the study • seizure-free for at least 6 months and be on anticonvulsants or seizure-free for three years without taking anticonvulsants • any non-pharmacological interventions must have been continuing for at least 2 months prior to the study. Exclusion criteria: • participants with other conditions including drug or alcohol abuse • plan to change interventions during the study • have taken other investigational drugs in the past 30 days • unable to take oral medications • an allergy or intolerance to arbaclofen Location/setting: 25 sites across USA Sample size: 150 were randomised, arbaclofen 76, placebo 74 Mean age: 11.6 years (range 5-21 years) Mean IQ: IQ > 70 in approximately 50% of participants Gender: arbaclofen 63% were male; placebo 61% were male Baseline ABC-I scores: arbaclofen group 17.2; placebo 15.6 Reasons for dropouts: arbaclofen 15 discontinued (LTFU (1), AEs (8), protocol violation (1), withdrew consent (4), other (1)). Placebo 5 discontinued (AE (2), withdrew consent (2), other (1)) Concomitant medications: arbaclofen 14 were on concomitant psychoactive medication; placebo: 12 were on concomitant psychoactive medication Previous medications: details not provided
Interventions	Intervention (arbaclofen) for 12 weeks: starting dose of arbaclofen was 5 mg twice daily increasing to 10 mg twice daily up to a maximum dose of 10 mg 3 times daily for children < 12 years. Children ≥ 12 years could have 15 mg 3 times daily Comparator (placebo) for 12 weeks: matching placebo tablets
Outcomes	Primary outcomes: • ABC-I (change from baseline) (Aman 1985)

Veenstra-VanderWeele 2017 *(Continued)*

	• AEs Secondary outcomes: none reported Timing of outcome assessments: baseline and week 12 (endpoint)
Notes	Study start date: May 2011 Study end date: September 2012 Funding: Seaside Therapeutics (pharmaceutical company) Conflicts of interest: various study authors received funding from and consulted with pharmaceutical companies. Trial registry: NCT01288716

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised 1: 1 to either arbaclofen or placebo according to a centrally generated randomisation list, with stratification by age (5–11 or 12–21 years) and concomitant use of psychoactive medication.
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Blinding was maintained by utilizing identical tablets containing either STX209 or placebo"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Apart from "Double-blinded" details were not provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	Large dropout (20%) with many dropping out in treatment group due to AEs
Selective reporting (reporting bias)	Low risk	Same primary outcome on trial reg
Other bias	High risk	Funded by Seaside Therapeutics and the team has interests in a range of pharma companies

Wasserman 2006

Study characteristics

Methods	Parallel trial of levetiracetam versus placebo
Participants	Inclusion criteria: • children 5-17 years (average age 8.72 years) • diagnosis of autism according to DSM-4 criteria

Wasserman 2006 *(Continued)*

	Exclusion criteria: • responding well to previous interventions or had only mild global severity • having DSM-4 psychotic disorders, a history of seizures, and any clinically significant medical illness • free of any psychotropic medications for 4 weeks before participation • no concomitant psychiatric medications or initiation of new behavioral therapies was allowed during the study Location/ Setting: autism centre, USA Sample size: 20 (10 in each group) Number of withdrawals/dropouts: 1 from placebo group dropped out due to increased hyperactivity and 1 dropped out of levetiracetam group after having a seizure, and another due to lack of efficacy. Gender: 8 male levetiracetam group, 9 male in placebo group Mean age: 8.72 IQ: 75.75 Baseline ABC-I or other BoC: not reported adequately Concomitant medications: patients were free of any psychotropic medications for 4 weeks before participation and no concomitant psychiatric medications or initiation of new behavioral therapies was allowed during the study. History of previous medications: details not provided
Interventions	Intervention (levetiracetam) for 10 weeks: commenced at 125 mg/day up to maximum of 20-30 mg/kg/day (mean maximum dose 862.50 ± 279.19 mg/day) Comparator (placebo) for 10 weeks: equivalent placebo
Outcomes	Primary outcomes: ABC-I (although not reported) Secondary outcomes: none reported Timing of outcome assessments: assessed weekly for first 4 weeks then bi-weekly for next 6 weeks
Notes	Study start date: not reported Study end date: not reported Source of funding: supported by a grant from UCB Pharma Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Quote: "Levetiracetam and placebo were distributed in identical forms" no further details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided. Only that it was double-blinded

Wasserman 2006 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Primary outcomes were the CGI and the parent and teacher-rated ABC subscales. Data were not supplied, only "there were no significant findings on ABC subscale of irritability" (and Z score, SE, and P value provided).
Selective reporting (reporting bias)	High risk	ABC-I baseline not reported, and endpoint figures only reported as standard score, rather than by group.
Other bias	Unclear risk	Study supported by pharmaceutical company - nature and extent of their involvement is unclear

Willemsen-Swinkels 1995

Study characteristics	
Methods	Cross-over trial of naltrexone versus placebo
Participants	Inclusion criteria: • aged 18-46 years • meet the DSM-III-R criteria for autistic disorder • social impairment had to be more serious than could be expected on the basis of the level of intellectual disability Exclusion criteria: details not provided Location/setting: the Netherlands Sample size: 33 Number of withdrawals/dropouts: one 28-year old woman (with autism and self-injurious behaviour) "manifested an acute and severe increase in SIB and acting out behavior. She had to be isolated for several weeks, and her condition improved only gradually after naltrexone treatment was stopped and lithium treatment was instituted" Gender: 27 men, 6 women Mean age: 29 years IQ: details not provided Baseline ABC-I or other BoC: not an outcome Concomitant medications: details not provided History of previous medications: details not provided
Interventions	Intervention (naltrexone) for 4 weeks: *a*fter 2 weeks of placebo capsule taken once daily, naltrexone hydrochloride was given at 100 mg (mean 1.61 (0.24) mg/kg) in 1 dose at the start of week 3. For the remainder of that week, the participant received a placebo capsule every morning. From week 4, naltrexone was given at 50 mg per day for 4 weeks. This was followed by a 4-week washout period then cross-over to continue on placebo. Comparator (placebo) for 4 weeks: matching placebo tablets
Outcomes	Primary outcomes: AEs

Willemsen-Swinkels 1995 *(Continued)*

	Secondary outcomes: none reported Timing of outcome assessments: participants were observed twice at baseline, 6 and 24 h after the single-dose administration, and after 2 and 4 weeks of daily treatment
Notes	Study start date: not reported Study end date: not reported Source of funding: Janusz Korczak Foundation, Huizen Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided apart from "double-blinding used"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Treatment doses were changed for second cross-over phase after review of outcome measures, implying that assessors or investigators knew which group was being given naltrexone in first phase - i.e. not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 participant didn't complete trial due to AEs detailed - data were excluded due to early discontinuation (week 2 of 16)
Selective reporting (reporting bias)	High risk	Self-injurious behaviour was measured using the ABC-Stereotypies subscale. The authors mention that "it included three items on SIB". Incorrect. The ABC-Stereotypies subscale does not.
Other bias	High risk	Active treatment was provided in part by employee of pharmaceutical company. Nature of funding support unclear. Participant details were not provided in terms of age, gender, diagnosis, rate of SIB etc, in addition to incorrectly claiming to have assessed SIB using the ABC

Willemsen-Swinkels 1996

Study characteristics

Methods	Cross-over trial of naltrexone versus placebo
Participants	Inclusion criteria: • children aged 3-7 years • either outpatients of the Department of Child Psychiatry of the Utrecht University or members of the Dutch Autism Association • met the DSM-III-R criteria for autistic disorder

Willemsen-Swinkels 1996 *(Continued)*

	Exclusion criteria: details not provided Location/ Setting: the Netherlands Sample size: 20 total (23 originally randomised) Number of withdrawals/dropouts: 2 children were excluded from analysis because "they had taken up the habit of chewing the capsules", and 1 participant dropped out after the first treatment due to parents withdrawing consent. Gender: 16 male, 4 female Mean age: 5.5 years IQ: details not provided Baseline ABC-I or other BoC: naltrexone ABC-I 18.5, placebo 14 Concomitant medications: participants were free of psychotropic drugs for at least 6 weeks before the study. 1 participant with epilepsy was treated with carbamazepine in a fixed dosage during the study period. None of the participants had previously been treated with psychotropic drugs. History of previous medications: details not provided
Interventions	Intervention (single-dose naltrexone) for 4 weeks: naltrexone was given at 40 mg (approximately 2 mg/kg) in a single-dose capsule. After 11 weeks, this group was given a placebo in a matched capsule. Long-term daily dose study 1996: after a 2-week baseline period, naltrexone was given at 20 mg per day (approximately 1 mg/kg) over 4 weeks, with the exception of 1 participant with the weight of 42 kg who was given 40 mg per day over 4 weeks. Comparator (placebo) for 4 weeks: matching placebo tablet was given daily over 4 weeks
Outcomes	Primary outcomes: irritability, measured using the ABC-Irritability subscale (Aman 1985) Secondary outcomes: none reported Timing of outcome assessments: 2 weeks before baseline, baseline, day 1 and day 2 (for each phase)
Notes	Study start date: details not reported Study end date: details not reported Source of funding: supported by Janusz Korczak Foundation. Du Pont Pharma supplied part of the drug required. Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Further details not provided
Allocation concealment (selection bias)	Unclear risk	Further details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided

Willemsen-Swinkels 1996 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Baseline ABC-I scores were significantly higher in the naltrexone group compared to placebo.
Selective reporting (reporting bias)	Unclear risk	Results only graphically presented
Other bias	High risk	Only single dosage used. Active treatment supplied in part by pharmaceutical company. The nature of foundation support is unclear.

Wink 2016

Study characteristics	
Methods	Parallel trial of N-acetylcysteine versus placebo
Participants	Inclusion criteria: • aged 4-12 years • diagnosis of autistic disorder, Asperger's disorder, or PDD NOS • if taking concomitant psychotropic medications the medication must be at a constant dose for 60 days with no dose changes planned for the duration of the trial • able to swallow capsules Exclusion criteria: • presence of any medical condition that significantly increases risk or hampers assessment (e.g., unstable hypertension or cardiac disease, unstable asthma, kidney disease, unstable seizure disorder, pregnancy or any other medical condition as determined by the investigator) • weight < 15 kg • taking concomitant medications or supplements known for their glutamatergic effects (e.g., dextromethorphan, D-cycloserine, amantadine, memantine, lamotrigine, riluzole) or antioxidant properties (high-dose vitamin supplements, DMG, TMG, many alternative treatments) within 30 days of the baseline visit with the exception of short-term use of dextromethorphan as needed as a cough suppressant. The use of this medicine must be stopped at least 7 days prior to the baseline visit. Regular multivitamins will be allowed • taking daily acetaminophen (paracetmol) or nonsteroidal anti-inflammatory drugs within 30 days of the baseline visit • profound intellectual disabilites as evidenced by a mental age < 18 months • taking concomitant medications with the potential for pharmacokinetic or pharmacodynamic drug-drug interactions (e.g., carbamazepine) within 30 days of the baseline visit • likely to experience significant changes in their ongoing psychosocial or medical treatments for autism over the course of the trial (e.g., initiation of new behavioral therapy, initiation of new medication or alternative treatment [e.g., chelation]). Minor changes in ongoing treatment (e.g., missed therapy sessions due to holiday/vacation; planned break in therapy due to school holidays) will not be considered significant • History of prior treatment with N-acetylcysteine • hypersensitivity/allergy to N-acetylcysteine • neurodevelopmental disorders such as Fragile X Syndrome, tuberous sclerosis, or other neurological disorders known to be associated with autism or autistic features

Wink 2016 *(Continued)*

	• Rett's disorder, childhood disintegrative disorder, schizophrenia, bipolar disorder, another psychotic disorder, or substance abuse disorder Location/setting: USA Sample size: N-acetylcysteine 13; placebo 12 Number of withdrawals/dropouts: N-acetylcysteine 3 (2 lLTFU, 1 AE); placebo 3 (2 LTFU, 1 AE) Gender: 24/31 male Mean age: N-acetylcysteine 7.6 and 8.2 years IQ: 86 Baseline ABC-I or other BoC: ABC-I N-acetylcysteine 17.0, placebo 18.3 Concomitant medications: 16/31 were taking other medications. Participants taking concomitant psychotropic medications, must be taking the medication at a constant dose for 60 days with no dose changes planned for the duration of the trial. History of previous medications: details not provided
Interventions	Intervention (N-acetylcysteine) for 12 weeks: started at 300 mg/day for people weighing 15-30 kg. For people weighing > 30 kg, NAC was started at 600 mg/day. This was titrated to the target dose of 60 mg/kg/day in 3 divided doses and a maximum dose of 4200 mg/day over the first 3 weeks, then remained stable in the last 9 weeks of the study. Dose reductions due to AEs were permitted at any time. Comparator (placebo) for 12 weeks: equivalent placebo
Outcomes	Primary outcomes: • irritability, measured using the ABC-Irritability subscale (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessments: baseline, and weeks 4, 8 and 12
Notes	Study start date: December 2006 Study end date: November 2009 Source of funding: "Dr. Wink's current research is supported by the Simons Research Foundation, Autism Speaks, Riovant Sciences Ltd, and Cures Within Reach. Dr. Wink has also served as a past consultant for Otsuka. Dr. Erickson is a past consultant to Alcobra Pharmaceuticals, the Roche Group, and Novartis. Dr. Erickson holds non-related IP held by CCHMC and Indiana University. Dr. Erickson receives research grant support from the John Merck Fund, Cincinnati Children's Hospital Medical Center, Autism Speaks, the National Fragile X Foundation, The Roche Group, Neuren Pharmaceuticals, and Riovant Sciences Ltd. Dr. Adams, Dr. Wang, Dr. Klaunig, Dr. Plawecki, Dr. Posey, and Dr. McDougle report no potential conflicts of interest. This study was funded by the Autism Speaks." Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Following screening and baseline measures, participants were randomised 1:1 via computer - by the investigational pharmacy".

Wink 2016 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "all participants, guardians and investigators remained blind to study assignment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all participants guardians and investigators remained blind to study assignment"
Incomplete outcome data (attrition bias) All outcomes	High risk	6 participants from a total of 31 (19%) withdrew from the study after baseline and 25 participants were included in the final analysis.
Selective reporting (reporting bias)	Low risk	All outcomes were reported at baseline and endpoint in both the paper and clinical trials registry.
Other bias	Low risk	None identified

Wink 2018

Study characteristics	
Methods	5-week cross-over study of riluzole versus placebo
Participants	Inclusion criteria: • 12-25 years of age • diagnosis of ASD based on ADOS-2 criteria • ABC-I score of at least 18 at baseline • concomitant medications (including those targeting irritability) were required to be stable for ≥ 5 half-lives prior to baseline and throughout the study • weighing at least 50 kg Exclusion criteria: "participants prescribed > 2 psychotropic drugs targeting irritability, taking medications with known interactions with riluzole or prescribed concomitant glutamatergic or GABA (A) modulating drugs." Location/setting: the USA Mean IQ: details not reported Mean age: 16.0 years Gender: 6/7 were male Sample size: 8 in total Number analysed: 7 in total Reasons for dropouts: "one participant withdrew due to worsening aggressive behavior necessitating adjustment of his concomitant psychotropic medications after receiving five doses of study drug." Baseline ABC-I or other BoC scale: riluzole ABC-I 24.29 (6.2); placebo 25.71 (7.3) Current or previous medications:

Wink 2018 *(Continued)*

- participant 1: benztropine, clonidine, haloperidol, melatonin, propranolol;
- participant 2: chlorpromazine, guanfacine extended release, melatonin, naltrexone, olanzapine, sertraline, topiramate, zolpidem;
- participant 3: amphetamine/dextroamphetamine, guanfacine, melatonin, olanzapine, quetiapine, trazodone;
- participant 4: methylphenidate, quetiapine, sertraline, topiramate;
- participant 5: melatonin, propranolol, quetiapine, risperidone, vistaril;
- participant 6: buspirone, paliperidone;
- participant 7: melatonin, naltrexone, risperidone, sertraline, trazodone

Interventions	Intervention (riluzole): initially dosed at 50 mg/day. Dosing was then increased by 50 mg weekly to a maximum potential optimal dose of 200 mg/day (100 mg twice daily) by week 4. Comparator (placebo): initially dosed at 50 mg/day. Dosing was then increased by 50 mg weekly to a maximum potential optimal dose of 200 mg/day (100 mg twice daily) by week 4
Outcomes	Primary outcomes: • irritability (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessments: screening, baseline, weeks 3, 5, 7, and 12
Notes	Study start date: September 2013 Study end date: May 2015 Funding: "This study was funded by the Center for Clinical and Translational Science and Training at the University of Cincinnati via an Institutional Clinical and Translational Science Award, NIH/NCRR Grant No. 8UL1TR000077-04" Conflicts of interest: "The authors declare that they have no interests that compete directly with this work, though LKW, CRT, RSC, EVP, and CAE do receive research support from various sources for other work". Trial registry: NCT02081027

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Participants were randomized by the CCHMC investigational pharmacy"
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants, guardians, and investigators remained blind to study assignment throughout the study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Participants, guardians, and investigators remained blind to study assignment throughout the study"
Incomplete outcome data (attrition bias)	Low risk	The 7 participants who completed the trial were included in all the analyses.

Wink 2018 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	The ABC-I and CGI were the only outcomes listed on the trials registry. They were reported in full.
Other bias	Low risk	No other bias sources identified

Woodard 2007

Study characteristics	
Methods	4-week cross-over trial of dextromethorphan versus placebo
Participants	Inclusion criteria: • regular (at least weekly) problem behaviours (tantrums, self-talk, aggression etc.) that occurred with regularity recorded by classroom staff over a 2-month pre-study period • ≥ 16 (mean plus one standard deviation) on either the parent or the teacher rating of the ABC-I subscale at the close of the baseline condition Exclusion criteria: details not provided Location/setting: an educational treatment programme for people with autism and related developmental disorders (USA) Sample size: 8 in total (cross-over). Number of withdrawals/dropouts: none reported Gender: 7 male, 1 female Mean age: 13 years IQ: not reported Baseline ABC-I or other BoC: ABC-I of > 16 Concomitant medications: 3 were prescribed Risperdal and 1 participant received Depakote, Risperdal, Zoloft, and Seroquel. History of previous medications: not reported
Interventions	Intervention (dextromethorphan) for 4 weeks: each participant was administered dextromethorphan (Delsym) at the recommended dosage of 30 mg dextromethorphan, hydrobromide) every 12 h for ages 6-12, or 60 mg dextromethorphan hydrobromide every 12 h for ages 12 and over. Comparator (placebo) for 4 weeks: each participant was administered an identical volume of a similar sweetened syrup, packaged by a pharmacist in the same brown bottles as the Delsym.
Outcomes	Primary outcomes: • rritability, measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessment: baseline, week 4, endpoint (end of 2nd phase)
Notes	Study start date: not reported

Woodard 2007 *(Continued)*

Study end date: not reported

Source of funding: "this research was supported by a grant from Celltech Pharmaceuticals, Inc., a grant from the John Trimble Fund of The Groden Center, and NICHD grant HD30615."

Conflicts of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were only 8 participants and while individual endpoint data are provided for the ABC and each subscale, as well as the CGI, baseline data were not provided at all.
Selective reporting (reporting bias)	Unclear risk	The primary outcome measures were the ABC (and 5 subscales), the CGI-S, and the Treatment Emergent Side Effects Scale. All three of these measures were reported at endpoint, however baseline scores were not provided. Only that participants were required to have ≥ 16 on ABC-I.
Other bias	High risk	This research was supported by a grant from Celltech Pharmaceuticals, Inc.

Yamasue 2020

Study characteristics

Methods	6-week parallel trial of oxytocin versus placebo
Participants	Inclusion criteria: • male • aged 18-54 years • diagnosis of autism, Asperger's or PDD-NOS based on DSM-4-TR • verbal IQ > 85 and full IQ > 80 measured using the Wechsler Adult Intelligent Scale-III Exclusion criteria: • primary psychiatric diagnosis other than those listed in the inclusion criteria, mood or anxiety disorders • change in medication or psychotropics in the month prior to the study • currently treated with > 2 psychotropics • currently receiving medication for ADHD

Yamasue 2020 *(Continued)*

- history of oxytocin treatment
- hyper-sensitive to oxytocin
- history of seizures or traumatic brain injury with loss of consciousness > 5 minutes
- history of alcohol disorders, abuse or addiction

Location/setting: The University of Tokyo Hospital, Nagoya University Hospital, Kanazawa University, and University of Fukui Hospital in Japan

Sample size: 53 were randomised to oxytocin and 53 to placebo groups

Number of withdrawals/dropouts: 2 in oxytocin group were LTFU, 1 withdrew due to tumoural swelling of breast; 1 LTFU in placebo group due to worsening of repetitive behaviours

Gender: all participants were male

Mean age: 18-54 years, mean age oxytocin 27.6 years, mean age placebo 26.3 years

IQ: details not provided

Baseline ABC-I scores or other BoC: baseline scores not reported

Concomitant medications: "12 continued their psychotropic medications throughout the period (4 antidepressants, 4 antipsychotics, 2 anticonvulsants (mood stabilizers), 2 hypnotics)".

Previous medications: details not provided

Interventions	Intervention (oxytocin): 24 IU (Syntocinon Spray; Novartis, Switzerland) in the morning and afternoon for 6 consecutive weeks Comparator (placebo): 24 IU in the morning and afternoon for 6 consecutive weeks
Outcomes	Primary outcomes: AEs Secondary outcomes: tolerability Timing of outcome assessments: baseline and week 6 (endpoint)
Notes	Study start date: January 2015 Study end date: March 2016 Funding: "the Strategic Research Program for Brain Sciences from Japan Agency for Medical Research and Development" Conflicts of interest: "Neither the funder nor the sponsor, the Strategic Research Program for Brain Sciences from Japan Agency for Medical Research and Development, had any involvement in the data collection, analyses, writing, or interpretation of the study. However, the sponsor participated in the discussion regarding which sites should be included in the trial and how to best interpret the results" Trial registry: JPRN-UMIN000015264

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were randomly assigned to receive oxytocin or placebo at a one-to-one ratio using a computer-generated minimization design."
Allocation concealment (selection bias)	Low risk	"The registration, allocation, and data management procedures were defined separately... The following procedures were performed by the individual in charge of allocating and coding the test drug... confidentiality of the test drug allocation code table until the end of the trial and until the inclusion of each

Yamasue 2020 *(Continued)*

		participant was fixed The registration, allocation, and data management procedures were defined separately."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Apart from "double blinded" no further details were provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of dropouts described don't add up to difference in randomised/analysed (see fig 1)
Selective reporting (reporting bias)	Low risk	All outcomes listed on trials registry were reported in the paper or journal website.
Other bias	High risk	The sponsor participated in the discussion regarding which sites should be included in the trial and how to best interpret the results

ABC: Aberrant Behaviour Checklist; **ABC-I:** Aberrant Behaviour Checklist Irritability subscale; **ADHD:** Attention Deficit Hyperactivity Disorder; **ADI-R:** Autism Diagnostic Interview-Revised; **ADOS-2:** Autism Diagnostic Observation Schedule, 2nd edition; **AE**: adverse effects; **ASD:** autism spectrum disorder; **BoC:** behaviours of concern; **BSE:** Behavioral Summarized Evaluation; **CARS:** Childhood Autism Rating scale; **CBCL:** Child Behaviour Checklist; **CGI-S:** Clinical Global Impression Scale—Severity; **CPRS:** Conners' Parent Rating Scale; **CYBOCS-PDD:** Children's Yale-Brown Obsessive Compulsive Scale modified for pervasive developmental disorders; **DSM-4:***Diagnostic and Statistical Manual of Mental Disorders(4th edition);* **DSM-4 (TR):***Diagnostic and Statistical Manual of Mental Disorders(4th edition - text revision)*; **DSM-5:***Diagnostic and Statistical Manual of Mental Disorders(5th edition)*; **ECG:** electrocardiogram; **EEG:** electroencephalogram; **ICD-10:** International Classification of Diseases-10; **IQ:** intelligience quotient; **ITT:** intention-to-treat; **IU:** International Units; **LOCF:** last observation carried forward; **LTFU:** lost to follow-up; **MAOI:** monoamine oxidase inhibitor; **MDMA:** 3,4-methylenedioxy-methamphetamine; **MRI:** magnetic resonance imaging; **MSEL:** Mullen Scales of Early Learning; **NAC:** N-acetylcysteine; **PedsQL:** Pediatric Quality of Life inventory; **PDD-NOS:** pervasive developmental disorder not otherwise specified; **QoL:** quality of life; **RCT:** randomised controlled trial; **RFRLRS:** Ritvo Freeman Real Life Rating Scale; **SD:** standard deviation; **SNAP:** Swanson, Nolan and Pelham; **SSRI:** selective serotonin reuptake inhibitor; **TSO:***Trichuris suis* ova; **WHO:** World Health Organization; **WHOQOL:** World Health Organization Quality of Life scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Althaus 2015	Ineligible comparator
Aman 1997	Non-RCT
Aman 2009	Ineligible comparator
Anderson 1984	Focus not on unwanted behaviours (irritability, aggression, self-injury)
Anderson 1989	Focus not on unwanted behaviours (irritability, aggression, self-injury)
Anderson 1997	Non-RCT
Anderson 2007	Ineligible outcomes
Arman 2003	Non-RCT

Study	Reason for exclusion
Arnold 2012b	Ineligible comparator
August 1987	Focused on core symptoms of ASD
Bachmann 2013	Non-RCT
Barnard-Brak 2016	Non-RCT
Beeghly 1987	Focused on core symptoms of ASD
Castellanos 2019	Foccused on core symptoms of ASD
Chez 2002	Non-pharmacological
Chez 2003	Focused on core symptoms of ASD
Du 2015	Focused on core symptoms of ASD
Duker 1991	Focused on core symptoms of ASD
Dunn-Geier 2000	Focused on core symptoms of ASD
Ekman 1989	Focused on core symptoms of ASD
Fahmy 2013	Focused on core symptoms of ASD
Fang 2018	Non-pharmacological intervention (e.g. herbal etc.)
Findling 1997a	Non-pharmacological intervention (e.g. herbal etc.)
Groden 1987	Non-RCT
Guglielmo 2013	Non-RCT
Handen 2013	Did not focus on BoC
Hellings 2006a	Non-RCT
Hellings 2010	Non-RCT
Hellings 2015	Non-RCT
Hess 2010	Non-RCT
Hollander 2003	Focus not on BoC
Hollander 2006c	Did not focus on people with ASD
Hollander 2020c	Retracted study
Horovitz 2012	Non-RCT
Horrigan 1997	Non-RCT
Hughes 2002	Non-RCT

Study	Reason for exclusion
Jacob 2020	Terminated study
Jordan 2012	Non-RCT
JPRN-UMIN000007250 2012	Terminated study
Jun 2000	Focused on core symptoms of ASD
Kolmen 1995	Focused on core symptoms of ASD
Kolmen 1997	Non-RCT
Krusch 2004	Focus not on BoC
Leboyer 1993	Non-RCT
Lemonnier 2012	Focused on core symptoms of ASD
Leventhal 1993	Focus not on BoC (irritability, aggression, self-injury)
Levine 1997	Non-RCT
Malone 2002	Non-RCT
Moharreri 2017	Focused on core symptoms of ASD
Nagaraj 2006	Scales ineligible and AEs were not specified for each group
NCT00198120 2005	Focused on lethargy and improvement in CGI
NCT01078844	Terminated study
Nickels 2008	Non-RCT
Niederhofer 2007	Non-RCT
Posey 2004	Focused on core symptoms of ASD
Preckel 2016	Focused on core symptoms of ASD
Purdon 1994	Non-RCT
Radzivil 2006	Non-RCT
Ratcliff-Schaub 2005	Focus not on BoC (irritability, aggression, self-injury)
Ritvo 1971	Non-RCT
Ritvo 1983	Non-RCT
Ritvo 1984	Non-RCT
Roberts 2001	Focus not on BoC (irritability, aggression, self-injury)
Scifo 1996	Ineligible outcomes

Study	Reason for exclusion
Sponheim 2002	Focus not on BoC (irritability, aggression, self-injury)
Steiner 1999	Focus not on BoC (irritability, aggression, self-injury)
Stubbs 1986	Focus not on BoC (irritability, aggression, self-injury)
Sugie 2003	Non-RCT
Sugiyama 1998	Ineligible outcomes and measures used were not specific to BoC (e.g. CGI)
Tachibana 2013	Non-RCT
Taylor 1993	Did not focus on people with ASD
Tolbert 1993	Ineligible outcomes
Troost 2006	Non-RCT
Volkmar 1983	Non-RCT
Volkmar 2009	Ineligible study design
Wasserman 2005	Focus not on BoC
Wei 2011	Non-RCT
Witwer 2005	Did not focus on BoC
Yarbrough 1987	Outcomes - insufficient data reported
Yui 2012	Focus not on BoC (irritability, aggression, self-injury)
Zingarelli 1992	Non-RCT

ABC-I: Aberrant Behaviour Checklist (Irritability subscale); **AE:** adverse effect; **ASD:** autism spectrum disorder; **BoC:** behaviours of concern; **CGI:** Clinical Global Impression; **RCT:** randomised controlled trial

Characteristics of studies awaiting classification *[ordered by study ID]*

Anagnostou 2018

Methods	12-week trial of tideglusib versus placebo
Participants	Inclusion criteria: not specified apart from aged 12-18 years Exclusion criteria: details not provided (conference poster) Location/setting: not specified but assumed to be either the USA or Canada Number of participants randomly assigned: not specified apart from 83 were randomised in a 1:1 manner Number of withdrawals/dropouts: not reported Gender: not reported Mean age: not reported

Anagnostou 2018 *(Continued)*

	IQ: not reported Concomitant medications: not reported History of previous medications: not reported
Interventions	Intervention (tideglusib): once-daily oral administration of tideglusib commenced at 400 mg increasing to 1000 mg (1g) Comparator (placebo): not described Timing of outcome assessments: baseline and 12 weeks (endpoint)
Outcomes	Primary outcomes: • AEs • Repetitive Behaviour Scale-Revised (not clear which subscales/outcomes measured)
Notes	Study start date: not reported Study end date: not reported Funding: not reported Conflicts of interest: not reported

Buitelaar 1996

Methods	Parallel trial of ORG 2766, an ACTH-(4–9) analog versus placebo
Participants	Inclusion criteria: • diagnosis of autistic disorder according to the DSM-IIIR criteria • performance IQ of > 60 on the the Wechsler Intelligence Scale for Children-Revised • aged 7-15 years Exclusion criteria: taking concurrent psychotropic medications Location/setting: outpatient clinic of the Department of Child and Adolescent Psychiatry of the Utrecht University Hospital, The Netherlands Sample size: 50 (30 to ORG2766 group, 20 to placebo group) Number analysed: 30 ORG 2766; 20 placebo Number of withdrawals/dropouts: 2 on placebo and 1 on ORG 2766 dropped out because of "an increase in anxiety, nervousness and irritability after they had ingested the tablets for 3 weeks, 4 days and 2 days respectively" Gender: not reported Mean age: "aged between 7 and 15 years" IQ: "a performance IQ of more than 60". Concurrent medications: participants could not have been on any concurrent psychotropic medications History of previous medications: details not provided

Buitelaar 1996 *(Continued)*

	Baseline ABC-I or other BoC: parent-rated total ABC score: ORG2766 responders 51.0 (18.5), ORG2766 non-responders 46.9 (29.5); placebo responders 42.3 (16.4), placebo non-responders 46.5 (22.5)
Interventions	Intervention: (ORG 2766) for 6 weeks: 40 mg/day of ORG 2766 Comparator: (placebo) for 6 weeks: 40 mg/day of placebo
Outcomes	Primary outcomes: • BoC measured using the Teacher-rated ABC (total score; only ABC total scores provided) • AEs (not reported) Secondary outcomes: none reported Timing of outcome assessments: baseline, week 2, 4, and 6 (endpoint)
Notes	Study start date: not reported Study end date: not reported Source of funding: not reported Conflicts of interest: not reported

Campbell 1982a

Methods	4-week trial haloperidol versus placebo
Participants	Inclusion criteria: meet the DSM criteria for autism Exclusion criteria: not reported Location/Setting: appears to be in the USA Number of participants randomly assigned: 40 in total Number of withdrawals/dropouts: Gender: not reported Mean age: 4.7 years (range 2.3-7.9 years) IQ: not reported Concomitant medications: not reported History of previous medications: not reported
Interventions	Intervention (haloperidol): mean 1.12 mg/day (0.5 mg-3.0 mg/day) Comparator (placebo): equivalent placebo
Outcomes	No relevant outcomes reported (behaviours were stereotypies, fidgeting, hyperactivity, and withdrawal)
Notes	Comment: insufficient information provided and scales used were not relevant (CGI, Children's Psychiatric Rating Scale)

Carminati 2016

Methods	Parallel trial of venlafaxine versus placebo
Participants	Inclusion criteria: • ICD-10 diagnosis of intellectual disability from mild to profound (F7X.1) with PDD (F84.X) • crisis linked to irritability and agitation (ABC F1 score ≥ 18) and/or hyperactivity/noncompliance (ABC F4 score ≥ 15) • aged 18-45 years Exclusion criteria: • epilepsy or any indication against somatic–psychotropic treatments • pregnancy Location/setting: University Hospitals of Geneva, Switzerland Sample size: 14 in total, 13 analysed Number of withdrawals/dropouts: 3 participants withdrew consent: 2 at day 14, 1 day 28 but were included in analysis; 1 was not included in analysis due to taking paroxetine during the study Gender: 11/13 were male Mean age: median age venlafaxine group: 22 years (range 18-30); median age placebo group: 19 (range 19-32) IQ: all participants had a mild, moderate or severe intellectual disability Baseline ABC-I or other BoC: ABC-I median 18.0, self-injurious behaviour median 8.5; aggression median 5.5 Concomitant medications: psychotropic treatment were prohibited during the trial History of previous medications: not reported
Interventions	Intervention (venlafaxine) for 8 weeks: 18.75 mg/day of venlafaxine Comparator (placebo) for 8 weeks: matching placebo
Outcomes	Primary outcomes: • irritability, measured using the ABC-I (Aman 1985) • self-injurious behaviour, measured using the Behaviour Problem Inventory (BPI)-Self-Injurious Behaviour subscale (Rojahn 2001) • Aggression, measured using the Behaviour Problem Inventory (BPI)-Aggression/Destruction subscale (Rojahn 2001) Secondary outcomes: none reported Timing of outcomes assessment: baseline, and weeks 2 and 8
Notes	Study start date: not reported Study end date: not reported Source of funding: “the Unit of Mental Development of the Department of Mental Health and Psychiatry of the Geneva University Hospitals, Geneva, Switzerland and the Foundation Handicap Mental & Société (FHMS), Geneva, Switzerland, (N. CGR 73166 PS-Venlafaxine). The funding sources had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication."

Carminati 2016 *(Continued)*

	Conflicts of interest: none declared

Gabis 2019

Methods	12-week cross-over trial of donepezil versus placebo
Participants	Inclusion criteria: • clinical diagnosis of ASD or PDD-NOS • aged 10-18 years • parental consent provided to participate in the study Exclusion criteria: • any infectious disease, chromosomal abnormalities, metabolic disorders, neurological conditions • "use of psychostimulants, anti-depressants, neuroleptics or anti-convulsive agents within the past month" • brain damage; or significant head injury Location/setting: Israel Sample size: target of 84 participants Number randomised: 60 in total (donepezil + choline (29) or placebo (31)) Number analysed: 48 (intervention (23), placebo (25)) Number and reason for dropouts: 14 were reported to have dropped out ("Six subjects dropped out after the first assessment due to lack of compliance, and three additional subjects subsequently failed to attend follow-up for the second assessment. Three subjects (one in the placebo group and two in the treatment group) were excluded during treatment due to side effects"). Gender: not reported Mean age: not reported IQ: not reported Concomitant medications: not reported Previous medications: not reported
Interventions	Intervention (donepezil + choline) for 12 weeks: maximum donepezil 5 mg/day taken once daily, choline 250 mg/day (children up to 40 kg) or 500 mg/day (children 40 kg and over) Comparator (placebo) for 12 weeks: equivalent placebo
Outcomes	Primary outcomes: AEs Secondary outcomes: none reported Timing of outcome assessments: baseline, weeks 4, 8 and 12 (endpoint)
Notes	Study start date: March 2010 Study end date: December 2017 Source of funding: not reported

Gabis 2019 *(Continued)*

	Conflicts of interest: not reported

Handen 2000

Methods	Cross-over trial of 0.3 mg/kg methylphenidate, 0.6 mg/kg methylphenidate or placebo

Participants	Inclusion criteria:
	• while off all psychotropic medication
	  ○ score of ≥ 30 on a parent-completed CARS
	  ○ diagnosis of autism or PDD-NOS made by a board-certified child psychiatrist
	  ○ score of ≥ 15 points on the Hyperactivity Index of the Teacher Conners' Rating Scale
	Exclusion criteria: not reported
	Location/setting: participants were recruited from either special education programmes, a psychiatric inpatient unit, or intensive day-treatment programme.
	Sample size: 13 in total (cross-over)
	Number of withdrawals/dropouts: 1 person was not included in the analysis; however, reasons were not provided.
	Gender: 10 male participants, 3 female participants
	Mean age: median 7.4 years
	IQ: 3 had severe/profound disability, 5 had moderate intellectual disability, 4 had mild intellectual disability, 1 had average IQ
	Baseline ABC-I or other BoC: not reported
	Concomitant medications: not reported
	History of previous medications: not reported

Interventions	Intervention 1 (0.3 mg/kg methylphenidate for 7 days): 0.3 mg/kg doses of methylphenidate rounded to the nearest 2.5 mg was given 2-3 times/day for 7 consecutive days. Doses were given at breakfast and 4 h later with lunch. Intervention 2 (0.6 mg methylphenidate for 7 days): 0.6 mg/kg doses of methylphenidate rounded to the nearest 2.5 mg was given 2-3 times/day for 7 consecutive days. Doses were given at breakfast and 4 h later with lunch. Comparator (placebo for 7 days)*:* equivalent placebo doses
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • AEs Secondary outcomes: not reported Timing of outcome assessment: not reported
Notes	Study start date: not reported Study end date: not reported Source of funding: "This research was supported by a grant to the third author from the Fanny Pushin Rosenberg Research Foundation."

Handen 2000 *(Continued)*

	Conflicts of interest: none declared

IRCT2017041333406N1

Methods	12-week parallel trial of donepezil versus placebo
Participants	Inclusion criteria: • children 6-17 years • diagnosis of ASD • no other psychiatric disorders or other medical conditions • IQ > 50 based on the Weiland test • not taking any other psychotropics apart from risperidone Exclusion criteria: "patients who have been treated with other psychotropic drugs and also patients with other psychiatric disorders" Location/setting: Iran Sample size: target sample size is 66 Number of withdrawals/dropouts: it is unknown if the trial has been completed or not, as there is insufficient information on the trial registry. Gender: not reported Mean age: not reported IQ: > 50 based on the Weiland test Concurrent medications: only risperidone was allowed History of previous medications: not reported
Interventions	Intervention (donepezil + risperidone) for 12 weeks: maximum of 10 mg/day of donepezil taken twice daily; maximum of 2 mg/day of risperidone Comparator (placebo + risperidone) for 12 weeks: placebo + maximum of 2 mg/day of risperidone
Outcomes	Primary outcomes: AEs Secondary outcomes: none reported Timing of outcome assessments: baseline, week 6, week 12 (endpoint)
Notes	Study start date: September 2017 Study end date: not reported Source of funding: not reported Conflicts of interest: not reported

IRCT20190714044199N1

Methods	10-week parallel trial of N-acetylcysteine versus placebo
Participants	Inclusion criteria:

IRCT20190714044199N1 *(Continued)*

	• children 3-12 years • no serious medical conditions or psychiatric conditions • IQ > 50 Exclusion criteria: • taking any other antipsychotics apart from risperidone • history of allergic reactions to risperidone or n-acetylcysteine Location/setting: Iran Number randomised: target sample size of 66 Number of withdrawals/dropouts: not reported Gender: not reported Mean age: not reported IQ: > 50 Baseline ABC-I or other BoC: not reported Concomitant medications: not reported History of previous medications: not reported
Interventions	Intervention (N-acetylcysteine + risperidone) for 10 weeks: maximum of 600 mg/day + risperidone (maximum of 1.5 mg/day) Comparator (placebo + risperidone) for 10 weeks: placebo + risperidone (maximum of 1.5 mg/day) Timing of outcome assessments: baseline, week 5, week 10 (endpoint)
Outcomes	Primary outcomes: AEs Secondary outcomes: not reported
Notes	Study start date: November 2019 Study end date: not reported Source of funding: not reported Conflicts of interest: not reported

JPRN-JMA-IIA00438

Methods	8-week parallel trial of pyridoxamine versus placebo
Participants	Inclusion criteria: • boys and girls • at least 12 years old • parent, legal guardian or individual provide consent to participate • minimum score of 18 on the Japanese version of the ABC (ABC-J) Exclusion criteria • known sensitivity to vitamin B6

JPRN-JMA-IIA00438 *(Continued)*

	• diagnosed with schizophrenia, biploar, major depressive disorder, or undergoing oral treatment for a mental disorder • severe liver or heart disease, or impaired renal function; any gastrointestinal, respiratory, endocrine, blood, immune, or other disorders • epileptic seizures within the past 6 months • also taking B6, or other psychotropic medications at the time of trial commencement • participating in other clinical trials Target sample size: 78
Interventions	Intervention 1: high-dose pyridoxamine plus 20 mg vitamin B1 Intervention 2: low-dose pyridoxamine plus 20 mg vitamin B1 Comparator: placebo plus 2 0mg vitamin B1
Outcomes	Primary outcomes irritability, measured using the ABC-Japanese version Secondary outcomes: none reported Timing of outcome assessments: baseline, 4 and 8 weeks
Notes	Contact name: Mitugu Uematsu Contact details: not provided Other clinical trial numbers: UMIN000035172; jRCT2021200001

Jung 2000

Methods	4-week cross-over trial of dimethylglycine versus placebo
Participants	Inclusion and exclusion criteria: unclear, details not provided Location/setting: China Sample size: 106 (unclear how many in each group) Number of dropouts/withdrawals: 61 participants in total "(At the end of the first 4 weeks 22 cases (21%) were lost. At the end of 10 weeks 61 cases (58%) were lost which was inadequate for analysis. Therefore we decided to use the data from the first 4 weeks for our main analysis."
Interventions	Phase one Intervention (dimethylglycine): participants received between 6.94 mg and 10.41 mg/kg body weight for 4 weeks. This was followed by a 2-week wash-out period before commencing placebo. Comparator: equivalent placebo for 4 weeks. This was followed by a 2-week wash-out period before commencing dimethylglycine.
Outcomes	Primary outcomes: • AEs • irritability (although unclear which scale was used) Secondary outcomes: it appears that none were reportd although it is difficult to know Timing of outcome assessments: details not provided
Notes	Contact person: details not provided

Jung 2000 *(Continued)*

	Contact details: details not provided

Jørgensen 2002

Methods	Written in Danish, and we have not found an abstract or full-text copy in either Danish or English. No further information on participants, interventions or outcomes.
Participants	
Interventions	
Outcomes	
Notes	

Kern 2001a

Methods	Parallel trial N, N-dimethylglycine versus placebo
Participants	Inclusion criteria: diagnosis of autism and/or PDD according to DSM-IV criteria Exclusion criteria: not reported Location/Setting: USA Sample size: placebo 19, dimethylglycine 18 Number of withdrawals/dropouts: 1 discontinued due to negative behavioural effects in dimethylglycine group; 1 child discontinued due to damage to the tablets in the placebo group Gender: not reported Mean age: 3-11 years IQ: not reported Baseline ABC-I or other BoC: not reported Concomitant medications: 7 children were on psychoactive medication (clonidine, thioridazine, paroxetine, imipramine, methylphenidate and fluoxetine) History of previous medications: not reported
Interventions	Intervention (dimethylglycine) for 4 weeks: started at 1 x 125 mg tablet/day for children weighing < 40 lbs (approx 18 kg) for 4 weeks. The dosage was 2 tablets (250 mg/day) for children weighing 41-70 lbs (approx 18-32 kg), 3 tablets (375 mg/day) for 71-100 lbs (approx 32-45 kg), 4 tablets (500 mg/day) for 101-130 lbs (approx 45-59 kg), and 5 tablets (725 mg/day) for > 131 lbs (approx 59 kg). Comparator (placebo) for 4 weeks: 1 x 125 mg tablet each morning for 4 weeks for children weighing < 40 lbs (approx 18 kg), 2 tablets for 41-70 lbs (approx 18-32 kg), 3 tablets for 71-100 lbs (approx 32-45 kg), 4 tablets for 101-130 lbs (approx 45-59 kg), and five tablets for > 131 lbs (approx 59 kg)
Outcomes	Primary outcomes: irritability, measured using the ABC-I subscale (Aman 1985); however, it was not reported fully (only t-scores) Secondary outcomes: none reported

Kern 2001a *(Continued)*

	Timing of outcome assessments: before treatment and 4 weeks after treatment
Notes	Study start date: 1998 Study end date: 1999 Source of funding: supported by FoodScience Corporation Conflicts of interest: none declared

Kern 2002

Methods	Cross-over trial of secretin versus placebo
Participants	Inclusion criteria: • confirmed diagnosis of autism and/or PDD-NOS or PDD • aged 3-10 years • no previous secretin exposure Exclusion criteria: • chronic constipation • history of chronic diarrhoea (in remission) because these two groups did not clearly fall into the proposed groups (no GI problems or chronic diarrhea) Location/setting: a neurology clinic at Children's Medical Centre of Dallas, USA Sample size: 19 children in total Number of withdrawals/dropouts: none reported Gender: 15 boys, 4 girls Mean age: 6.3 years IQ: not reported Baseline ABC-I or other BoC: not reported Concomitant medications: not reported History of previous medications: not reported
Interventions	Intervention (secretin) for 3 weeks: "each Secretin-Ferring vial contained 75 CU porcine secretin, 1mg L-cysteine hydrochloride, and 20mg mannitol. The dose was 2 CUs/kg" Comparator (placebo) for 3 weeks: placebo was sterile normal saline and identical in appearance to the porcine secretin
Outcomes	Primary outcomes: irritability, measured using the ABCt-I subscale (Aman 1985) Secondary outcomes: none reported Timing of outcome assessments: baseline and weeks 3 and 6 (not reported)
Notes	Study start date: not reported Study end date: not reported Source of funding: not reported

Kern 2002 *(Continued)*

	Conflicts of interest: none declared
	Comments: study authors divided participants into normal GI and participants with chronic diarrhea. Outcome scores could not be used.

Li 2016

Methods	8-week parallel trial of paliperidone versus aripiprazole
Participants	Inclusion criteria: unknown (the only available details are in the abstract) Exclusion criteria: unknown Location/setting: unknown, but assumed to be China Number randomised: 62 (31 to each group) Number of withdrawals/dropouts: unknown (the only available details are in the abstract) Gender: details not provided Mean age: not known - unable to find the full-text paper IQ: not known - unable to find the full-text paper Baseline ABC-I or other BoC: unknown Concurrent medications: unknown History of previous medications: unknown
Interventions	Intervention (paliperidone) for 8 weeks: details not reported Comparator (aripiprazole) for 8 weeks: details not reported
Outcomes	Primary outcomes: AEs Timing of outcome assessments: baseline, weeks 4,6, 8 (endpoint)
Notes	Study start date: details not reported Study end date: details not reported Source of funding: details not reported Conflicts of interest: details not reported

Malone 2010

Methods	Parallel trial of olanzapine versus placebo
Participants	Inclusion criteria: • male and female • aged 3-12 years • autistic disorder according to DSM-IV criteria • a score of at least moderately impaired on the CGI-S • clinical judgment that medication treatment for autism is indicated

Malone 2010 *(Continued)*

	Exclusion criteria: • Rett's disorder, childhood disintegrative disorder, Asperger's disorder, and PDD, NOS. • psychotic disorder (DSM-IV) (including schizophreniform disorder and schizophrenia). • major depressive disorder (DSM-IV). • bipolar disorder (DSM-IV). • history of psychoactive drug in the previous 2 weeks prior to phase 1 • history of treatment with olanzapine for a cumulative period of > 2 weeks prior to entering phase 1. • systemic diseases such as cardiac, renal, thyroid diseases, uncontrolled seizure disorder (seizure disorder that is not controlled by anti-epileptic medication - a child who is seizure free for a period of 6 months on a stable dose of antiepileptic drug would be considered controlled), or diabetes mellitus • children with a known medical cause for autistic disorder • abnormal fasting blood glucose or history of diabetes • baseline body mass index (BMI) > the 90th percentile for age and gender (CDC growth charts) (because of risk of weight gain) • baseline QTc > 450 msec Location/setting: Drexel University, College of Medicine, Philadelphia, PA, USA Sample size: 33 Number of withdrawals/dropouts: none reported Gender: 25 male participants, 8 female participants Mean age: 6.58 years IQ: not reported Baseline ABC-I or other BoC: not reported Concomitant medications: not reported History of previous medications: not reported
Interventions	Intervention (olanzapine) for 6 weeks: olanzapine tablets given twice daily at a dosage of 2.5-20 mg/day for up to 12 weeks Comparator (placebo) for 6 weeks: matching placebo treatment
Outcomes	Primary outcomes: AEs Secondary outcomes: none reported Timing of outcome assessments: baseline and week 12
Notes	Study start date: May 2003 Study end date: September 2005 Source of funding: Food and Drug Administration (FD-R-002190), National Institute of Mental Health (MH073524). Placebo and drugs were provided by Eli Lilly Conflicts of interest: none declared

Martsenkovsky 2016

Methods	16-week parallel trial of memantine versus placebo

Martsenkovsky 2016 *(Continued)*

Participants	Inclusion criteria: children 18–36 months old with ASD (based on DSM-IV criteria) Exclusion criteria: not reported Location/setting: not specifically mentioned but assumed to be in the Ukraine Sample size: 76 Number of withdrawals/dropouts Gender: not reported Mean age: 18-36 months of age IQ: not reported Baseline ABC-I or other BoC: unknown Concomitant medications: not reported History of previous medications: not reported
Interventions	Intervention (memantine) for 16 weeks: maximum of 15 mg/day (mean daily dose of 7.5 mg/day for children 18-25 months, 10.3 mg/day for children 26-36 months) Comparator (placebo) for 16 weeks: equivalent placebo
Outcomes	Primary outcomes: AEs ABC (subscales unknown or if the measure is the Aberrant Behaviour Checklist or a different ABC scale)
Notes	Study start date: details not reported Study end date: details not reported Source of funding: details not reported Conflicts of interest: details not reported Comments: only F values provided

Miller 1979

Methods	Unable to obtain abstract or full-text. The paper is written in German and published in 1979. If we obtained at least an abstract we could have had it translated but it is not available (partly due to the fact it was published over 40 years ago). No further information on methods, participants, interventions (except Sulpiride) or outcomes
Participants	
Interventions	Intervention: Sulpiride Comparator: unclear
Outcomes	
Notes	

Molloy 2002

Methods	Cross-over trial of single dose secretin versus placebo
Participants	Inclusion criteria: • 2–15 years of age • met the criteria for autism as outlined in the DSM-IV following multidisciplinary evaluation, "Children not evaluated at our center were accepted into the sampling frame if documentation of diagnosis by a multidisciplinary team was sufficient as determined by a developmental pediatrician (SS)." Exclusion criteria: "had known chromosomal or other genetic disorders, a structural abnormality on neuroimaging, had previously received secretin, had acute or chronic pancreatic disease or a medical condition that might make participation in the study unsafe". Location/setting: Children's Hospital Medical Centre, Cincinnati, Ohio, USA Sample size: 60 Number analysed: secretin first: 19, placebo first: 23 Number of withdrawals/dropouts: 18 dropped out from original 60, although reasons for only 1 participant provided (from placebo/secretin group) - they did not return for the final assessment. Gender: 37/42 analysed were male participants Mean age: 6.8 years IQ: not reported Baseline ABC-I or other BoC: not reported Concurrent medications: not reported History of previous medications: not reported
Interventions	Intervention (single dose secretin): a single dose of 2 IU/kg of intravenous synthetic human secretin was given at the first visit of the phase. Comparator (single dose placebo): a single dose of 2 IU/kg of placebo was given at first visit of the phase.
Outcomes	Primary outcomes: • parent-rated ABC (not reported) (Aman 1985) • AEs (not reported) Secondary outcomes: none reported Timing of outcome assessments: baseline, and weeks 1, 3, 6, 9 and 12
Notes	Study start date: not reported Study end date: not reported Source of funding: "supported by Grant #4 T73 MC 00032-10 awarded by the Maternal and Child Health Bureau, Health Resources and Service Administration, DHHS and by Grant #M01 RR-08084, NIH. The human synthetic secretin used in the study was supplied by ChiRoClin (Silver Spring, MD) free of charge". Conflicts of interest: none declared

Molloy 2002 *(Continued)*

	Comment: author was contacted for information but no reply

Naruse 1982

Methods	Cross-over trial of pimozide versus haloperidol versus placebo
Participants	87 children (3-16 years), 69 boys and 18 girls from 12 hospitals; 34 with autistic disturbance, 27 with behaviour disturbance caused by organic damage, 17 with mental retardation, 5 with neurosis and 4 with psychosis Location/setting: 12 hospitals in Germany Sample size: 87 Number of withdrawals/dropouts: not reported (unable to obtain full text) Gender: 69 boys, 18 girls Mean age: 3-16 years IQ: not reported Concurrent medications: not reported History of previous medications: not reported Baseline ABC-I or other BoC: not reported
Interventions	Intervention 1 (pimozide) for 8 weeks: the initial dose was pimozide 1 tablet (1 mg). The maximum daily dose was 9 tablets (pimozide 9 mg). Intervention 2 (haloperidol) for 8 weeks: 1 tablet (0.75 mg). The maximum daily dose was 9 tablets (haloperidol 6.75 mg). Comparator (placebo) for 8 weeks: equivalent placebo
Outcomes	Primary outcomes: anger/aggression/injury and violence to others Secondary outcomes: none reported Timing of outcome assessments: not reported
Notes	Study start date: not reported Study end date: not reported Source of funding: not reported Conflicts of interest: not reported Comment: not able to obtain the full text

Noone 2014

Methods	Parallel trial of milnacipran versus placebo
Participants	Inclusion criteria: • aged 18-50 years

Noone 2014 *(Continued)*

	• diagnosis of ASD according to DSM-IV-R • IQ > 70 Exclusion criteria: • pregnant • deemed by comprehensive psychiatric interview to have a significant risk of suicide • "comorbid medical, neurological and psychiatric illnesses with the exception of ADHD and OCD were excluded" Location/setting: USA Sample size: 10 in total Number of withdrawals/dropouts: not reported Gender: not reported Mean age: 19-41 years IQ: > 70 Baseline ABC-I or other BoC: not reported Concomitant medications: not reported, although comorbid neurological, psychiatric and medical condition excluded except for ADHD or OCD History of previous medications: not reported
Interventions	Intervention (milnacipran) for 12 weeks: participants were given a titrated dose of milnacipran increasing to a maximum of 100 mg a day over the 12-week study period. Dosing was based on a fixed schedule that was monitored using a side-effect profile. Comparator (placebo) for 12 weeks: participants were given placebo tablets at dosing corresponding to the fixed schedule between 12.5 mg and 100 mg.
Outcomes	Primary outcomes: ABC-I (Aman 1985) (not reported in paper or clinicaltrials.gov website) Secondary outcomes: none reported Timing of outcome assessments: twice-weekly
Notes	Study start date: February 2011 Study end date: July 2014 Source of funding: "funded by an investigator initiated grant from Forest Pharmaceuticals, Inc" Conflicts of interest: none declared

Novotny 2004

Methods	Parallel trial of single-dose M-chlorophenylpiperazine (m-cpp) versus placebo
Participants	Inclusion criteria: • aged 18-53 years old • met diagnostic criteria for ASD according to the Autism Diagnostic Interview-Research version and the DSM-IV

Novotny 2004 *(Continued)*

	Exclusion criteria: "meeting criteria for current or past psychotic disorders diagnosed by SCID – Axis disorders; reporting a history of seizures or medical illnesses" Location/setting: USA Sample size: oral m-CPP 11, placebo 8 Number of withdrawals/dropouts: no LTFU reported Gender: 10 male participants, 1 female participant Mean age: 34.3 years IQ: not reported Baseline ABC-I or other BoC: not reported Concomitant medications: participants were required to be drug-free for 2 weeks prior to study. History of previous medications: not reported
Interventions	Intervention (single dose of oral m-CPP): 0.5 mg/kg at least 48 h apart from the placebo single dose, and after a drug-free period of at least 2 weeks or 6 weeks for those on fluoxetine, and a 72-h low monoamine diet Comparator (single-dose placebo): equivalent placebo
Outcomes	Primary outcomes: self-injurious behaviours (not reported) Secondary outcomes: none reported Timing of outcome assessments: baseline and at 60, 120, 180, 240 min (single dose)
Notes	Study start date: not reported Study end date: not reported Source of funding: "supported in part by grants from the Seaver Foundation, National Alliance for Research on Schizophrenia and Depression, Cure Autism Now, National Alliance for Autism Research and grant 5 MO1 RR00071 for the Mount Sinai General Clinical Research Center from the National Center for Research Resources, National Institutes of Health.: Conflicts of interest: none declared

Sandler 1999

Methods	Parallel trial of single-dose secretin versus single-dose placebo
Participants	Inclusion criteria: • children 3-14 years • diagnosis of autism or PDD • no previous secretin treatment • no diagnosis of pancreatitis, inflammatory bowel disease, or gastrinoma • written, voluntary informed consent for participation by a parent or legal guardian Location/setting: Department of Psychiatry, University of North Carolina. Children were referred by the Treatment and Evaluation of Autism and Communication Handicaps program of the Department of Psychiatry at the University of North Carolina or whose parents responded to notices about this study placed in the newsletter of an autism-support group.

Sandler 1999 *(Continued)*

	Sample size: 60 children were randomised Number of withdrawals/dropouts: 4 could not be evaluated (2 received secretin outside the study, and 2 did not return for follow-up) Gender: not reported Mean age: secretin 7.6 years, placebo 7.4 years IQ: secretin 65.6, placebo 60.1 Baseline ABC-I or other BoC: not reported Concomitant medications: secretin 8/30, placebo 11/30 were taking psychotropic medications History of previous medications: not reported
Interventions	Intervention (single-dose secretin): 0.4 ug per kg of body weight Comparator (single-dose placebo): saline placebo
Outcomes	Primary outcomes: • severity of autistic symtoms, measured using the Autism Behaviour Checklist and the CGI • AEs, measured using the Treatment Emergent Symptoms Scale (not reported) Secondary outcomes: none reported Timing of outcome assessments: baseline, weeks 1, 2 and 4 postinfusion
Notes	Study start date: not reported Study end date: not reported Source of funding: Thoms Health Services Foundation and by a Public Health Service grant (30615) from the National Institutes of Child Health and Human Development Conflicts of interest: none declared Comment: study author contacted twice for information about AEs but no reply

Stern 1990

Methods	Cross-over trial of fenfluramine versus placebo
Participants	Inclusion criteria: "infantile autism with or without mental retardation [intellectual disability]" diagnosis based on DSM-III, previously under the care of paediatricians and paediatric neurologists Exclusion criteria: chromosomal anomalies, including the fragile X chromosome Location/setting: Adelaide Children's hospital, Australia Sample size: 20 in total Number of withdrawals/dropouts: "one child moved to another state half way through the trial" Gender: 14 boys, 6 girls Mean age: 10 years IQ: not reported

Stern 1990 *(Continued)*

	Baseline ABC-I or other BoC: not reported Concomitant medications: 15/20 were on no medications, 3 were on anticonvulsants, 1 was on benzodiazepine and 1 was on the contraceptive pill History of previous medications: not reported
Interventions	Intervention (fenfluramine) for 5 months: "the dose of Fenfluramine was 1.5mg/kg/day given twice daily for a 5 month period". At the end of the period all children were given placebo for 2 months before the groups crossed over for a second 5-month period. Comparator (placebo) for 5 months: All children were given placebo for a month to get used to the routine of taking tablets regularly. The children were then randomised to either fenfluramine or placebo for a 5-month period. At the end of the period all children were given placebo for 2 months before the groups crossed over for a second 5-month period.
Outcomes	Primary outcomes: AEs (weight change, measured in kgs) Secondary outcomes: none reported Timing of outcome assessments: not reported
Notes	Study start date: not reported Study end date: not reported Source of funding: "this study was supported by a grant from the Apex Foundation. The authors thank Dr Grant Sutherland for the karyotypes and Mrs Robyn Clements for the manuscript preparation. Fenfluramine and placebo tablets were supplied by Servier Laboratories (Australia) Pty, Ltd." Conflicts of interest: none declared

Wink 2020

Methods	6 week cross-over trial of ketamine versus placebo
Participants	Inclusion criteria: Aged 12-30 years old * Weight of at least 50kg *general good health as determined by physical exam, medical history, laboratory work up, and EKG, diagnostic and Statistical Manual of Mental Disorders 5th Edition diagnosis of autism spectrum disorder (not associated with Fragile X Syndrome or other known genetic syndrome) as confirmed by the Autism Diagnostic Observation Schedule at screen or previous (within last 5 years) if available; IQ of at least 50 as confirmed via testing (Leiter-3) at screen or previous (within last 5 years, any valid testing acceptable); clinical Global Impressions-Severity score of 4 (Moderately Ill); score of 10 on the Social Withdrawal subscale of the Aberrant Behavior Checklist; stable dosing of all concomitant psychotropic medications for five half-lives prior to screening visit and during the study; presence of parent/guardian or significant other or caregiver willing to serve as informant for behavioral outcome measures" Exclusion criteria: "Presence of co-morbid schizophrenia, schizoaffective disorder, bipolar disorder with psychosis, bipolar disorder or psychosis not otherwise specified; comorbid diagnoses determined by psychiatrist clinical interview and use of Diagnostic and Statistical Manual of Mental Disorders 5th Edition diagnostic criteria; history of drug or alcohol abuse; presence of cardiac disease including coronary artery disease, congestive heart failure, or uncontrolled hypertension per medical history (individuals with ≥ 2 blood pressure readings of ≥140/90 during screen/baseline will be excluded); airway instability, tracheal surgery, or tracheal stenosis per medical history; central ner-

Wink 2020 *(Continued)*

	vous system masses or hydrocephalus per medical history; porphyria, thyroid disorder, or thyroid medication use per medical history; glaucoma or other cause of increased intraocular pressure per medical history; allergy to ketamine; current use of drugs with concomitant modification of non-competitive N-methyl-D-aspartate glutamate activity (acamprosate, amantadine, memantine, d-cycloserine etc.); for female subjects of child bearing potential, a positive pregnancy test; any major chronic medical or chronic respiratory illness considered to be uncontrolled by the Principal Investigator; inability to tolerate study procedures or study drug per the discretion of the Principal Investigator." Location/setting: "Cincinnati Children's Hospital Medical Center (CCHMC)". USA Sample size: 21 in total Number analysed: 17 Number of withdrawals/dropouts: "Four subjects withdrew from the study, one due to emesis following frst dose of study drug (ketamine), one due to seizure during the two-week washout period (seven days post-ketamine; determined unrelated to study drug), and two due to scheduling issues after Phase 1 (one ketamine, one placebo)". Gender: 19 male, 2 female Mean age (SD): 9.48 (3.83) Mean IQ (SD): 102.14 (23.62) Concurrent medications: History of previous medications: details not provided Baseline ABC-I or other BoC: Mean ABC-I (and standard deviation) 10.05 (5.86)
Interventions	Intervention: 2 doses of intranasal ketamine (30 mg and 50 mg) provided 1 week apart followed by a 2-week washout period before starting phase 2 of the trial Comparator: 2 equivalent doses of placebo (saline spray) provided 1 week apart followed by a 2-week washout period before starting phase 2 of the trial.
Outcomes	Primary outcomes: AEs Secondary outcomes: none reported Timing of outcomes assessment: baseline and endpoint
Notes	Study start date: December 22, 2015 Study end date: May 7, 2018 Funding: "Funding for this project was provided by Cures Within Reach and Roivant Sciences." Conflicts of interest: "The authors report no competing financial interests related to the work described". Trial registry: NCT02611921

Yatawara 2016

Methods	14-week cross-over trial of oxytocin versus placebo
Participants	Inclusion criteria: "children aged between 3 and 8 years of age who met the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision) criteria for Autistic Disorder, Asperger's Disorder or Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS)."

Yatawara 2016 *(Continued)*

	Exclusion criteria: "Exclusion criteria included known sensitivity to preservatives in the nasal spray (in particular, E216, E218 and chlorobutanol hemihydrates)." Location/setting: "The study was conducted at the Brain and Mind Centre (BMC), The University of Sydney (Australia)". Number of participants: 39 were randomised, 17 to oxytocin (phase 1); 22 to placebo (phase 1). Number of withdrawals/dropouts: phase 1, 2 were excluded from oxytocin group (adverse reaction (1), competing time commitments (1)); 5 in placebo were excluded (intolerance of nasal spray (2); adverse reaction (1); competing time commitments (1); respiratory illness (1)). An additional person was excluded during phase 2 (oxytocin group). Gender: 27 male, 4 female Mean age (SD) in years: 6.2 (1.7) Mean IQ (SD): non-verbal IQ 83.6 (24.2) Concomitant medications: atomoxetine (1); melatonin (1); anticonvulsant (2); risperidone (2); selective serotonin reuptake inhibitor (sertraline) (2) History of previous medications: not reported
Interventions	Intervention: oxytocin nasal spray 12 IU twice daily (24 IU daily) for 5 weeks with a 4-week wash-out period before starting phase 2 of the trial. Comparator (placebo): equivalent placebo nasal spray twice-daily for 5 weeks with a 4-week wash-out period before starting phase 2 of the trial.
Outcomes	Primary outcomes: repetitive behaviour scale (not clear which subscales); adverse effects Secondary outcomes: none reported Timing of outcome assessments: baseline and endpoint of each phase
Notes	Study start date: October 2010 Study end date:October 2012 Funding: "We acknowledge an National Health Medical Research Council Australian Fellowship (APP 511921) to IBH, an NHMRC Career Development Fellowship (APP 1061922) to AJG and a generous donation by Mr Geoff Stein toward the completion of this trial. These funders had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication." Conflicts of interest: "the authors declare no conflict of interest"

ABC: Aberrant Behaviour Checklist; **AE:** adverse effect; **BoC:** behaviours of concern; **CARS:** Child Autism Rating Scale; **CDC:** Centers for Disease Control; **CGI:** Clinical Global Impression; **ICD-10:** International Classification of Diseases, 10th revision; **IQ:** intelligence quotient; LTFU: loss to follow-up; **M:** median; **PDD-(NOS):** pervasive developmental disorders (not otherwise specified); **SD:** standard deviation

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12617000441314

Study name	A course of oxytocin to improve social communication in young children with autism
Methods	15-week parallel trial of oxytocin versus placebo
Participants	Inclusion criteria:

ACTRN12617000441314 *(Continued)*

	• boys and girls • aged 3-12 years • meet the DSM-5 criteria for ASD Exclusion criteria: "known to be hypersensitive to the preservatives in the nasal spray (E216, E218, and chlorobutanol hemihydrates). Participants with severe nasal obstruction/blockage will be excluded as this is likely to reduce the efficacy of the nasal spray medication. Further, participants whose caregivers report that they have a serious medical condition from one of the following categories will be excluded (evidenced through medical examination): 1. severely compromised cardiac function 2. severely compromised hepatic function 3. severely compromised renal function". Setting/location: Sydney and Perth (Australia) Target sample size: details not provided
Interventions	Intervention: oxytocin basal spray 16 IU twice daily (32 IU in total) for 12 weeks Comparator: equivalent placebo for 12 weeks
Outcomes	Primary outcomes: AEs Secondary outcomes: none reported Timing of outcome assessments: 6 weeks and 12 weeks (endpoint)
Starting date	April 2017
Contact information	Contact name: Adam Guastella Contact details: adam.guastella@sydney.edu.au.
Notes	Source of funding: University of Sydney Conflicts of interest

ChiCTR1800017720

Study name	A random, double-blind, placebo controlled trial for oxytocin nasal spray in the treatment for ASD social dysfunction
Methods	Parallel trial of oxytocin versus placebo
Participants	Inclusion criteria: • meet the DSM-V criteria for ASD • aged 6-12 years • not in receipt of any psychotropic drugs in the previous 3 months • patient or parent consent to participate Exclusion criteria: • other diagnosed mental disorders • neurological conditions • any other serious medical conditions, including renal, endocrine or gastrointestinal disorders • positive pregnancy test • people with chronic nasal disease who cannot use nasal sprays • abnormal renal or liver function • allergic to oxytocin

ChiCTR1800017720 *(Continued)*

	Setting/location: unclear although assumed to be in China Sample size: unclear
Interventions	Intervention (oxytocin): 12 IU morning and night Comparator (placebo): equivalent placebo morning and night
Outcomes	Primary outcomes: • AEs • BoC measured using the Repetitive Behaviour Scale (not sure which subscales) (Bodfish 2000) Secondary outcomes: unclear Timing of outcome assessments: unclear
Starting date	Registered in August 2018
Contact information	Name: Xu Chen E-mail: yinuo0311@163.com
Notes	Source of funding: Beijing Anding Hospital Capital Medical University Conflicts of interest: unclear

Crutel 2020

Study name	Bumetanide oral liquid formulation for the treatment of children and adolescents with autism spectrum disorder: design of two phase III studies (SIGN Trials)
Methods	6-month parallel trial of bumetanide versus placebo
Participants	Inclusion criteria: "a primary diagnosis of ASD as per DSM-5 criteria, plus ASD criteria met on ADOS-2 and ADI-R", aged 7-17 years (study 1) or 2-6 years (study 2), moderate to severe ASD according to CGI score of at least 4, CARS2 total score of at least 34 Exclusion criteria: "concomitant participation in another study, or previous participation in a study of another medicinal product for 3 months prior to enrollment; known monogenic syndrome (e.g. Fragile X, Rett Syndrome); high suicide risk or psychiatric conditions considered likely to interfere with the conduct of the study; chronic hepatic disease, renal dysfunction or cardiac dysfunction; unstable psychotherapy, behavioral, cognitive, or cognitive-behavioral therapy; concomitant psychotropic medication (exceptions: aripiprazole and risperidone in study 1, which are permitted if a stable dose is used between selection and inclusion, and up to Week 26; methylphenidate, atomoxetine, or guanfacine, which are permitted in both studies if stabilized for at least 4 weeks prior to inclusion and not planned to be modifed or stopped up to Week 26) or other contraindicated medication; and previous treatment with bumetanide that was not effective for the treatment of ASD symptoms" Setting/ location: across 13 countries Sample size: 170 per trial
Interventions	Intervention (bumetanide) for 6 months: oral solution of 0.04 mL/kg twice daily for participants weighing < 25 kg; participants ≥ 25 kg will receive 0.5 mg twice daily Comparator (placebo) for 6 months: equivalent placebo, twice daily depending on weight

Crutel 2020 *(Continued)*

Outcomes	Primary outcomes: AEs Secondary outcomes: QoL measured using the Pediatric Quality of Life Inventory (Varni 2001) and the WHOQoL (WHO 1998). Timing of outcome assessments: unclear
Starting date	Unclear
Contact information	Simon Kyaga E-mail: simon.kyaga@servier.com
Notes	Source of funding: Servier (pharmaceutical company) Conflicts of interest: most study authors are employees of the funder (pharmaceutical company)

CTRI/2021/12/038721

Study name	Comparison of the efficacy of oral risperidone and aripiprazole in children with autism spectrum disorders (ASDs) aged 6-18 years: a double blind randomized controlled trial - RAAT
Methods	12-week parallel trial of risperidone versus aripiprazole
Participants	Inclusion criteria : • aged 6-18 years • weight of at least 15 kg • meet DSM-V criteria for of ASD • ABC-Irritability subscale score of > 18 • mental age of at least 18 months • if female, not sexually active • medication-free or adequate washout period (2-4 weeks prior to enrolment) of psychoactive drugs (anticonvulsants permitted for seizure management if dosage is stable for 4 weeks) • parent/guardian able to read and provide informed consent Exclusion criteria: • Prior diagnosis or evidence of genetic or other disorder that may interfere with assessments (e.g. Fragile X syndrome, Rett syndrome, history of very low birth weight) assessed by personal and family history, dysmorphology, and clinical judgement • prior use of risperidone or aripiprazole for > 2 weeks • seizure during the past 6 months • history or evidence of a medical condition that would expose them to an undue risk of a significant AEt or interfere with assessments during the trial including but not limited to hepatic, renal, respiratory, cardiovascular, endocrine, haematologic or immunologic disease as determined by the clinical judgement of the investigator • current suicidal or homicidal risk • dependent on other substances, except nicotine or caffeine. Location/setting: India Target sample size: 120 participants
Interventions	Intervention (risperidone in tablet form): 0.5 mg/day daily for 12 weeks

CTRI/2021/12/038721 *(Continued)*

	Comparator (aripiprazole in tablet form): 2.5 mg/day daily for 12 weeks
Outcomes	Primary outcomes: • irritability subscale of autism behavior checklist (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessments: baseline and endpoint (week 12)
Starting date	Unclear: was not recruiting as at February 2022
Contact information	Contact person: Prateek Kumar Panda Contact details: drprateekpanda@gmail.com
Notes	Source of funding Conflicts of interest

EUCTR2008-003712-36-FR

Study name	Etude de la réponse clinique et neurofonctionnelle à la fluoxétine dans l'autisme infantile
Methods	20-week parallel trial of fluoxetine versus placebo
Participants	Inclusion criteria: • diagnosis of ASD or PDD • 5-13 years of age at baseline • IQ ≥ 45 3 Exclusion criteria: • neurological conditions • current treatment with antipsychotics, benzodiazepines, neuroleptics or thermoregulators • history of or an allergy to fluoxetine • IQ < 45 Location: France Setting: unclear Target sample size: unclear
Interventions	Intervention (fluoxetine) for 20 weeks, 20 mg/5 mL Comparator (placebo) for 20 weeks, equivalent oral solution of placebo
Outcomes	Primary outcomes: BoC (total score of ABC) Secondary outcomes: unclear Timing of outcome assessments: baseline and 20 weeks
Starting date	Registered November 2008
Contact information	Contact name: not reported

EUCTR2008-003712-36-FR *(Continued)*

	Contact details: not reported
Notes	Source of funding: Public Assistance - Hopitaux De Paris (AP-HP) Conflicts of interest: unclear

EUCTR2010-024202-34-DE

Study name	Effect of oxytocin on therapy results of a group based social skill training in adolescents with autism spectrum disorder
Methods	Parallel trial of oxytocin versus placebo
Participants	Inclusion criteria: • male participants • aged 8-18 years • diagnosis of ASD according to ICD-10 • native German speaker • no or stable psychopharmacotherapy • consent is provided to participate Exclusion criteria: • IQ < 80 • female • any psychiatric diagnoses • any serious medical condition • allergic or hypersensitive to oxytocin • lesions to the brain Location/setting: Germany Sample size: not known
Interventions	Intervention (oxytocin): 40 IU oxytocin nasal spray (trial registry does not state the frequency) Comparator (placebo): equivalent placebo nasal spray
Outcomes	Primary outcomes: unclear Secondary outcomes: QoL (scale not reported) Timing of outcome assessments: unclear
Starting date	Registered December 2013
Contact information	Contact name: Tanja Schad-Hansjosten E-mail: tanja.schad@zi-mannheim.de
Notes	Source of funding: appears to be a pharmaceutical company (Universitätsmedizin Göttingen, Georg-August-Universität, Klinik für Kinder- und Jugendpsychiatrie/Psychotherapie) Conflicts of interest: unclear

EUCTR2014-003080--38-DE

Study name	Glutamatergic medication in the treatment of obsessive compulsive disorder (OCD) and autism spectrum disorder (ASD)
Methods	12-week parallel trial of memantine versus placebo
Participants	Inclusion criteria: • aged 6-17 years • IQ of at least 71 • either a DSM-5 diagnosis for ASD or OCD • CGI-S score of at least 4 • informed consent provided by parents • negative pregnancy test Exclusion criteria: • IQ of < 71 • weight < 20 kg at baseline • concomitant psychotropic medications are not permitted during the trial • significant medical cnditions affecting the cardiovascular, endocrine or gastrointestinal systems • allergy or hypersensitivity to memantine • pregnant or breastfeeding • failure to respond to an adequate dose of memantine previously Setting/location: 4 centres across England, Germany, and the Netherlands Sample size: target is 50 participants each group (100 in total), 50% with ASD, 50% with OCD
Interventions	Intervention (memantine + regular treatment) for 12 weeks: 5-15 mg/day, administered once daily Comparator (placebo + regular treatment) for 12 weeks: equivalent placebo
Outcomes	Primary outcomes: • irritability, measured using the ABC (Aman 1985) • self-injurious behaviour, measured using the Repetitive Behaviour Scale (Bodfish 2000) • AEs Secondary outcomes: unclear Timing of outcome assessments: unclear
Starting date	Registered July 2014
Contact information	Name: Alexander Häge E-mail: alexander.haege@zi-mannheim.de
Notes	**Source of funding:** "European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement number 278948, TACTICS (Translational Adolescent and Childhood Therapeutic Interventions in Compulsive Syndromes)". **Conflicts of interest:** unclear

IRCT20090117001556N124

Study name	Cilostazol as adjunctive treatment of autism: a double blind and placebo controlled trial in children 5 to 11 years old
Methods	10-week parallel trial of cilostazol versus placebo
Participants	Inclusion criteria: • aged 5-11 • DSM-V diagnosis of autism • minimum ABC-I score of 12 Exclusion criteria: • any psychiatric disorder • history of allergies to cilostazol or risperidone • any medical conditions such as seizure disorders or heart conditions • receipt of psychotropic medicines in the 2 weeks prior to the study
Interventions	Intervention (cilostazol + risperidone): 100 mg cilostazol morning and night plus risperidone 1-3 mg/day Comparator (placebo + risperidone): 1-3 mg/day of risperidone plus placebo
Outcomes	Primary outcomes: irritability, measured using the ABC-I (Aman 1985) Secondary outcomes: unclear Timing of outcome assessments: baseline, week 5 and 10 (endpoint)
Starting date	30 May 2020
Contact information	Contact name: S. Akhondzadeh E-mail: s.akhond@sina.tums.ac.ir
Notes	Source of funding: Tehran University of Medical Sciences Conflicts of interest: not reported

IRCT20200317046801N2

Study name	Effect of ondansetron combination therapy with risperidone in children with autism spectrum disorder in a randomized, double-blind, placebo-controlled clinical trial
Methods	8-week parallel trial of ondansetron versus placebo
Participants	Inclusion criteria: • children aged 5-17 years • DSM-V diagnosis of autism Exclusion criteria: • any active medical condition • any psychiatric conditions • taking risperidone or other psychotropics in the 2 weeks prior to the study • liver, heart, or kidney disease

IRCT20200317046801N2 *(Continued)*

	• allergy to ondansetron Setting: Roozbeh Hospital, Tehran, Iran Target sample size: 40
Interventions	Intervention: risperidone and ondansetron (05 mg/kg/day for children > 40 kg) for 8 weeks Comparator: risperidone and placebo for 8 weeks - the dosage of risperidone is unclear. Ondansetron: 05 mg/kg/day for children > 40 kg; placebo is 05 mg/kg/day for children > 40 kg
Outcomes	Primary outcomes: irritability, measured using the ABC-I (Aman 1985) Secondary outcomes: unclear Timing of outcome assessments: baseline, weeks 4 and 8 (endpoint)
Starting date	11 September 2020
Contact information	Name: Rahim Badrfam E-mail: rbadrfam@gmail.com
Notes	Source of funding: Tehran University of Medical Sciences Conflicts of interest: unclear

ISRCTN15984604

Study name	Sertraline for anxiety in adults with a diagnosis of autism
Methods	14-week parallel trial of sertraline versus placebo
Participants	Inclusion criteria: "Aged ≥18 years and have a diagnosis of autism (including autism spectrum disorder/condition or other variations, Asperger syndrome, or pervasive developmental disorder); experience anxiety for which participants are willing to try treatment with medication; able to complete online or paper-based questionnaires about things such as anxiety, other symptoms, and healthcare usage; able to provide informed consent to take part". Exclusion criteria: "currently taking medication(s) for depression and/or anxiety, or have taken them in the past 8 weeks, or are using St John's Wort; have a moderate or severe learning disability which means they may not be able to provide informed consent and/or understand and complete the study questionnaires; have/had other mental health conditions such as bipolar disorder or psychosis; have epilepsy that is not well controlled; have current problematic use of alcohol or illicit drugs; have allergies to sertraline or placebo; have/had severe liver problems, bleeding disorders, some heart problems; have swallowing difficulties or are unable to take medication in capsule form; taking part in another clinical trial; or are pregnant, planning pregnancy during the study period, or breastfeeding." Location/setting: the UK and Australia Target sample size: 306 participants
Interventions	Intervention (sertraline): the first 2 weeks participants will receive 25 mg of sertraline in tablet form, increasing to 25 mg twice daily for the next 4 weeks. Dose can be increased by 50 mg every 4 weeks until the optimal dose is reached.

ISRCTN15984604 *(Continued)*

	Comparator: the first 2 weeks participants will receive 25 mg of placebo in tablet form, increasing to 25 mg twice daily for the next 4 weeks. Dose can be increased by 50 mg every 4 weeks until the optimal dose is reached.
Outcomes	Primary outcomes: AEs Secondary outcomes: health-related QoL measured using EQ-5D-5L questionnaire Timing of outcome assessments: baseline, 12, 16, 24 and 52 weeks
Starting date	October 2019
Contact information	Contact name: Adam Taylor Contact details: research-governance@bristol.ac.uk
Notes	Source of funding: National Institute for Health Research Health Technology Assessment programme (NIHR HTA) (UK) and the National Health and Medical Research Council (NHMRC) (Australia) Conflicts of interest: details not reported

JPRN-UMIN000017876

Study name	Effects of long-term administration of intranasal oxytocin in children with autism spectrum disorder
Methods	14-week cross-over trial of oxytocin versus placebo
Participants	Inclusion criteria: • male • aged 6-10 years • diagnosis of ASD based on DSM-5 criteria and further confirmed by ADOS • at Osaka university hospital • IQ 35-75 • parents provide written informed consent to participate Exclusion criteria • female • co-occurring cardiovascular or renal disease • allergy to oxytocin • previously used oxytocin • doctors judged the trial to be inappropriate for the patient. Location/setting: Japan Target sample size: 10 in total
Interventions	Intervention: intranasal oxytocin 24 IU twice daily, followed by a 1-week wash-out period before phase 2 of the trial. Comparator: equivalent intranasal placebo twice daily, followed by a 1-week wash-out period before phase 2 of the trial.
Outcomes	Primary outcomes:

JPRN-UMIN000017876 *(Continued)*

	• ABC-I subscale (Japanese version) • AEs Secondary outcomes: none reported Timing of outcome assessments: baseline and endpoint of phase
Starting date	First registered June 2015
Contact information	Contact person: Masako Taniike Contact details: masako@ped.med.osaka-u.ac.jp
Notes	Source of funding: sponsored by the United Graduate School of Child Development, Osaka University Conflicts of interest: details not provided

NCT00198120

Study name	Safety and effectiveness of D-cycloserine in children with autism
Methods	8-week parallel trial of D-cycloserine versus placebo
Participants	Inclusion criteria: • aged 3-12 years • clinical diagnosis of autism based on DSM-IV • ABC-lethargy subscale of ≥ 13 Exclusion criteria: • severe or profound intellectual disability • weight < 11 kg • other neurodevelopmental disorders • any psychiatric disorders requiring treatment • significant renal, hepatic, or cardiovascular disorders Setting/location: assumed to be in the USA Sample size: target sample size is 80
Interventions	Intervention (D-Cycloserine) for 8 weeks: maximum 1.7 mg/kg/day Comparator (placebo) for 8 weeks: equivalent placebo
Outcomes	No relevant outcomes
Starting date	Trial registry last updated 2016
Contact information	Name: Christopher J McDougle Contact details: not provided
Notes	Source of funding: Indiana University Conflicts of interest: unclear

NCT01914939

Study name	A randomized, controlled trial of intranasal oxytocin as an adjunct to behavioral therapy for autism spectrum disorder
Methods	12-week parallel trial of oxytocin versus placebo
Participants	Inclusion criteria: • male participants • aged 18-40 years • normal or corrected vision • English-speaking • able to attend sessions in Boston • no history of brain injury, genetic disorders, or motor development difficulties Exclusion criteria: • substance dependency apart from caffeine and tobacco • serious medical conditions • current psychiatric disorders Setting/location: Boston, USA Sample size: target is 92 participants
Interventions	Intervention (oxytocin) for 12 weeks: intranasal spray of oxytocin 24 IU (unclear how often) Comparator (placebo) for 12 weeks: intranasal placebo
Outcomes	Primary outcomes: AEs Secondary outcomes: QoL (measured using the Quality of Life Enjoyment and Satisfaction Questionnaire) Timing of outcome assessments: unclear
Starting date	First registered in 2013
Contact information	Name: John Gabrieli Address: Massachusetts General Hospital/MIT
Notes	Source of funding: Massachusetts General Hospital Conflicts of interest: not reported

NCT01970345

Study name	A pilot treatment study of insulin-like growth factor-1 (IGF-1) in autism spectrum disorder
Methods	12-week cross-over trial of insulin-like growth factor-1 (IGF-1) versus placebo
Participants	Inclusion criteria: • children aged 5-12 years • meet the DSM-5 criteria for ASD

NCT01970345 *(Continued)*

	• language delay "(lack of fluent phrase speech) reflected by use of ADOS Module 1 or 2" • must be on stable medication in the 3 months prior to the trial Exclusion criteria: • intolerance or allergy to IGF-1 • hepatic or renal insufficiency, intracranial hypertension, cardiomegaly/valvulopathy, or significant medical conditions deemed by the investigators to affect the safe administration of IGF-1 Setting/location: unknown, although assumed to be in the USA Number of participants: target is 10
Interventions	Intervention (insulin-like growth factor-1 (IGF-1)) for 12 weeks: initiated at 0.04 mg/kg twice daily by injection, increasing to maximum of 0.12 mg/kg twice daily Comparator (placebo) for 12 weeks: equivalent placebo
Outcomes	Primary outcomes: BoC (measured using the Repetitive Behaviour Scale (Bodfish 2000) (subscales unknown)) Secondary outcomes: unclear Timing of outcome assessments: unclear
Starting date	First registered in 2013 and expected to be completed in 2022
Contact information	Name: Bonnie Lerman E-mail: bonnie.lerman@mssm.edu
Notes	Source of funding: Icahn School of Medicine at Mount Sinai, Autism Science Foundation Conflicts of interest: unclear

NCT03553875

Study name	Memantine for the treatment of social deficits in youth with disorders of impaired social interactions
Methods	12-week parallel trial of memantine hydrochloride versus placebo
Participants	Inclusion criteria: • male or female participants • aged 8-18 years • DSM-V diagnosis of ASD, and "at least moderate severity of social impairment as measured by a total raw score of ≥85 on the parent/guardian-completed Social Responsiveness Scale-Second Edition (SRS-2)14 and a score of ≥4 on the clinician-administered Clinical Global Impression-Severity scale (CGI-S)17" Exclusion criteria: • IQ < 70 • currently taking lamatrogine, amantadine, N-Acetycysteine, or D-cycloserine • any other psychotropics that have not been stable for past 4 weeks • co-administration of drugs that compete with memantine such as hydrochlorothiazide, triamterene, metformin, cimetidine, ranitidine, quinidine, and nicotine

NCT03553875 *(Continued)*

	• pregnant or breastfeeding; history of or current liver or kidney disease • serious medical conditions • known hypersensitivity to memantine Location/setting: Massachusetts General Hospital, USA Target sample size: 100 participants
Interventions	Intervention (memantine) for 12 weeks: maximum daily dose of 20 mg, administered twice daily for 12 weeks Comparator (placebo) for 12 weeks: equivalent placebo pill twice daily
Outcomes	Primary outcomes: CGI-Improvement Scale Secondary outcomes: unclear Timing of outcome assessments: not known
Starting date	First registered in November 2018
Contact information	Name: Chloe Hutt Vater E-mail: chuttvater@mgh.harvard.edu
Notes	Source of funding: Massachusetts General Hospital Conflicts of interest: unclear

NCT03887676

Study name	Arbaclofen versus placebo in the treatment of children and adolescents with ASD
Methods	16-week parallel trial of arbaclofen versus placebo
Participants	Inclusion criteria: • males and female • aged 5-17 years • outpatients • meet the DSM-V criteria for ASD • on stable medications in the 6 weeks prior to the study and during the study • ability to obtain written informed consent from the participant or a legal guardian or parent to participate in the study. Exclusion criteria: • pregnant or sexually active female participants who are on inadequate contraception • any serious medical condition including renal, cardiovascular, endocrine, or gastrointestinal disorders • unstable epilepsy (defined as seizures within the past 6 months) • history of drug abuse • hypersensitivity to arbaclofen • unable to tolerate blood sampling • actively involved in another trial • regularly taking racaemic baclofen, vigabatrin, tiagabine, riluzole, clobazam or regular benzodiazepine use ('as needed') use is allowed)

NCT03887676 *(Continued)*

	• unable to take oral medications • inability to speak and understand English sufficiently enough to allow for the completion of all study assessments Setting/ location: Canada Sample size: 90 participants
Interventions	Intervention: arbaclofen administered orally in tablet form in the following doses 5 mg, 10 mg, 15 mg and 20 mg for 16 weeks Comparator: equivalent placebo for 16 weeks
Outcomes	Primary outcomes: AEs Secondary outcomes: none reported Timing of outcome assessments: 16 weeks (endpoint)
Starting date	March 2019
Contact information	Evdokia Anagnostou Contact details: not provided
Notes	Source of funding: Holland Bloorview Kids Rehabilitation Hospital; McMaster University; University of Western Ontario, Canada; Queen's University; Unity Health Toronto; University of Toronto Conflicts of interest: details not provided

NCT04520685

Study name	CASCADE: CAnnabidiol Study in Children with Autism spectrum DisordEr (CASCADE)
Methods	12-week cross-over trial of cannabidiol versus placebo
Participants	Inclusion criteria: • male or female participants • 5-17 years of age • documented diagnosis of ASD • participants taking psychotropic medications should be on a stable dose and no more than 2 medications in the 4 weeks prior to the study • people with epilepsy cannot take more than 2 different anticonvulsants in the 3 months prior to the study, • BMI of 12-32 • negative pregnancy test Exclusion criteria: • pregnant or breastfeeding • history of hypersensitivities or allergies to cannibidiol • planned changes to pharmacological or behavioural interventions • acute or progressive psychiatric conditions • history or treatment for substance abuse Setting/location: University of Colorado, Denver

NCT04520685 *(Continued)*

	Sample size: target is 70 participants
Interventions	Intervention (cannabidiol) for 12 weeks then placebo for 15 weeks: "Each study period is 12 weeks and dose will be titrated up for 1 week at the beginning of a treatment period and titrated down for 1 week at the end of a treatment period, with a two week placebo washout between periods for Arms 1 and 2. The titration dose will be 5mg/kg/day and the treatment dose will be 10mg/kg/day" Comparator (placebo) for 15 weeks then cannabidiol for 12 weeks: participants will begin placebo in period 1 and receive cannabidiol in period 2 (same as above)
Outcomes	Primary outcomes: • ABC-Irritability (Aman 1985), from baseline to week 12 • self-injurious behaviour (measured using the Repetitive behaviour scale) (Bodfish 2000) Secondary outcomes: QoL (measured using the PedsQL - Core Scale) (Varni 2001) Timing of outcome assessments - baseline, week 12 (endpoint)
Starting date	First registered in August 2020
Contact information	Name: Nana Welnick E-mail: CBDinAutismStudy@childrenscolorado.org
Notes	Source of funding: University of Colorado, Denver Conflicts of interest: unclear

NCT04725383

Study name	Amitriptyline for repetitive behaviors in autism spectrum disorders
Methods	12-week parallel trial of amitripyline versus placebo
Participants	Inclusion criteria • male and female • aged 6-17 years • diagnosis of ASD • IQ > 35 Exclusion criteria: • an allergy to amitriptyline • absence of a reliable caregiver • previous neuroleptic malignant syndrome • seizures in the past 3 months • bipolar disorder • current or past psychosis • unstable medical illness • previous adequate treatment with amitriptyline • using other psychotropic medications apart from melatonin for sleep or lorazepam 1 mg as needed up to once a day Target sample size: 30 participants

NCT04725383 *(Continued)*

	Location/setting: USA
Interventions	Intervention: "Subjects will receive active amitriptyline compounded into look-alike capsules to resemble placebo capsules. Dosing will be as tolerated, up to a maximum of 100mg/day or 1.5mg/kg/day, for 12 weeks." Comparator: "Subjects in this arm will receive placebo compounded into capsules that resemble the compounded amitriptyline capsules, up to 4 capsules a day, for 12 weeks."
Outcomes	Primary outcomes: • irritability (measured using the ABC-I (Aman 1985) • self-injurious behaviour (measured using the Repetitive Behaviour Scale) (Bodfish 2000) Secondary outcomes: none reported Timing of outcome assessments: baseline and 12 weeks (endpoint)
Starting date	First registered January 2021
Contact information	Jessica Hellings Jessica.Hellings@tmcmed.org
Notes	Source of funding: sponsored by the University of Missouri, Kansas City Conflicts of interest: details not provided

NCT04745026

Study name	An exploratory, phase 2, randomized, double-blind, placebo-controlled trial to investigate the safety and efficacy of cannabidiol oral solution (GWP42003-P; CBD-OS) in children and adolescents with autism spectrum disorder
Methods	12-week parallel trial of GWP42003-P (cannabidiol) versus placebo
Participants	Inclusion criteria: • male and female • aged 6-17 years • weight at least 12 kg • participants and their parent(s)/legal representative are willing and able to give informed consent • diagnosis of ASD as per DSM-5 criteria, confirmed by ADOS-2 criteria (conducted within 2 years at the trial site or at screening by a qualified assessor or ADI-R if ADOS-2 is not available • CGI-S ≥ 4 (moderately ill) at screening and randomisation • ABC-I subscale score ≥ 15 at screening • IQ ≥ 70 at screening, or measured within 1 year of screening, using Wechsler Abbreviated Scale of Intelligence Scale Second Edition (WASI-II) • all medications or interventions (including psychosocial interventions, dietary supplements, probiotics, speech therapy, etc.) for ASD-related symptoms must have been stable for 4 weeks prior to screening and randomisation, and the patient/caregiver should be willing to maintain a stable regimen throughout the trial • able to swallow the investigational medicinal product (IMP), provided as a liquid solution • participant and/or parent(s)/legal representative willing to allow the responsible authorities to be notified of participation in the trial, if necessary. Exclusion criteria

NCT04745026 *(Continued)*

- Current diagnosis of bipolar disorder, psychosis, schizophrenia, schizoaffective disorder, or major depression (participants with depression in remission may be included)
- diagnosis other than ASD that dominates the clinical presentation (e.g. ADHD)
- progressive neurological condition
- seizures in the past 24 weeks
- changes in anticonvulsive therapy within the last 12 weeks
- currently taking more than 2 anti-epileptic drugs
- taking sirolimus, everolimus, temsirolimus, or tacrolimus; taking clobazam; taking omeprazole, lansoprazole, tolbutamide, or warfarin; taking repaglinide, pioglitazone, rosiglitazone, montelukast, bupropion, or efavirenz; currently using or has used recreational or medicinal cannabis, cannabinoid-based medications (including Sativex®, or Epidiolex®) within the 12 weeks prior to screening and is unwilling to abstain for the duration of the trial
- participant has any known or suspected hypersensitivity to cannabinoids or any of the intervention drug's excipients, such as sesame oil
- moderately impaired hepatic function at screening, defined as serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 × upper limit of normal (ULN) or total bilirubin (TBL) > 2 × ULN
- participant is male and fertile (i.e. after puberty unless permanently sterile by bilateral orchidectomy) unless willing to ensure that they use male contraception (condom) or remain sexually abstinent during the trial and for 12 weeks thereafter
- participant is female and of childbearing potential (i.e., following menarche and until becoming postmenopausal for ≥ 12 consecutive months unless permanently sterile by hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) unless willing to ensure that they use a highly effective method of birth control (e.g., hormonal contraception, intrauterine device/hormone-releasing system, bilateral tubal occlusion, vasectomized partner, sexual abstinence) during the trial and for 12 weeks thereafter; female participant who is pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the trial or within 12 weeks thereafter
- received an IMP within the 12 weeks prior to the screening visit
- brain surgery or traumatic brain injury within 1 year of screening
- any other significant disease or disorder which, in the opinion of the investigator, may either put the participant, other participants, or site staff at risk because of participation in the trial, may influence the result of the trial, or may affect the participant's ability to take part in the trial
- any abnormalities identified following a physical examination of the participant that, in the opinion of the investigator, would jeopardise the safety of the participant if they took part in the trial; any history of suicidal behaviour (lifelong) or any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) in the last 4 weeks or at screening or randomisation
- donated blood during the past 12 weeks and is unwilling to abstain from donation of blood during the trial
- any known or suspected history of alcohol or substance abuse or positive drugs of abuse test at screening (not justified by a known concurrent medication)
- previously been randomised into this trial
- participant has plans to travel outside their country of residence during the trial, unless the participant has confirmation that the IMP is permitted in the destination country/state".

Setting/location: 7 sites in the USA, and 2 sites in both Canada and the UK

Sample size: 160 participants

Interventions	Intervention GWP42003-P (100 mg/mL cannabidiol (CBD) in sesame oil with anhydrous ethanol, ethanol sweetener [sucralose], and strawberry flavouring), administered twice a day (morning and evening) Comparator: "Oral placebo to match GWP42003-P oral solution containing sesame oil with anhydrous ethanol, sweetener (sucralose), strawberry flavoring, and beta carotene, administered twice a day (morning and evening)".
Outcomes	Primary outcomes:

NCT04745026 *(Continued)*

	• change from screening in ABC subscale scores (Aman 1985) • AEs Secondary outcomes: none reported Timing of outcome assessments: baseline, endpoint
Starting date	May 2021
Contact information	Contact person: not provided Contact details: ClinicalTrialDisclosure@JazzPharma.com; info@gwpharm.com (UK contact)
Notes	Source of funding Conflicts of interest

NCT04895215

Study name	A three-arm, parallel group, randomized, double-blind, placebo-controlled study of the efficacy, safety, and tolerability of AB-2004 in a 13 to 17 year-old autism spectrum disorder population
Methods	8-week parallel trial of two doses of AB-2004 versus placebo
Participants	Inclusion criteria: • clinically diagnosed, documented ASD DSM-5 criteria • ABC-I score ≥ 18 at the screening visit • CGI-S scale score ≥ 4 at the screening visit Exclusion criteria: • use of an oral, injected, or inhaled antibiotic within 30 days prior to screening. Prophylactic oral antibiotic use of no more than 1 dose will be permitted • current use of an oral controlled or extended-release medication • have a comorbid major psychiatric condition (e.g. schizophrenia or bipolar disorder) at screening that in the opinion of the Investigator may interfere with the participant's ability to complete study procedures/comply with study requirements • current use of antipsychotics (eg, aripiprazole or risperidone) Setting/location: "13 sites in the U.S., and two sites in Australia/New Zealand combined." Sample size: target sample size is 195
Interventions	Intervention: AB-2004 (high-dose) taken 3 times daily; or AB-2004 (low-dose) taken 3 times daily Comparator: equivalent placebo taken 3 times daily
Outcomes	Primary outcomes: • mean change in ABC-I score (Aman 1985) from baseline to endpoint • AEs Secondary outcomes: none reported Timing of outcome assessments: baseline and endpoint (week 8)
Starting date	August 2021

NCT04895215 *(Continued)*

Contact information	Name:Jeffrey Young E-mail: jeffrey@axialtx.com
Notes	Source of funding: details not reported Conflicts of interest: not reported

NCT05015439

Study name	Cannabidiol (CBD) in adults with ASD
Methods	14-week cross-over trial of cannabiodiol versus placebo
Participants	Inclusion criteria: • male and female • aged ≥ 18 years • ASD based on DSM-5 criteria • significant mood disorder, sleep disturbance, or exhibit agitation, aggression, or other aberrant behaviour that is interfering with function and QoL, as determined by their psychiatric interview Exclusion criteria: "history of alcohol or substance use disorder; positive urine tetrahydrocannabinol screen at onset of study; positive urine tetrahydrocannabinol screen at onset of study; individuals with unstable liver disease; individuals taking medications where CBD interaction might significantly alter drug levels, such as clobazam". Setting/location: USA Sample size: target sample size is 40
Interventions	Intervention (cannabidiol): 100 mg cannabidiol twice daily in capsule form, increasing to 200 mg twice daily by week 3. This is followed by a 2-week wash-out period before starting phase 2 of the cross-over. Comparator (placebo): equivalent placebo for 6 weeks. This is followed by a 2-week wash-out period before starting phase 2 of the cross-over.
Outcomes	Primary outcomes: • change in aberrant behaviours as assessed by the ABC (Aman 1985) • adverse effects Secondary outcomes: none reported Timing of outcome assessments: baseline and six weeks (end of phase)
Starting date	Estimated start date: September 2022
Contact information	Contact name: Elizabeth Wise Contact details: ewise11@jhmi.edu
Notes	Source of funding: Johns Hopkins University; Canopy Growth Corporation Conflicts of interest: details not provided

NCT05163717

Study name	INP105 proof-of-concept study for the acute treatment of agitation in adolescents with ASD (CALM 201)
Methods	Cross-over trial of single-dose INP105 (olanzapine) versus placebo
Participants	Inclusion criteria: • male and female • aged 12-17 years • confirmed ASD diagnosis • admitted as an inpatient to a behavioral unit prior to informed consent • displays episodes of moderate to severe agitation Exclusion criteria: • hypersensitivity to olanzapine • currently diagnosed with a genetic or other syndromic form of neurodevelopmental disorder • seizure in the past 6 months • history of severe head trauma, stroke, endocrine disorder, or cardiovascular disease • history of hypotension • currently on a chronic dose of olanzapine, or currently taking ciprofloxacin, enoxacin, fluvoxamine, or carbamazepine Location/setting: USA Target sample size: 32 participants Gender: details not provided Mean age: details not provided IQ: details not provided Concomitant medications: details not provided Previous medications: details not provided
Interventions	Intervention (olanzapine): a single dose of 5 mg of olanzapine Comparator (placebo): a single dose of equivalent placebo
Outcomes	Primary outcomes: • irritability (measured using the ABC-I subscale (Aman 1985) • aggression (measured using the Overt Aggression Scale) • AEs Secondary outcomes: none reported Timing of outcome assessments: AEs measured up to 48 h post-dose; aggression and irritability measured 30 minutes post-dose.
Starting date	
Contact information	Contact name: Stephen Shrewsbury Contact details: sshrewsbury@impelpharma.com
Notes	Study start date: June 2022

NCT05163717 *(Continued)*

	Study end date: estimated to be January 2023 Source of funding: Impel NeuroPharma Inc. Conflicts of interest: details not provided

NCT05182697

Study name	SCI-210 in the treatment of children and young adults with autism evaluate the safety, tolerability and efficacy of SCI-210 in children with autism spectrum disorder (ASD)
Methods	Cross-over trial of palmitoylethanolamide versus placebo
Participants	Inclusion criteria: • male and female • aged 5-18 years • diagnosis of ASD confirmed by the ADOS-2 or the DSM-5 criteria • moderate or greater behavioural problems measured by a rating of moderate or higher (at least 4) on the CGI-S • parent or legal guardian who will provide consent • must be "eligible for cannabis treatment as regulated by the Israeli Ministry of Health, as out lined in the Medical Cannabis unit circular on Licenses for cannabis use, Procedure number 106, version 5 dated Jan 2021". Exclusion criteria: • children who already receive cannabis, antipsychotics or stimulants • heart, liver, renal, or blood disorders • history of seizure disorders or have had a seizure within the past 3 months • exposure to any other investigational agent in the 30 days prior to the trial • current diagnosis of schizophrenia, major depressive disorder, bipolar, psychosis or post traumatic stress disorder (PTSD) • people who have had changes to other non-exclusionary psychotropic medications within 4 weeks of starting the trial; allergic to cannabinoids • history of substance abuse • any other condition in the opinion of the investigator that places the participant at unacceptable risk if they participate Setting/location: Israel Sample size:
Interventions	Intervention: oral cannabidiol oil plus pills of CannAmide (palmitoylethanolamide (PEA) 400 mg twice daily Comparator: active cannabidiol oil with twice-daily placebo pills matched in appearance and taste to CannAmide active pill
Outcomes	Primary outcomes: • AEs • BoC (measured using the ABC) (Aman 1985) Secondary outcomes: none reported

NCT05182697 *(Continued)*

	Timing of outcome assessments: the ABC will be measured at baseline and weeks 4 and 8 of each phase
Starting date	Approximately October 2022
Contact information	Contact person: Gal Meiri Contact details: not provided
Notes	

Parellada 2021

Study name	Arbaclofen in children and adolescents with ASD (AIMS2-CT1)
Methods	16-week parallel trial of arbaclofen versus placebo
Participants	Inclusion criteria: • outpatients • male and female • aged 5-17 years with a diagnosis of ASD • if on psychotropic medications, must remain stable throughout the study • written informed consent to participate in the trial Exclusion criteria: • pregnant women • any serious medical conditions, including unstable epilepsy • history of drug abuse • hypersensitivity or allergy to arbaclofen • enroled in a different intervention study • inability to take oral medication Setting/location: France, Spain and the UK Sample size: target sample size is 130
Interventions	Intervention (arbaclofen) for 16 weeks: maximum of 15 mg 3 times daily for children aged 5-11 years, and a maximum of 20 mg/day for children aged 12-17 years Comparator (placebo for 16 weeks): equivalent placebo
Outcomes	Primary outcomes: • irritability, measured using the ABC-I subscale (Aman 1985) • adverse effects Secondary outcomes: health-related QoL (unclear the measure used) Timing of outcome assessments: unclear
Starting date	September 2019
Contact information	Contact person: Inge Winter Contact details: I.Winter@umcutrecht.nl

Parellada 2021 *(Continued)*

Notes	Source of funding: "This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under the grant agreement No. 777394 for the project AIMS-2-TRIALS. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program, EFPIA, Autism Speaks, Autistica, and the Simons Foundation". Conflicts of interest: various authors had a consultancy or other working relationship with pharmaceutical companies Trial registry - NCT03682978

UMIN000017876

Study name	Effects of long-term administration of intranasal oxytocin in children with autism spectrum disorder
Methods	4-week cross-over trial of oxytocin versus placebo
Participants	Inclusion criteria: • male participants • aged 6-10 years • diagnosis of ASD based on the DSM-V • IQ 35-75 • written informed consent provided by the parent/s Exclusion criteria: • comorbid renal or cardiovascular disease • allergy to oxytocin • female • previous use of oxytocin Setting/location: Japan Sample size: target sample size is 10
Interventions	Intervention (oxytocin for 4 weeks followed by placebo): 24 IU of oxytocin twice daily for 4 weeks, then 1-week washout followed by 4 weeks of placebo Comparator (placebo for 4 weeks followed by oxytocin): placebo for 4 weeks followed by 1-week washout period then 4 weeks of 24 IU oxytocin twice daily
Outcomes	Primary outcomes: • irritability, measured using the ABC-J (Japanese version of ABC-Irritability) (Aman 1985) • adverse effects Secondary outcomes: unclear Timing of outcome assessments: unclear
Starting date	Registered in 2015
Contact information	Name: Masako Taniike E-mail: masako@ped.med.osaka-u.ac.jp

UMIN000017876 *(Continued)*	
Notes	Source of funding: unclear

ABC-I: Aberrant Behaviour Checklist: Irritability subscale; **ADOS:** Autism Diagnostic Observation Schedule; **AE:** adverse effect; **ASD:** Autism Spectrum Disorder; **BoC:** behaviours of concern; **DSM:IV:** Diagnostic and statistical Manual of Mental disorders (4th edition); **DSM-V:** Diagnostic and statistical Manual of Mental disorders (5th edition); **ICD-10:** International classification of diseases (10th edition); **IGF-1:** insulin-like growth factor-1; **PedsQL:** Pediatric Quality of Life inventory; **QoL:** quality of life

DATA AND ANALYSES

Comparison 1. Atypical antipsychotic vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Irritability	12	973	Std. Mean Difference (IV, Random, 95% CI)	-0.90 [-1.25, -0.55]
1.1.1 Aripiprazole vs placebo	5	492	Std. Mean Difference (IV, Random, 95% CI)	-0.90 [-1.52, -0.29]
1.1.2 Risperidone vs placebo	6	333	Std. Mean Difference (IV, Random, 95% CI)	-1.11 [-1.47, -0.76]
1.1.3 Lurasidone vs placebo	1	148	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.50, 0.19]
1.2 Relapse	2	56	Risk Ratio (IV, Random, 95% CI)	0.30 [0.13, 0.68]
1.3 Improvement	4	470	Risk Ratio (IV, Random, 95% CI)	2.08 [1.39, 3.12]
1.3.1 Risperidone vs placebo	2	167	Risk Ratio (IV, Random, 95% CI)	3.37 [1.21, 9.43]
1.3.2 Ariprazole vs placebo	2	303	Risk Ratio (IV, Random, 95% CI)	1.57 [1.09, 2.27]
1.4 Aggression	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.4.1 Risperidone vs placebo	1	77	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-0.89, 0.01]
1.5 Self-injury	1	30	Std. Mean Difference (IV, Random, 95% CI)	-1.43 [-2.24, -0.61]
1.5.1 Risperidone vs placebo	1	30	Std. Mean Difference (IV, Random, 95% CI)	-1.43 [-2.24, -0.61]
1.6 Adverse effects: cardiovascular	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.6.1 Tachycardia	2	179	Risk Ratio (IV, Random, 95% CI)	7.53 [1.40, 40.52]
1.7 Adverse effects: gastrointestinal	11		Risk Ratio (IV, Random, 95% CI)	Subtotals only

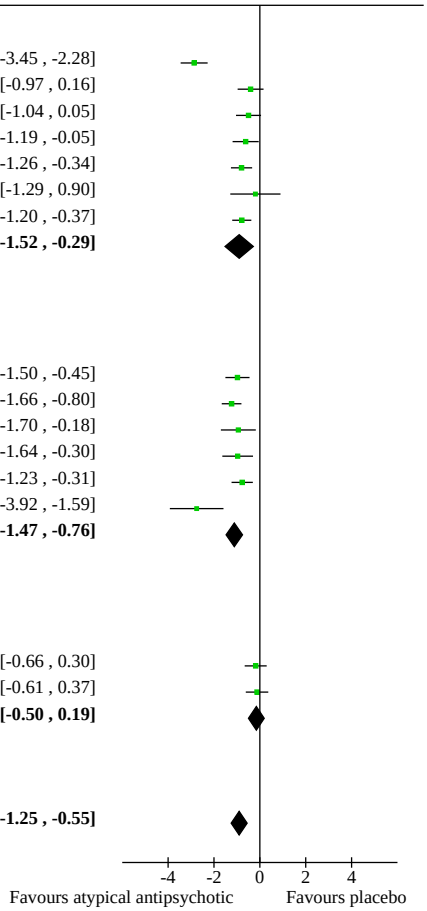
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.1 Abdominal pain	4	400	Risk Ratio (IV, Random, 95% CI)	2.70 [1.04, 7.07]
1.7.2 Constipation	7	596	Risk Ratio (IV, Random, 95% CI)	2.36 [1.28, 4.34]
1.7.3 Diarrhoea	5	318	Risk Ratio (IV, Random, 95% CI)	0.93 [0.46, 1.88]
1.7.4 Drooling	2	313	Risk Ratio (IV, Random, 95% CI)	9.64 [1.29, 72.10]
1.7.5 Dyspepsia (indigestion)	1	31	Risk Ratio (IV, Random, 95% CI)	3.19 [0.14, 72.69]
1.7.6 Dry mouth	2	131	Risk Ratio (IV, Random, 95% CI)	1.97 [0.75, 5.20]
1.7.7 Hypersalivation	5	449	Risk Ratio (IV, Random, 95% CI)	4.15 [1.77, 9.71]
1.7.8 Nausea	4	531	Risk Ratio (IV, Random, 95% CI)	1.47 [0.61, 3.56]
1.7.9 Stomach ache	2	166	Risk Ratio (IV, Random, 95% CI)	0.50 [0.19, 1.32]
1.7.10 Vomiting/nausea	9	920	Risk Ratio (IV, Random, 95% CI)	1.79 [1.16, 2.74]
1.8 Adverse effects: immune system	7		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.8.1 Cough	3	444	Risk Ratio (IV, Random, 95% CI)	1.50 [0.67, 3.34]
1.8.2 Earache	1	100	Risk Ratio (IV, Random, 95% CI)	0.52 [0.10, 2.71]
1.8.3 Flu-like symptoms	1	79	Risk Ratio (IV, Random, 95% CI)	1.95 [0.38, 10.04]
1.8.4 Pyrexia	5	540	Risk Ratio (IV, Random, 95% CI)	1.81 [0.85, 3.86]
1.8.5 Sore throat	1	100	Risk Ratio (IV, Random, 95% CI)	5.20 [0.63, 42.96]
1.9 Adverse effects: metabolic (dichotomous)	10		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.9.1 Decreased appetite	4	426	Risk Ratio (IV, Random, 95% CI)	2.12 [0.84, 5.33]
1.9.2 Increased appetite	8	702	Risk Ratio (IV, Random, 95% CI)	2.38 [1.69, 3.34]
1.9.3 Weight gain	4	470	Risk Ratio (IV, Random, 95% CI)	2.30 [0.84, 6.30]
1.9.4 Thirst	3	382	Risk Ratio (IV, Random, 95% CI)	1.51 [0.59, 3.87]
1.10 Adverse effects: metabolic (continuous)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.10.1 Weight gain (kg)	1	23	Mean Difference (IV, Random, 95% CI)	2.35 [0.73, 3.97]
1.11 Adverse effects: musculoskeletal	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.11.2 Dyskinesia	1	100	Risk Ratio (IV, Random, 95% CI)	2.08 [0.55, 7.87]
1.11.3 Movement disorder	1	82	Risk Ratio (IV, Random, 95% CI)	5.50 [0.27, 111.14]
1.11.4 Rigidity	1	100	Risk Ratio (IV, Random, 95% CI)	5.20 [0.63, 42.96]
1.12 Adverse effects: neurological	11		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.12.1 Aggression	4	461	Risk Ratio (IV, Random, 95% CI)	0.34 [0.12, 0.98]
1.12.2 Agitation/excitation	2	97	Risk Ratio (IV, Random, 95% CI)	0.46 [0.13, 1.62]
1.12.3 Apathy	1	79	Risk Ratio (IV, Random, 95% CI)	10.73 [0.61, 187.79]
1.12.4 Dizziness	2	139	Risk Ratio (IV, Random, 95% CI)	4.19 [1.10, 16.00]
1.12.5 Drowsiness	1	97	Risk Ratio (IV, Random, 95% CI)	4.26 [0.95, 19.02]
1.12.6 Extrapyramidal disorder	1	216	Risk Ratio (IV, Random, 95% CI)	7.83 [0.47, 130.01]
1.12.7 Fatigue	8	881	Risk Ratio (IV, Random, 95% CI)	2.58 [1.68, 3.97]
1.12.8 Headache	6	597	Risk Ratio (IV, Random, 95% CI)	1.17 [0.63, 2.15]
1.12.9 Hyperactivity	3	305	Risk Ratio (IV, Random, 95% CI)	0.47 [0.13, 1.70]
1.12.10 Hypersomnia	2	282	Risk Ratio (IV, Random, 95% CI)	2.67 [0.43, 16.52]
1.12.11 Insomnia	7	679	Risk Ratio (IV, Random, 95% CI)	0.72 [0.50, 1.04]
1.12.12 Lethargy	1	216	Risk Ratio (IV, Random, 95% CI)	6.58 [0.39, 110.35]
1.12.13 Presyncope	1	216	Risk Ratio (IV, Random, 95% CI)	0.94 [0.04, 22.72]
1.12.14 Restlessness (akathisia)	4	531	Risk Ratio (IV, Random, 95% CI)	0.99 [0.40, 2.43]
1.12.15 Sedation	5	366	Risk Ratio (IV, Random, 95% CI)	2.98 [1.15, 7.73]
1.12.16 Somnolence	9	869	Risk Ratio (IV, Random, 95% CI)	4.84 [3.18, 7.36]
1.12.17 Tremor	5	574	Risk Ratio (IV, Random, 95% CI)	5.99 [1.87, 19.19]
1.13 Adverse effects: psychological	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.13.1 Anxiety	2	139	Risk Ratio (IV, Random, 95% CI)	1.34 [0.65, 2.76]
1.13.2 Depression	2	79	Risk Ratio (IV, Random, 95% CI)	3.86 [0.46, 32.60]
1.14 Adverse effects: respiratory	8		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.14.1 Ear infection	1	66	Risk Ratio (IV, Random, 95% CI)	5.62 [0.28, 112.84]
1.14.2 Epistaxis	1	66	Risk Ratio (IV, Random, 95% CI)	5.62 [0.28, 112.84]
1.14.3 Nasal congestion	2	313	Risk Ratio (IV, Random, 95% CI)	2.39 [0.52, 11.00]
1.14.4 Nasopharyngitis	6	702	Risk Ratio (IV, Random, 95% CI)	1.26 [0.73, 2.17]
1.14.5 Pharyngolaryngeal pain	1	216	Risk Ratio (IV, Random, 95% CI)	0.31 [0.06, 1.48]
1.14.6 Rhinitis	1	79	Risk Ratio (IV, Random, 95% CI)	2.68 [0.93, 7.71]
1.14.7 Upper respiratory tract infection	6	640	Risk Ratio (IV, Random, 95% CI)	2.15 [1.08, 4.27]
1.15 Adverse effects: skin	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.15.1 Bruise	1	92	Risk Ratio (IV, Random, 95% CI)	0.32 [0.03, 2.96]
1.15.2 Rash	2	228	Risk Ratio (IV, Random, 95% CI)	0.79 [0.14, 4.62]
1.16 Adverse effects: urinary	6		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.16.1 Enuresis	6	552	Risk Ratio (IV, Random, 95% CI)	1.12 [0.67, 1.86]
1.17 Quality of life	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.18 Tolerability/acceptability: loss to follow-up	13		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.19 Subgroup analysis: age - irritability	11	938	Std. Mean Difference (IV, Random, 95% CI)	-0.87 [-1.24, -0.50]
1.19.1 Adults only	1	30	Std. Mean Difference (IV, Random, 95% CI)	-0.94 [-1.70, -0.18]
1.19.2 Children only	10	908	Std. Mean Difference (IV, Random, 95% CI)	-0.87 [-1.26, -0.47]
1.20 Subgroup analysis: age - aggression	1	77	Mean Difference (IV, Random, 95% CI)	-3.80 [-7.61, 0.01]
1.20.1 Children only	1	77	Mean Difference (IV, Random, 95% CI)	-3.80 [-7.61, 0.01]
1.21 Subgroup analysis: cognitive ability - irritability	10	925	Std. Mean Difference (IV, Random, 95% CI)	-0.91 [-1.29, -0.52]
1.21.1 Mixed IQ	10	925	Std. Mean Difference (IV, Random, 95% CI)	-0.91 [-1.29, -0.52]

Analysis 1.1. Comparison 1: Atypical antipsychotic vs placebo, Outcome 1: Irritability

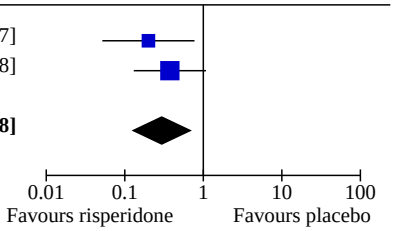
Study or Subgroup	Atypical antipsychotic Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Aripiprazole vs placebo								
Ichikawa 2017	-11.4	1.3	47	-7.5	1.4	45	6.8%	-2.87 [-3.45 , -2.28]
Marcus 2009 (1)	-12.4	9.81	52	-8.4	9.73	16	6.9%	-0.40 [-0.97 , 0.16]
Marcus 2009 (2)	-13.2	9.6	59	-8.4	9.73	17	7.0%	-0.49 [-1.04 , 0.05]
Marcus 2009 (3)	-14.4	9.54	53	-8.4	9.73	16	6.9%	-0.62 [-1.19 , -0.05]
NCT00198107	18.6	8.52	38	25.5	8.6	40	7.3%	-0.80 [-1.26 , -0.34]
NCT00468130	6.83	6.87	7	8.67	10.69	6	4.6%	-0.19 [-1.29 , 0.90]
Owen 2009	-12.9	9.77	46	-5	10.11	50	7.5%	-0.79 [-1.20 , -0.37]
Subtotal (95% CI)			**302**			**190**	**47.0%**	**-0.90 [-1.52 , -0.29]**
Heterogeneity: Tau² = 0.59; Chi² = 50.95, df = 6 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 2.87 (P = 0.004)								
1.1.2 Risperidone vs placebo								
Kent 2013	-12.4	6.52	29	-3.5	10.67	34	7.1%	-0.98 [-1.50 , -0.45]
McCracken 2002	11.3	7.4	49	21.9	9.5	51	7.5%	-1.23 [-1.66 , -0.80]
McDougle 1998	0.35	0.37	14	0.82	0.57	16	6.0%	-0.94 [-1.70 , -0.18]
NCT01624675	-9.7	7.29	21	-2.8	6.62	18	6.4%	-0.97 [-1.64 , -0.30]
Shea 2004	-12.1	5.8	39	-6.5	8.4	38	7.3%	-0.77 [-1.23 , -0.31]
Troost 2005	1.5	1.7	12	7.6	2.5	12	4.3%	-2.76 [-3.92 , -1.59]
Subtotal (95% CI)			**164**			**169**	**38.6%**	**-1.11 [-1.47 , -0.76]**
Heterogeneity: Tau² = 0.10; Chi² = 10.46, df = 5 (P = 0.06); I² = 52%								
Test for overall effect: Z = 6.10 (P < 0.00001)								
1.1.3 Lurasidone vs placebo								
Loebel 2016 (4)	-9.4	10.21	51	-7.5	10.64	25	7.3%	-0.18 [-0.66 , 0.30]
Loebel 2016 (5)	-8.8	10.39	48	-7.5	10.64	24	7.2%	-0.12 [-0.61 , 0.37]
Subtotal (95% CI)			**99**			**49**	**14.5%**	**-0.15 [-0.50 , 0.19]**
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%								
Test for overall effect: Z = 0.87 (P = 0.38)								
Total (95% CI)			**565**			**408**	**100.0%**	**-0.90 [-1.25 , -0.55]**
Heterogeneity: Tau² = 0.37; Chi² = 80.89, df = 14 (P < 0.00001); I² = 83%								
Test for overall effect: Z = 5.09 (P < 0.00001)								
Test for subgroup differences: Chi² = 15.17, df = 2 (P = 0.0005), I² = 86.8%								



Footnotes
(1) 5mg/day aripiprazole
(2) 10mg/day aripiprazole
(3) 15mg/day aripiprazole
(4) Lurasidone 60mg/day
(5) Lurasidone 20mg/day

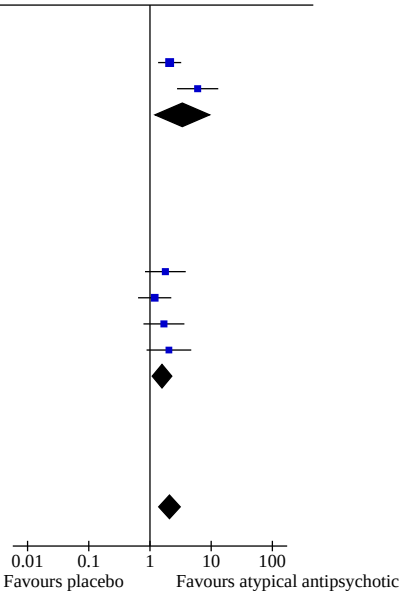
Analysis 1.2. Comparison 1: Atypical antipsychotic vs placebo, Outcome 2: Relapse

Study or Subgroup	Risperidone Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Research Units 2005	2	16	10	16	38.0%	0.20 [0.05 , 0.77]
Troost 2005	3	12	8	12	62.0%	0.38 [0.13 , 1.08]
Total (95% CI)		**28**		**28**	**100.0%**	**0.30 [0.13 , 0.68]**
Total events:	5		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 1 (P = 0.47); I² = 0%						
Test for overall effect: Z = 2.87 (P = 0.004)						
Test for subgroup differences: Not applicable						



Analysis 1.3. Comparison 1: Atypical antipsychotic vs placebo, Outcome 3: Improvement

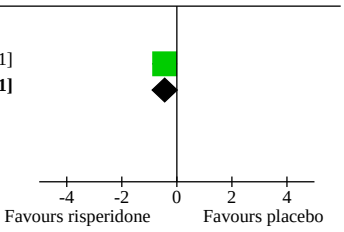
Study or Subgroup	Atypical antipsychotic Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.3.1 Risperidone vs placebo						
Kent 2013	26	31	14	35	23.6%	2.10 [1.36 , 3.24]
McCracken 2002	34	49	6	52	14.8%	6.01 [2.77 , 13.06]
Subtotal (95% CI)		**80**		**87**	**38.4%**	**3.37 [1.21 , 9.43]**
Total events:	60		20			
Heterogeneity: Tau² = 0.45; Chi² = 5.40, df = 1 (P = 0.02); I² = 81%						
Test for overall effect: Z = 2.32 (P = 0.02)						
1.3.2 Aripiprazole vs placebo						
Marcus 2009 (1)	29	52	5	16	15.0%	1.78 [0.83 , 3.84]
Marcus 2009 (2)	29	59	7	17	18.3%	1.19 [0.64 , 2.23]
Marcus 2009 (3)	28	53	5	16	14.9%	1.69 [0.78 , 3.65]
Owen 2009	16	51	6	39	13.5%	2.04 [0.88 , 4.73]
Subtotal (95% CI)		**215**		**88**	**61.6%**	**1.57 [1.09 , 2.27]**
Total events:	102		23			
Heterogeneity: Tau² = 0.00; Chi² = 1.25, df = 3 (P = 0.74); I² = 0%						
Test for overall effect: Z = 2.41 (P = 0.02)						
Total (95% CI)		**295**		**175**	**100.0%**	**2.08 [1.39 , 3.12]**
Total events:	162		43			
Heterogeneity: Tau² = 0.13; Chi² = 10.66, df = 5 (P = 0.06); I² = 53%						
Test for overall effect: Z = 3.55 (P = 0.0004)						
Test for subgroup differences: Chi² = 1.88, df = 1 (P = 0.17), I² = 46.8%						



Footnotes
(1) 15mg/day aripiprazole
(2) 5mg/day aripiprazole
(3) 10mg/day aripiprazole

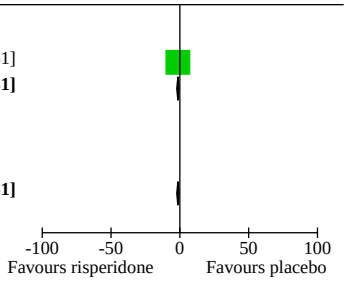
Analysis 1.4. Comparison 1: Atypical antipsychotic vs placebo, Outcome 4: Aggression

Study or Subgroup	Risperidone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.4.1 Risperidone vs placebo								
Shea 2004	-10.4	7.4	39	-6.6	9.5	38	100.0%	-0.44 [-0.89 , 0.01]
Subtotal (95% CI)			**39**			**38**	**100.0%**	**-0.44 [-0.89 , 0.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.92 (P = 0.06)								
Test for subgroup differences: Not applicable								



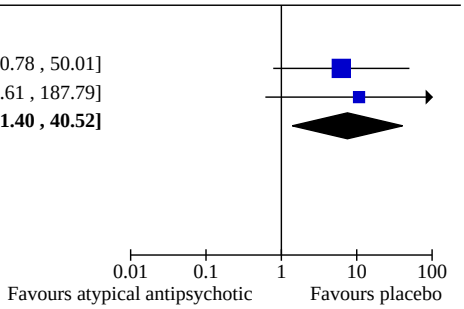
Analysis 1.5. Comparison 1: Atypical antipsychotic vs placebo, Outcome 5: Self-injury

Study or Subgroup	Risperidone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.5.1 Risperidone vs placebo								
McDougle 1998	-23.6	9.5	14	-4.9	15	16	100.0%	-1.43 [-2.24 , -0.61]
Subtotal (95% CI)			**14**			**16**	**100.0%**	**-1.43 [-2.24 , -0.61]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.43 (P = 0.0006)								
Total (95% CI)			**14**			**16**	**100.0%**	**-1.43 [-2.24 , -0.61]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.43 (P = 0.0006)								
Test for subgroup differences: Not applicable								



Analysis 1.6. Comparison 1: Atypical antipsychotic vs placebo, Outcome 6: Adverse effects: cardiovascular

Study or Subgroup	Atypical antipsychotic Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.6.1 Tachycardia						
McCracken 2002	6	49	1	51	65.4%	6.24 [0.78 , 50.01]
Shea 2004	5	40	0	39	34.6%	10.73 [0.61 , 187.79]
Subtotal (95% CI)		**89**		**90**	**100.0%**	**7.53 [1.40 , 40.52]**
Total events:	11		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 2.35 (P = 0.02)						
Test for subgroup differences: Not applicable						

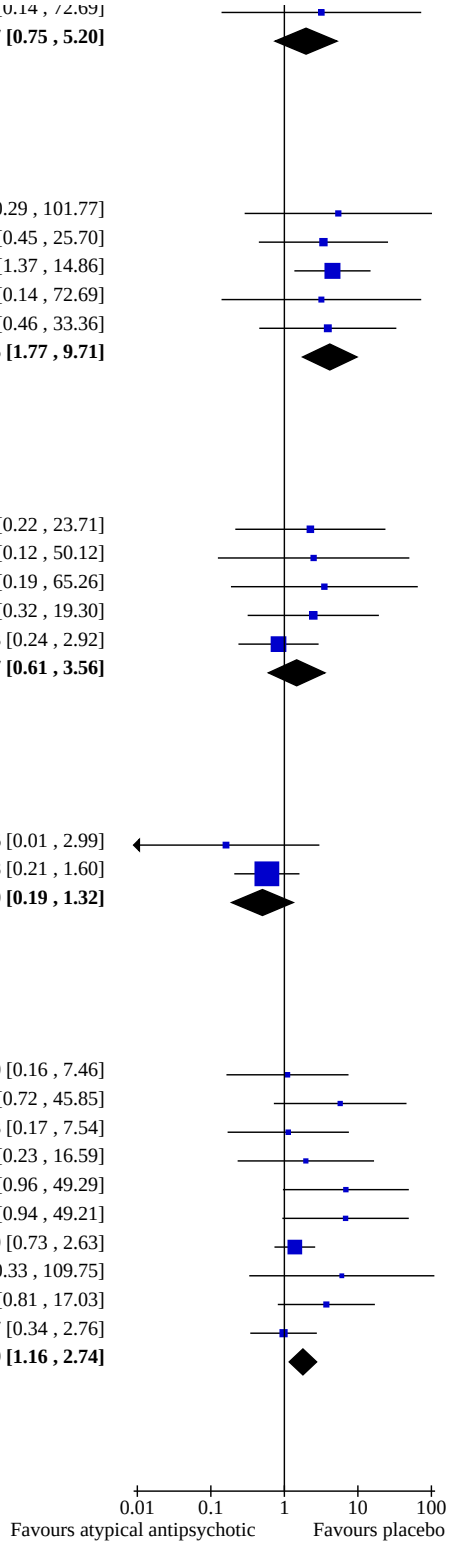


Analysis 1.7. Comparison 1: Atypical antipsychotic vs placebo, Outcome 7: Adverse effects: gastrointestinal

Study or Subgroup	Atypical antipsychotic Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.7.1 Abdominal pain						
Kent 2013	2	31	0	35	10.3%	5.63 [0.28 , 112.84]
Marcus 2009	7	165	1	51	21.5%	2.16 [0.27 , 17.17]
NCT01624675	1	21	0	18	9.3%	2.59 [0.11 , 59.93]
Shea 2004	8	40	3	39	58.9%	2.60 [0.74 , 9.09]
Subtotal (95% CI)		**257**		**143**	**100.0%**	**2.70 [1.04 , 7.07]**
Total events:	18		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 3 (P = 0.96); I² = 0%						
Test for overall effect: Z = 2.03 (P = 0.04)						
1.7.2 Constipation						
Findling 2014	2	39	0	43	4.1%	5.50 [0.27 , 111.14]
Kent 2013	2	31	1	35	6.7%	2.26 [0.22 , 23.71]
Loebel 2016 (1)	0	49	0	24		Not estimable
Loebel 2016 (2)	3	51	0	25	4.3%	3.50 [0.19 , 65.26]
Luby 2006	1	11	0	12	3.9%	3.25 [0.15 , 72.36]
McCracken 2002	14	49	6	51	48.9%	2.43 [1.02 , 5.81]
Owen 2009	5	47	4	50	23.7%	1.33 [0.38 , 4.66]
Shea 2004	5	40	1	39	8.4%	4.88 [0.60 , 39.86]
Subtotal (95% CI)		**317**		**279**	**100.0%**	**2.36 [1.28 , 4.34]**
Total events:	32		12			
Heterogeneity: Tau² = 0.00; Chi² = 1.68, df = 6 (P = 0.95); I² = 0%						
Test for overall effect: Z = 2.76 (P = 0.006)						
1.7.3 Diarrhoea						
Findling 2014	1	39	0	43	4.9%	3.30 [0.14 , 78.71]
Kent 2013	0	31	1	35	4.9%	0.38 [0.02 , 8.88]
McCracken 2002	9	49	11	51	78.6%	0.85 [0.39 , 1.87]
McDougle 1998	1	15	0	16	5.0%	3.19 [0.14 , 72.69]
NCT01624675	1	21	1	18	6.7%	0.86 [0.06 , 12.75]
Subtotal (95% CI)		**155**		**163**	**100.0%**	**0.93 [0.46 , 1.88]**
Total events:	12		13			
Heterogeneity: Tau² = 0.00; Chi² = 1.58, df = 4 (P = 0.81); I² = 0%						
Test for overall effect: Z = 0.19 (P = 0.85)						
1.7.4 Drooling						
Marcus 2009	15	165	0	51	51.7%	9.71 [0.59 , 159.51]
Owen 2009	4	47	0	50	48.3%	9.56 [0.53 , 172.93]
Subtotal (95% CI)		**212**		**101**	**100.0%**	**9.64 [1.29 , 72.10]**
Total events:	19		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 2.21 (P = 0.03)						
1.7.5 Dyspepsia (indigestion)						
McDougle 1998	1	15	0	16	100.0%	3.19 [0.14 , 72.69]
Subtotal (95% CI)		**15**		**16**	**100.0%**	**3.19 [0.14 , 72.69]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
1.7.6 Dry mouth						
McCracken 2002	9	49	5	51	90.4%	1.87 [0.68 , 5.20]
McDougle 1998	1	15	0	16	9.6%	3.19 [0.14 , 72.69]
Subtotal (95% CI)		**64**		**67**	**100.0%**	**1.97 [0.75 , 5.20]**

Analysis 1.7. (Continued)

McDougle 1998	1	15	0	16	9.6%	3.19 [0.14 , 72.69]
Subtotal (95% CI)		**64**		**67**	**100.0%**	**1.97 [0.75 , 5.20]**
Total events:	10		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 1.37 (P = 0.17)						
1.7.7 Hypersalivation						
Luby 2006	2	11	0	12	8.4%	5.42 [0.29 , 101.77]
Marcus 2009	11	165	1	51	17.7%	3.40 [0.45 , 25.70]
McCracken 2002	13	49	3	51	50.8%	4.51 [1.37 , 14.86]
McDougle 1998	1	15	0	16	7.4%	3.19 [0.14 , 72.69]
Shea 2004	4	40	1	39	15.7%	3.90 [0.46 , 33.36]
Subtotal (95% CI)		**280**		**169**	**100.0%**	**4.15 [1.77 , 9.71]**
Total events:	31		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 4 (P = 1.00); I² = 0%						
Test for overall effect: Z = 3.28 (P = 0.001)						
1.7.8 Nausea						
Kent 2013	2	31	1	35	14.1%	2.26 [0.22 , 23.71]
Loebel 2016 (1)	2	49	0	24	8.7%	2.50 [0.12 , 50.12]
Loebel 2016 (2)	3	51	0	25	9.1%	3.50 [0.19 , 65.26]
Marcus 2009	8	165	1	51	18.5%	2.47 [0.32 , 19.30]
McCracken 2002	4	49	5	51	49.6%	0.83 [0.24 , 2.92]
Subtotal (95% CI)		**345**		**186**	**100.0%**	**1.47 [0.61 , 3.56]**
Total events:	19		7			
Heterogeneity: Tau² = 0.00; Chi² = 1.62, df = 4 (P = 0.81); I² = 0%						
Test for overall effect: Z = 0.86 (P = 0.39)						
1.7.9 Stomach ache						
Kent 2013	0	31	3	35	10.9%	0.16 [0.01 , 2.99]
McCracken 2002	5	49	9	51	89.1%	0.58 [0.21 , 1.60]
Subtotal (95% CI)		**80**		**86**	**100.0%**	**0.50 [0.19 , 1.32]**
Total events:	5		12			
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 1.40 (P = 0.16)						
1.7.10 Vomiting/nausea						
Findling 2014	2	39	2	43	5.0%	1.10 [0.16 , 7.46]
Ichikawa 2017	6	47	1	45	4.3%	5.74 [0.72 , 45.85]
Kent 2013	2	31	2	35	5.1%	1.13 [0.17 , 7.54]
Loebel 2016 (1)	4	49	1	24	4.0%	1.96 [0.23 , 16.59]
Loebel 2016 (2)	14	51	1	25	4.7%	6.86 [0.96 , 49.29]
Marcus 2009	22	165	1	51	4.7%	6.80 [0.94 , 49.21]
McCracken 2002	16	49	12	51	45.2%	1.39 [0.73 , 2.63]
NCT01624675	3	21	0	18	2.2%	6.05 [0.33 , 109.75]
Owen 2009	7	47	2	50	7.9%	3.72 [0.81 , 17.03]
Shea 2004	6	40	6	39	16.9%	0.97 [0.34 , 2.76]
Subtotal (95% CI)		**539**		**381**	**100.0%**	**1.79 [1.16 , 2.74]**
Total events:	82		28			
Heterogeneity: Tau² = 0.00; Chi² = 8.71, df = 9 (P = 0.46); I² = 0%						
Test for overall effect: Z = 2.66 (P = 0.008)						
Test for subgroup differences: Chi² = 0.00, df = 9 (P < 0.00001), I² = 0%						



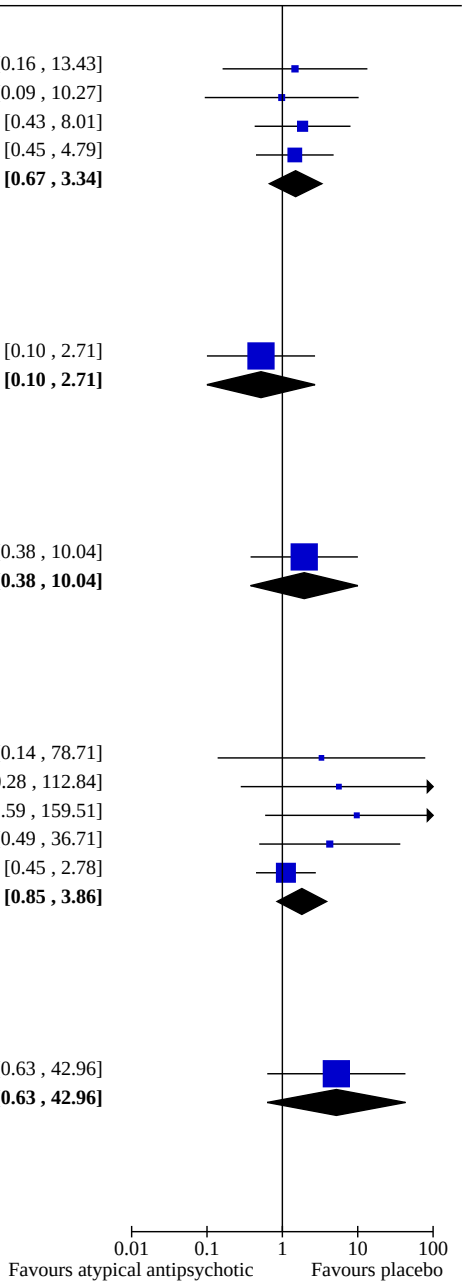
Footnotes

(1) 20mg/day lurasidone

(2) 60mg/day lurasidone

Analysis 1.8. Comparison 1: Atypical antipsychotic vs placebo, Outcome 8: Adverse effects: immune system

Study or Subgroup	Atypical antipsychotic Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.8.1 Cough						
Loebel 2016 (1)	3	51	1	25	13.1%	1.47 [0.16 , 13.43]
Loebel 2016 (2)	2	49	1	24	11.6%	0.98 [0.09 , 10.27]
Marcus 2009	12	165	2	51	29.9%	1.85 [0.43 , 8.01]
Shea 2004	6	40	4	39	45.5%	1.46 [0.45 , 4.79]
Subtotal (95% CI)		**305**		**139**	**100.0%**	**1.50 [0.67 , 3.34]**
Total events:	23		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 3 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.99 (P = 0.32)						
1.8.2 Earache						
McCracken 2002	2	49	4	51	100.0%	0.52 [0.10 , 2.71]
Subtotal (95% CI)		**49**		**51**	**100.0%**	**0.52 [0.10 , 2.71]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.78 (P = 0.44)						
1.8.3 Flu-like symptoms						
Shea 2004	4	40	2	39	100.0%	1.95 [0.38 , 10.04]
Subtotal (95% CI)		**40**		**39**	**100.0%**	**1.95 [0.38 , 10.04]**
Total events:	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.80 (P = 0.42)						
1.8.4 Pyrexia						
Findling 2014	1	39	0	43	5.7%	3.30 [0.14 , 78.71]
Kent 2013	2	31	0	35	6.3%	5.63 [0.28 , 112.84]
Marcus 2009	15	165	0	51	7.3%	9.71 [0.59 , 159.51]
Owen 2009	4	47	1	50	12.3%	4.26 [0.49 , 36.71]
Shea 2004	8	40	7	39	68.4%	1.11 [0.45 , 2.78]
Subtotal (95% CI)		**322**		**218**	**100.0%**	**1.81 [0.85 , 3.86]**
Total events:	30		8			
Heterogeneity: Tau² = 0.00; Chi² = 3.76, df = 4 (P = 0.44); I² = 0%						
Test for overall effect: Z = 1.54 (P = 0.12)						
1.8.5 Sore throat						
McCracken 2002	5	49	1	51	100.0%	5.20 [0.63 , 42.96]
Subtotal (95% CI)		**49**		**51**	**100.0%**	**5.20 [0.63 , 42.96]**
Total events:	5		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.53 (P = 0.13)						
Test for subgroup differences: Chi² = 0.00, df = 4 (P < 0.00001), I² = 0%						



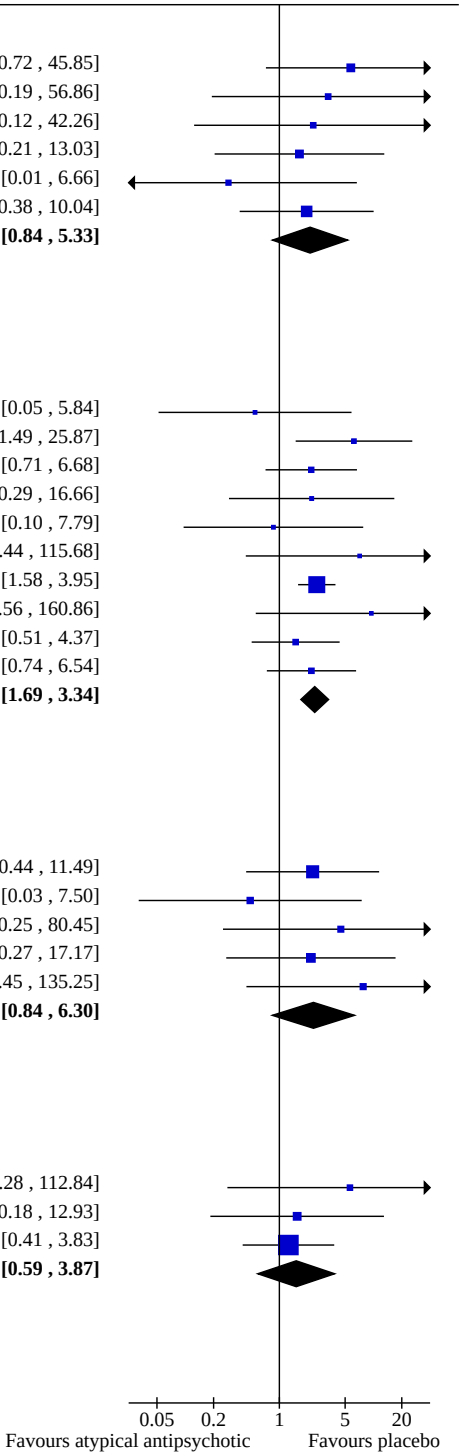
Footnotes

(1) 60mg/day

(2) 20mg/day

Analysis 1.9. Comparison 1: Atypical antipsychotic vs placebo, Outcome 9: Adverse effects: metabolic (dichotomous)

Study or Subgroup	Atypical antipsychotic Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.9.1 Decreased appetite						
Ichikawa 2017	6	47	1	45	19.7%	5.74 [0.72 , 45.85]
Marcus 2009 (1)	5	59	0	17	10.5%	3.30 [0.19 , 56.86]
Marcus 2009 (2)	3	54	0	17	10.0%	2.29 [0.12 , 42.26]
Marcus 2009 (3)	5	52	1	17	19.7%	1.63 [0.21 , 13.03]
NCT01624675	0	21	1	18	8.6%	0.29 [0.01 , 6.66]
Shea 2004	4	40	2	39	31.6%	1.95 [0.38 , 10.04]
Subtotal (95% CI)		**273**		**153**	**100.0%**	**2.12 [0.84 , 5.33]**
Total events:	23		5			
Heterogeneity: Tau² = 0.00; Chi² = 2.60, df = 5 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.60 (P = 0.11)						
1.9.2 Increased appetite						
Findling 2014	1	39	2	43	2.1%	0.55 [0.05 , 5.84]
Kent 2013	11	31	2	35	5.7%	6.21 [1.49 , 25.87]
Luby 2006	6	11	3	12	9.2%	2.18 [0.71 , 6.68]
Marcus 2009 (2)	7	54	1	17	2.8%	2.20 [0.29 , 16.66]
Marcus 2009 (1)	3	59	1	17	2.4%	0.86 [0.10 , 7.79]
Marcus 2009 (3)	10	52	0	17	1.5%	7.13 [0.44 , 115.68]
McCracken 2002	36	49	15	51	55.2%	2.50 [1.58 , 3.95]
NCT01624675	5	21	0	18	1.4%	9.50 [0.56 , 160.86]
Owen 2009	7	47	5	50	10.0%	1.49 [0.51 , 4.37]
Shea 2004	9	40	4	39	9.7%	2.19 [0.74 , 6.54]
Subtotal (95% CI)		**403**		**299**	**100.0%**	**2.38 [1.69 , 3.34]**
Total events:	95		33			
Heterogeneity: Tau² = 0.00; Chi² = 6.36, df = 9 (P = 0.70); I² = 0%						
Test for overall effect: Z = 4.99 (P < 0.00001)						
1.9.3 Weight gain						
Kent 2013	4	31	2	35	38.2%	2.26 [0.44 , 11.49]
Loebel 2016 (4)	1	49	1	24	13.6%	0.49 [0.03 , 7.50]
Loebel 2016 (5)	4	51	0	25	12.2%	4.50 [0.25 , 80.45]
Marcus 2009	7	165	1	51	23.6%	2.16 [0.27 , 17.17]
NCT01624675	4	21	0	18	12.4%	7.77 [0.45 , 135.25]
Subtotal (95% CI)		**317**		**153**	**100.0%**	**2.30 [0.84 , 6.30]**
Total events:	20		4			
Heterogeneity: Tau² = 0.00; Chi² = 2.14, df = 4 (P = 0.71); I² = 0%						
Test for overall effect: Z = 1.62 (P = 0.10)						
1.9.4 Thirst						
Kent 2013	2	31	0	35	9.8%	5.63 [0.28 , 112.84]
Marcus 2009	5	165	1	51	19.6%	1.55 [0.18 , 12.93]
McCracken 2002	6	49	5	51	70.5%	1.25 [0.41 , 3.83]
Subtotal (95% CI)		**245**		**137**	**100.0%**	**1.51 [0.59 , 3.87]**
Total events:	13		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 2 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.86 (P = 0.39)						
Test for subgroup differences: Chi² = 0.00, df = 3 (P < 0.00001), I² = 0%						



Footnotes

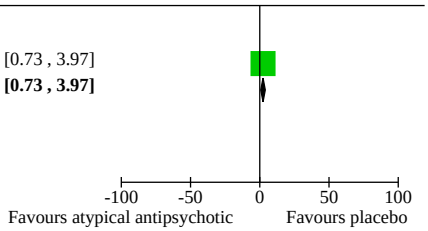
(1) Aripiprazole 10mg/day
(2) Aripiprazole 15mg/day
(3) Aripiprazole 5mg/day

Analysis 1.9. (Continued)

(2) Aripiprazole 15mg/day
(3) Aripiprazole 5mg/day
(4) 20mg/day
(5) 60mg/day

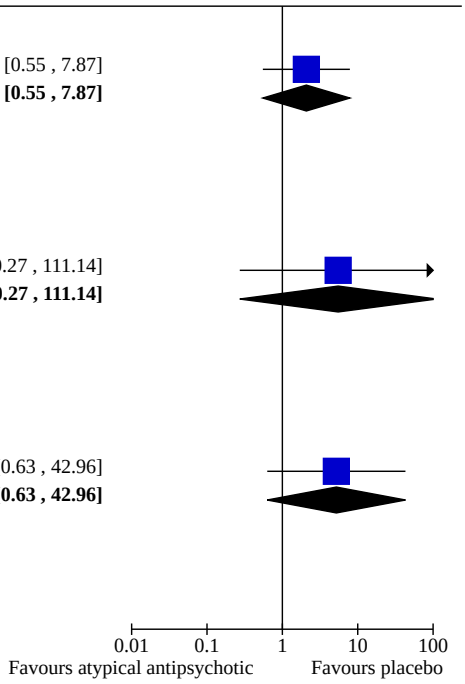
Analysis 1.10. Comparison 1: Atypical antipsychotic vs placebo, Outcome 10: Adverse effects: metabolic (continuous)

Study or Subgroup	Atypical antipsychotic Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.10.1 Weight gain (kg)								
Luby 2006	2.96	2.53	11	0.61	1.1	12	100.0%	2.35 [0.73 , 3.97]
Subtotal (95% CI)			**11**			**12**	**100.0%**	**2.35 [0.73 , 3.97]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.84 (P = 0.004)								
Test for subgroup differences: Not applicable								

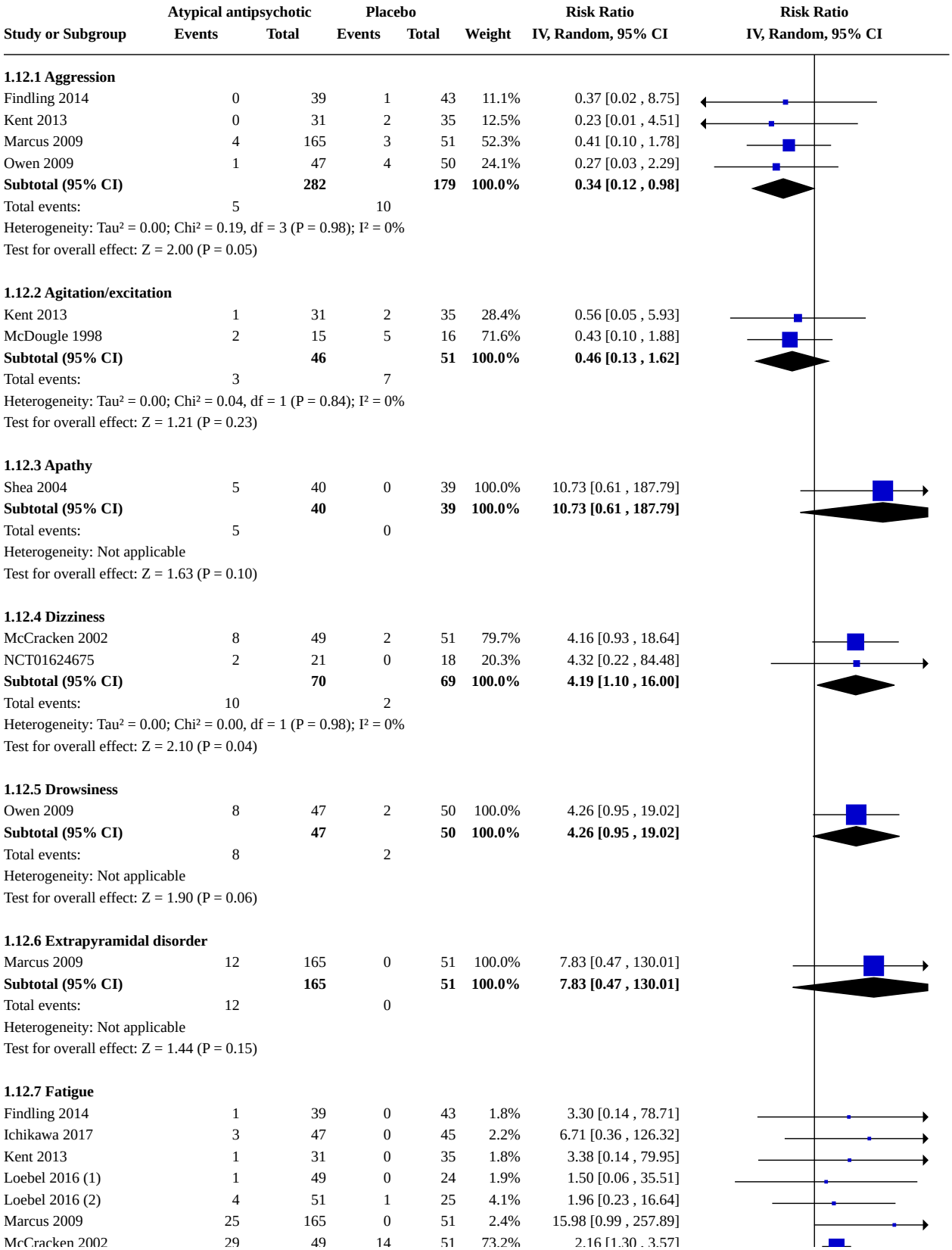


Analysis 1.11. Comparison 1: Atypical antipsychotic vs placebo, Outcome 11: Adverse effects: musculoskeletal

Study or Subgroup	Atypical antipsychotic Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.11.2 Dyskinesia						
McCracken 2002	6	49	3	51	100.0%	2.08 [0.55 , 7.87]
Subtotal (95% CI)		**49**		**51**	**100.0%**	**2.08 [0.55 , 7.87]**
Total events:	6		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						
1.11.3 Movement disorder						
Findling 2014	2	39	0	43	100.0%	5.50 [0.27 , 111.14]
Subtotal (95% CI)		**39**		**43**	**100.0%**	**5.50 [0.27 , 111.14]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						
1.11.4 Rigidity						
McCracken 2002	5	49	1	51	100.0%	5.20 [0.63 , 42.96]
Subtotal (95% CI)		**49**		**51**	**100.0%**	**5.20 [0.63 , 42.96]**
Total events:	5		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.53 (P = 0.13)						
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%						



Analysis 1.12. Comparison 1: Atypical antipsychotic vs placebo, Outcome 12: Adverse effects: neurological



Study or Subgroup	Atypical antipsychotic Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.12.1 Aggression						
Findling 2014	0	39	1	43	11.1%	0.37 [0.02 , 8.75]
Kent 2013	0	31	2	35	12.5%	0.23 [0.01 , 4.51]
Marcus 2009	4	165	3	51	52.3%	0.41 [0.10 , 1.78]
Owen 2009	1	47	4	50	24.1%	0.27 [0.03 , 2.29]
Subtotal (95% CI)		**282**		**179**	**100.0%**	**0.34 [0.12 , 0.98]**
Total events:	5		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 3 (P = 0.98); I² = 0%						
Test for overall effect: Z = 2.00 (P = 0.05)						
1.12.2 Agitation/excitation						
Kent 2013	1	31	2	35	28.4%	0.56 [0.05 , 5.93]
McDougle 1998	2	15	5	16	71.6%	0.43 [0.10 , 1.88]
Subtotal (95% CI)		**46**		**51**	**100.0%**	**0.46 [0.13 , 1.62]**
Total events:	3		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%						
Test for overall effect: Z = 1.21 (P = 0.23)						
1.12.3 Apathy						
Shea 2004	5	40	0	39	100.0%	10.73 [0.61 , 187.79]
Subtotal (95% CI)		**40**		**39**	**100.0%**	**10.73 [0.61 , 187.79]**
Total events:	5		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.63 (P = 0.10)						
1.12.4 Dizziness						
McCracken 2002	8	49	2	51	79.7%	4.16 [0.93 , 18.64]
NCT01624675	2	21	0	18	20.3%	4.32 [0.22 , 84.48]
Subtotal (95% CI)		**70**		**69**	**100.0%**	**4.19 [1.10 , 16.00]**
Total events:	10		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 2.10 (P = 0.04)						
1.12.5 Drowsiness						
Owen 2009	8	47	2	50	100.0%	4.26 [0.95 , 19.02]
Subtotal (95% CI)		**47**		**50**	**100.0%**	**4.26 [0.95 , 19.02]**
Total events:	8		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.90 (P = 0.06)						
1.12.6 Extrapyramidal disorder						
Marcus 2009	12	165	0	51	100.0%	7.83 [0.47 , 130.01]
Subtotal (95% CI)		**165**		**51**	**100.0%**	**7.83 [0.47 , 130.01]**
Total events:	12		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.44 (P = 0.15)						
1.12.7 Fatigue						
Findling 2014	1	39	0	43	1.8%	3.30 [0.14 , 78.71]
Ichikawa 2017	3	47	0	45	2.2%	6.71 [0.36 , 126.32]
Kent 2013	1	31	0	35	1.8%	3.38 [0.14 , 79.95]
Loebel 2016 (1)	1	49	0	24	1.9%	1.50 [0.06 , 35.51]
Loebel 2016 (2)	4	51	1	25	4.1%	1.96 [0.23 , 16.64]
Marcus 2009	25	165	0	51	2.4%	15.98 [0.99 , 257.89]
McCracken 2002	29	49	14	51	73.2%	2.16 [1.30 , 3.57]

Analysis 1.12. (Continued)

Marcus 2009	25	165	0	51	2.4%	15.98 [0.99 , 257.89]
McCracken 2002	29	49	14	51	73.2%	2.16 [1.30 , 3.57]
Owen 2009	10	47	2	50	8.6%	5.32 [1.23 , 23.02]
Shea 2004	4	40	1	39	4.0%	3.90 [0.46 , 33.36]
Subtotal (95% CI)		**518**		**363**	**100.0%**	**2.58 [1.68 , 3.97]**
Total events:	78		18			
Heterogeneity: Tau² = 0.00; Chi² = 3.85, df = 8 (P = 0.87); I² = 0%						
Test for overall effect: Z = 4.32 (P < 0.0001)						

1.12.8 Headache

Kent 2013	2	31	4	35	13.0%	0.56 [0.11 , 2.87]
Marcus 2009	13	165	2	51	16.0%	2.01 [0.47 , 8.61]
McCracken 2002	9	49	6	51	33.1%	1.56 [0.60 , 4.06]
NCT01624675	1	21	0	18	3.7%	2.59 [0.11 , 59.93]
Owen 2009	3	47	8	50	20.5%	0.40 [0.11 , 1.41]
Shea 2004	5	40	2	39	13.7%	2.44 [0.50 , 11.83]
Subtotal (95% CI)		**353**		**244**	**100.0%**	**1.17 [0.63 , 2.15]**
Total events:	33		22			
Heterogeneity: Tau² = 0.05; Chi² = 5.50, df = 5 (P = 0.36); I² = 9%						
Test for overall effect: Z = 0.49 (P = 0.62)						

1.12.9 Hyperactivity

Kent 2013	1	31	2	35	29.8%	0.56 [0.05 , 5.93]
Luby 2006	0	11	1	12	17.1%	0.36 [0.02 , 8.04]
Marcus 2009	3	165	2	51	53.1%	0.46 [0.08 , 2.70]
Subtotal (95% CI)		**207**		**98**	**100.0%**	**0.47 [0.13 , 1.70]**
Total events:	4		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 2 (P = 0.97); I² = 0%						
Test for overall effect: Z = 1.15 (P = 0.25)						

1.12.10 Hypersomnia

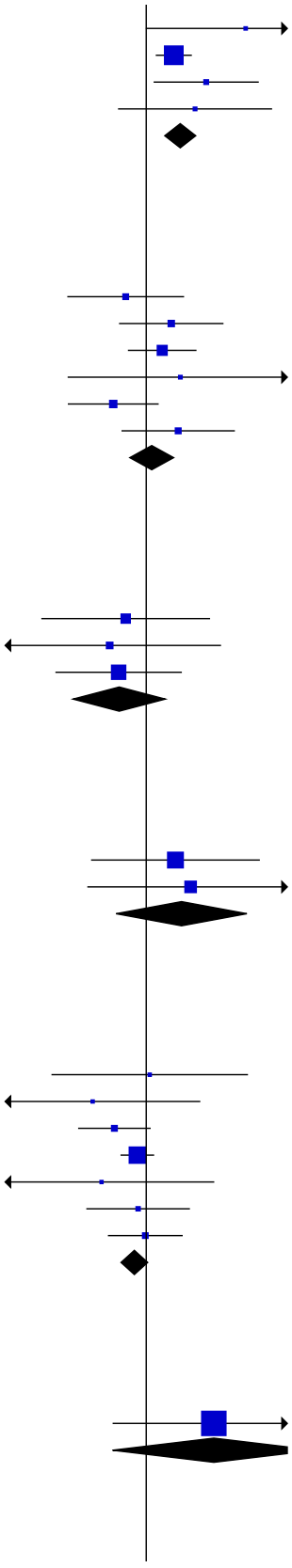
Kent 2013	2	31	1	35	60.0%	2.26 [0.22 , 23.71]
Marcus 2009	5	165	0	51	40.0%	3.45 [0.19 , 61.28]
Subtotal (95% CI)		**196**		**86**	**100.0%**	**2.67 [0.43 , 16.52]**
Total events:	7		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 1.06 (P = 0.29)						

1.12.11 Insomnia

Findling 2014	1	39	1	43	1.8%	1.10 [0.07 , 17.04]
Kent 2013	0	31	2	35	1.5%	0.23 [0.01 , 4.51]
Marcus 2009	8	165	6	51	13.4%	0.41 [0.15 , 1.13]
McCracken 2002	18	49	24	51	62.5%	0.78 [0.49 , 1.25]
NCT01624675	0	21	1	18	1.4%	0.29 [0.01 , 6.66]
Owen 2009	3	47	4	50	6.6%	0.80 [0.19 , 3.38]
Shea 2004	6	40	6	39	12.7%	0.97 [0.34 , 2.76]
Subtotal (95% CI)		**392**		**287**	**100.0%**	**0.72 [0.50 , 1.04]**
Total events:	36		44			
Heterogeneity: Tau² = 0.00; Chi² = 2.63, df = 6 (P = 0.85); I² = 0%						
Test for overall effect: Z = 1.75 (P = 0.08)						

1.12.12 Lethargy

Marcus 2009	10	165	0	51	100.0%	6.58 [0.39 , 110.35]
Subtotal (95% CI)		**165**		**51**	**100.0%**	**6.58 [0.39 , 110.35]**
Total events:	10		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						



Analysis 1.12. (Continued)

Test for overall effect: Z = 1.31 (P = 0.19)

1.12.13 Presyncope

Marcus 2009	1	165	0	51	100.0%	0.94 [0.04 , 22.72]
Subtotal (95% CI)		**165**		**51**	**100.0%**	**0.94 [0.04 , 22.72]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)

1.12.14 Restlessness (akathisia)

Kent 2013	2	31	1	35	14.7%	2.26 [0.22 , 23.71]
Loebel 2016 (2)	3	51	0	25	9.5%	3.50 [0.19 , 65.26]
Loebel 2016 (1)	3	49	0	24	9.5%	3.50 [0.19 , 65.16]
Marcus 2009	3	165	3	51	32.8%	0.31 [0.06 , 1.48]
McCracken 2002	3	49	3	51	33.5%	1.04 [0.22 , 4.91]
Subtotal (95% CI)		**345**		**186**	**100.0%**	**0.99 [0.40 , 2.43]**
Total events:	14		7			

Heterogeneity: Tau² = 0.01; Chi² = 4.02, df = 4 (P = 0.40); I² = 1%
Test for overall effect: Z = 0.03 (P = 0.98)

1.12.15 Sedation

Kent 2013	8	31	0	35	10.0%	19.13 [1.15 , 318.34]
Loebel 2016 (1)	3	49	1	25	14.9%	1.53 [0.17 , 13.97]
Loebel 2016 (2)	1	51	0	24	8.1%	1.44 [0.06 , 34.16]
Luby 2006	5	11	4	12	40.6%	1.36 [0.49 , 3.82]
McDougle 1998	9	15	0	16	10.3%	20.19 [1.28 , 319.17]
Owen 2009	5	47	1	50	16.1%	5.32 [0.65 , 43.86]
Subtotal (95% CI)		**204**		**162**	**100.0%**	**2.98 [1.15 , 7.73]**
Total events:	31		6			

Heterogeneity: Tau² = 0.31; Chi² = 6.34, df = 5 (P = 0.27); I² = 21%
Test for overall effect: Z = 2.25 (P = 0.02)

1.12.16 Somnolence

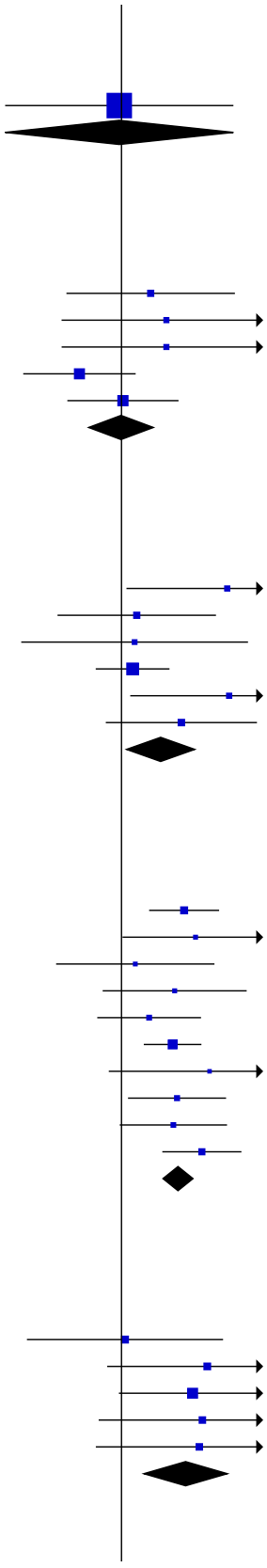
Ichikawa 2017	24	47	4	45	18.4%	5.74 [2.16 , 15.25]
Kent 2013	7	31	1	35	4.2%	7.90 [1.03 , 60.71]
Loebel 2016 (1)	3	49	1	24	3.6%	1.47 [0.16 , 13.39]
Loebel 2016 (2)	9	51	1	25	4.3%	4.41 [0.59 , 32.92]
Marcus 2009	14	165	2	51	8.4%	2.16 [0.51 , 9.20]
McCracken 2002	24	49	6	51	27.2%	4.16 [1.86 , 9.30]
McDougle 1998	5	15	0	16	2.2%	11.69 [0.70 , 194.79]
NCT01624675	11	21	2	18	9.4%	4.71 [1.20 , 18.53]
Owen 2009	8	47	2	50	7.8%	4.26 [0.95 , 19.02]
Shea 2004	29	40	3	39	14.4%	9.43 [3.13 , 28.42]
Subtotal (95% CI)		**515**		**354**	**100.0%**	**4.84 [3.18 , 7.36]**
Total events:	134		22			

Heterogeneity: Tau² = 0.00; Chi² = 4.60, df = 9 (P = 0.87); I² = 0%
Test for overall effect: Z = 7.37 (P < 0.00001)

1.12.17 Tremor

Findling 2014	1	39	1	43	18.1%	1.10 [0.07 , 17.04]
Marcus 2009	17	165	0	51	17.4%	10.96 [0.67 , 179.19]
McCracken 2002	7	49	1	51	32.0%	7.29 [0.93 , 57.07]
Owen 2009	4	47	0	50	16.2%	9.56 [0.53 , 172.93]
Shea 2004	4	40	0	39	16.3%	8.78 [0.49 , 157.85]
Subtotal (95% CI)		**340**		**234**	**100.0%**	**5.99 [1.87 , 19.19]**
Total events:	33		2			

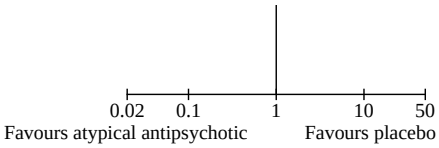
Heterogeneity: Tau² = 0.00; Chi² = 1.85, df = 4 (P = 0.76); I² = 0%
Test for overall effect: Z = 3.01 (P = 0.003)



Analysis 1.12. (Continued)

Heterogeneity: Tau² = 0.00; Chi² = 1.85, df = 4 (P = 0.76); I² = 0%
Test for overall effect: Z = 3.01 (P = 0.003)

Test for subgroup differences: Chi² = 0.00, df = 16 (P < 0.00001), I² = 0%

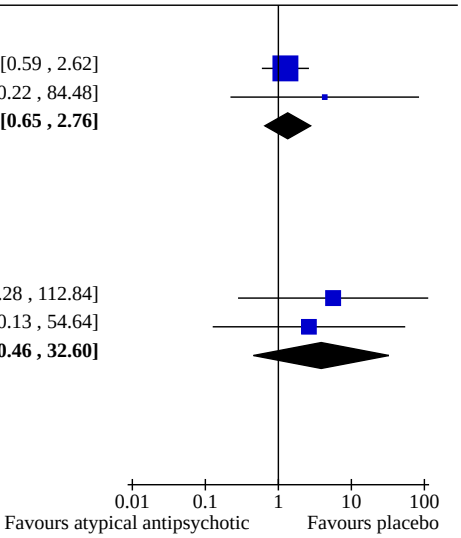


Footnotes
(1) 20mg/day
(2) 60mg/day

Analysis 1.13. Comparison 1: Atypical antipsychotic vs placebo, Outcome 13: Adverse effects: psychological

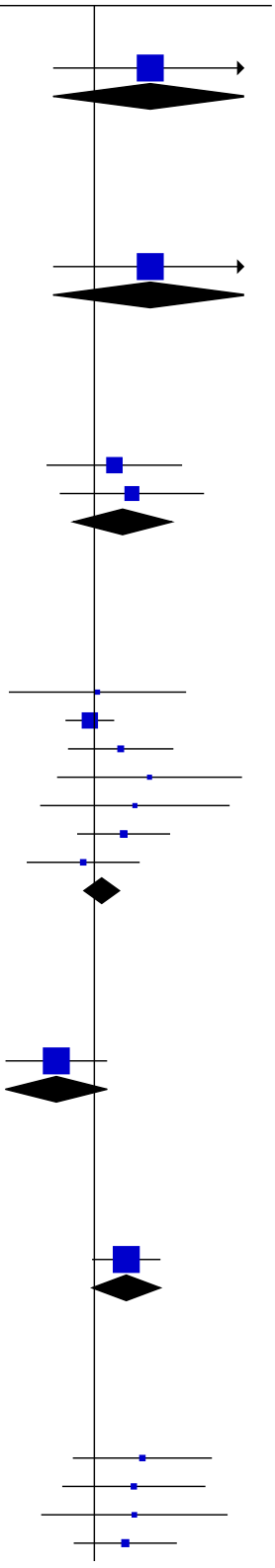
Study or Subgroup	Atypical antipsychotic Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.13.1 Anxiety						
McCracken 2002	12	49	10	51	94.1%	1.25 [0.59 , 2.62]
NCT01624675	2	21	0	18	5.9%	4.32 [0.22 , 84.48]
Subtotal (95% CI)		**70**		**69**	**100.0%**	**1.34 [0.65 , 2.76]**
Total events:	14		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.80 (P = 0.42)						
1.13.2 Depression						
Kent 2013	2	31	0	35	50.6%	5.63 [0.28 , 112.84]
NCT00468130	1	7	0	6	49.4%	2.63 [0.13 , 54.64]
Subtotal (95% CI)		**38**		**41**	**100.0%**	**3.86 [0.46 , 32.60]**
Total events:	3		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.73); I² = 0%						
Test for overall effect: Z = 1.24 (P = 0.21)						

Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%



Analysis 1.14. Comparison 1: Atypical antipsychotic vs placebo, Outcome 14: Adverse effects: respiratory

Study or Subgroup	Atypical antipsychotic Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.14.1 Ear infection						
Kent 2013	2	31	0	35	100.0%	5.63 [0.28 , 112.84]
Subtotal (95% CI)		**31**		**35**	**100.0%**	**5.63 [0.28 , 112.84]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.13 (P = 0.26)						
1.14.2 Epistaxis						
Kent 2013	2	31	0	35	100.0%	5.63 [0.28 , 112.84]
Subtotal (95% CI)		**31**		**35**	**100.0%**	**5.63 [0.28 , 112.84]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.13 (P = 0.26)						
1.14.3 Nasal congestion						
Marcus 2009	6	165	1	51	53.1%	1.85 [0.23 , 15.05]
Owen 2009	3	47	1	50	46.9%	3.19 [0.34 , 29.62]
Subtotal (95% CI)		**212**		**101**	**100.0%**	**2.39 [0.52 , 11.00]**
Total events:	9		2			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.12$, df = 1 (P = 0.73); $I^2 = 0\%$						
Test for overall effect: Z = 1.12 (P = 0.26)						
1.14.4 Nasopharyngitis						
Findling 2014	1	39	1	43	4.0%	1.10 [0.07 , 17.04]
Ichikawa 2017	10	47	11	45	53.0%	0.87 [0.41 , 1.85]
Kent 2013	4	31	2	35	11.3%	2.26 [0.44 , 11.49]
Loebel 2016 (1)	5	49	0	24	3.7%	5.50 [0.32 , 95.56]
Loebel 2016 (2)	3	51	0	25	3.5%	3.50 [0.19 , 65.26]
Marcus 2009	16	165	2	51	14.6%	2.47 [0.59 , 10.40]
Owen 2009	2	47	3	50	9.9%	0.71 [0.12 , 4.06]
Subtotal (95% CI)		**429**		**273**	**100.0%**	**1.26 [0.73 , 2.17]**
Total events:	41		19			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.19$, df = 6 (P = 0.65); $I^2 = 0\%$						
Test for overall effect: Z = 0.81 (P = 0.42)						
1.14.5 Pharyngolaryngeal pain						
Marcus 2009	3	165	3	51	100.0%	0.31 [0.06 , 1.48]
Subtotal (95% CI)		**165**		**51**	**100.0%**	**0.31 [0.06 , 1.48]**
Total events:	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.47 (P = 0.14)						
1.14.6 Rhinitis						
Shea 2004	11	40	4	39	100.0%	2.68 [0.93 , 7.71]
Subtotal (95% CI)		**40**		**39**	**100.0%**	**2.68 [0.93 , 7.71]**
Total events:	11		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.83 (P = 0.07)						
1.14.7 Upper respiratory tract infection						
Findling 2014	4	39	1	43	9.7%	4.41 [0.51 , 37.79]
Kent 2013	3	31	1	35	9.2%	3.39 [0.37 , 30.90]
Marcus 2009	5	165	0	51	5.5%	3.45 [0.19 , 61.28]
McCracken 2002	5	49	2	51	16.9%	2.60 [0.53 , 12.79]



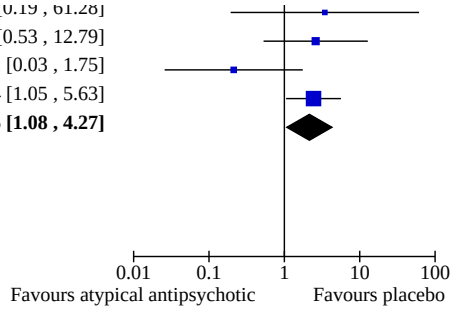
Analysis 1.14. (Continued)

Marcus 2009	5	165	0	51	5.5%	3.45 [0.19 , 61.28]
McCracken 2002	5	49	2	51	16.9%	2.60 [0.53 , 12.79]
Owen 2009	1	47	5	50	10.0%	0.21 [0.03 , 1.75]
Shea 2004	15	40	6	39	48.7%	2.44 [1.05 , 5.63]
Subtotal (95% CI)		**371**		**269**	**100.0%**	**2.15 [1.08 , 4.27]**
Total events:	33		15			

Heterogeneity: Tau² = 0.07; Chi² = 5.45, df = 5 (P = 0.36); I² = 8%

Test for overall effect: Z = 2.18 (P = 0.03)

Test for subgroup differences: Chi² = 0.00, df = 6 (P < 0.00001), I² = 0%



Footnotes

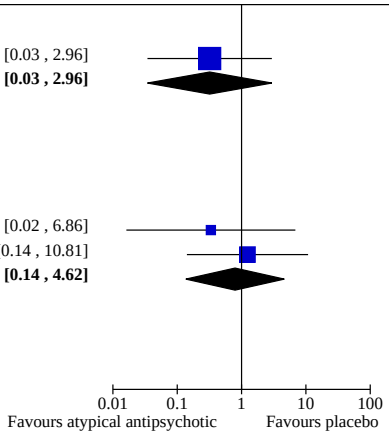
(1) 20mg/day

(2) 60mg/day

Analysis 1.15. Comparison 1: Atypical antipsychotic vs placebo, Outcome 15: Adverse effects: skin

Study or Subgroup	Atypical antipsychotic Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.15.1 Bruise						
Ichikawa 2017	1	47	3	45	100.0%	0.32 [0.03 , 2.96]
Subtotal (95% CI)		**47**		**45**	**100.0%**	**0.32 [0.03 , 2.96]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
1.15.2 Rash						
Malone 2001	0	6	1	6	34.0%	0.33 [0.02 , 6.86]
Marcus 2009	4	165	1	51	66.0%	1.24 [0.14 , 10.81]
Subtotal (95% CI)		**171**		**57**	**100.0%**	**0.79 [0.14 , 4.62]**
Total events:	4		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.26 (P = 0.80)						

Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

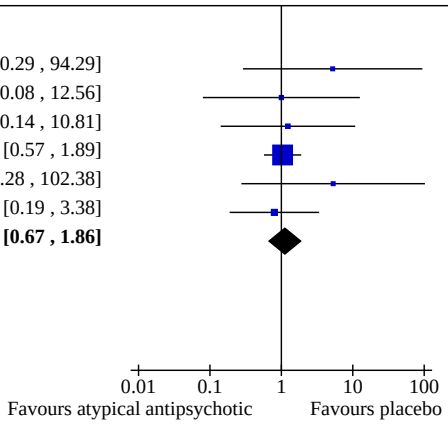
Analysis 1.16. Comparison 1: Atypical antipsychotic vs placebo, Outcome 16: Adverse effects: urinary

Study or Subgroup	Atypical antipsychotic Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.16.1 Enuresis						
Kent 2013	4	61	0	35	3.1%	5.23 [0.29 , 94.29]
Malone 2001	1	6	1	6	4.0%	1.00 [0.08 , 12.56]
Marcus 2009	4	165	1	51	5.5%	1.24 [0.14 , 10.81]
McCracken 2002	15	49	15	51	72.0%	1.04 [0.57 , 1.89]
McDougle 1998	2	15	0	16	3.0%	5.31 [0.28 , 102.38]
Owen 2009	3	47	4	50	12.4%	0.80 [0.19 , 3.38]
Subtotal (95% CI)		**343**		**209**	**100.0%**	**1.12 [0.67 , 1.86]**
Total events:	29		21			

Heterogeneity: Tau² = 0.00; Chi² = 2.44, df = 5 (P = 0.79); I² = 0%

Test for overall effect: Z = 0.43 (P = 0.66)

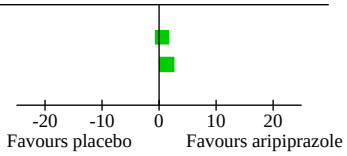
Test for subgroup differences: Not applicable



Analysis 1.17. Comparison 1: Atypical antipsychotic vs placebo, Outcome 17: Quality of life

Study or Subgroup	Aripiprazole Mean	SD	Total	Placebo Mean	SD	Total	Std. Mean Difference IV, Random, 95% CI
Marcus 2009	18.7	15.37	49	10.6	15.82	13	0.52 [-0.10 , 1.14]
Owen 2009	13.4	11.08	34	2	5	39	1.34 [0.83 , 1.86]

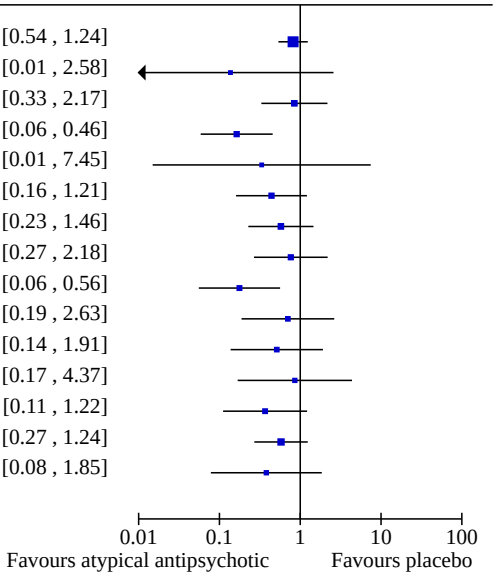
Test for subgroup differences: Not applicable



Analysis 1.18. Comparison 1: Atypical antipsychotic vs placebo, Outcome 18: Tolerability/acceptability: loss to follow-up

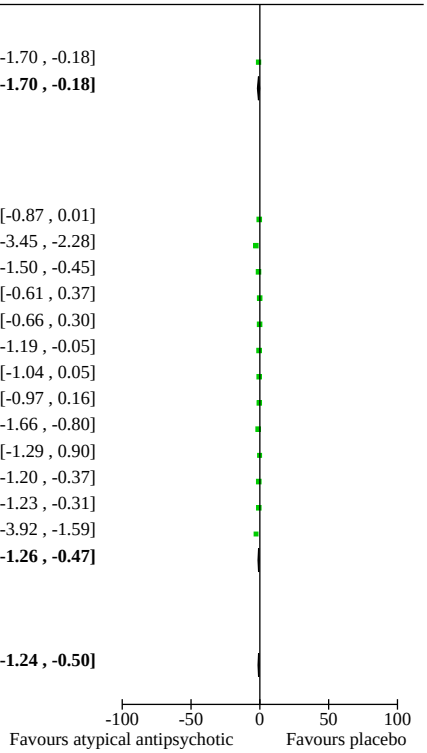
Study or Subgroup	Atypical antipsychotic Events	Total	Placebo Events	Total	Risk Ratio IV, Random, 95% CI
Findling 2014	19	41	25	44	0.82 [0.54 , 1.24]
Ichikawa 2017	0	47	3	45	0.14 [0.01 , 2.58]
Kent 2013	6	31	8	35	0.85 [0.33 , 2.17]
Loebel 2016	4	51	12	25	0.16 [0.06 , 0.46]
Luby 2006	0	12	1	12	0.33 [0.01 , 7.45]
Marcus 2009	7	54	5	17	0.44 [0.16 , 1.21]
Marcus 2009	10	59	5	17	0.58 [0.23 , 1.46]
Marcus 2009	9	53	4	18	0.76 [0.27 , 2.18]
McCracken 2002	3	49	18	52	0.18 [0.06 , 0.56]
McDougle 1998	3	16	4	15	0.70 [0.19 , 2.63]
NCT00198107	3	40	6	41	0.51 [0.14 , 1.91]
NCT00468130	2	7	2	6	0.86 [0.17 , 4.37]
NCT01624675	3	21	7	18	0.37 [0.11 , 1.22]
Owen 2009	8	47	15	51	0.58 [0.27 , 1.24]
Shea 2004	2	41	5	39	0.38 [0.08 , 1.85]

Test for subgroup differences: Not applicable



Analysis 1.19. Comparison 1: Atypical antipsychotic vs placebo, Outcome 19: Subgroup analysis: age - irritability

Study or Subgroup	Atypical antipsychotic Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.19.1 Adults only								
McDougle 1998	0.35	0.37	14	0.82	0.57	16	6.5%	-0.94 [-1.70 , -0.18]
Subtotal (95% CI)			**14**			**16**	**6.5%**	**-0.94 [-1.70 , -0.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.42 (P = 0.02)								
1.19.2 Children only								
Findling 2014	5.2	10.05	39	9.6	10.23	43	7.9%	-0.43 [-0.87 , 0.01]
Ichikawa 2017	-11.4	1.3	47	-7.5	1.4	45	7.2%	-2.87 [-3.45 , -2.28]
Kent 2013	-12.4	6.52	29	-3.5	10.67	34	7.5%	-0.98 [-1.50 , -0.45]
Loebel 2016 (1)	-8.8	10.39	48	-7.5	10.64	24	7.7%	-0.12 [-0.61 , 0.37]
Loebel 2016 (2)	-9.4	10.21	51	-7.5	10.64	25	7.7%	-0.18 [-0.66 , 0.30]
Marcus 2009 (3)	-14.4	9.54	53	-8.4	9.73	16	7.3%	-0.62 [-1.19 , -0.05]
Marcus 2009 (4)	-13.2	9.6	59	-8.4	9.73	17	7.4%	-0.49 [-1.04 , 0.05]
Marcus 2009 (5)	-12.4	9.81	52	-8.4	9.73	16	7.3%	-0.40 [-0.97 , 0.16]
McCracken 2002	11.3	7.4	49	21.9	9.5	51	7.9%	-1.23 [-1.66 , -0.80]
NCT00468130	6.83	6.87	7	8.67	10.69	6	5.0%	-0.19 [-1.29 , 0.90]
Owen 2009	-12.9	9.77	46	-5	10.11	50	8.0%	-0.79 [-1.20 , -0.37]
Shea 2004	-12.1	5.8	39	-6.5	8.4	38	7.8%	-0.77 [-1.23 , -0.31]
Troost 2005	1.5	1.7	12	7.6	2.5	12	4.7%	-2.76 [-3.92 , -1.59]
Subtotal (95% CI)			**531**			**377**	**93.5%**	**-0.87 [-1.26 , -0.47]**
Heterogeneity: Tau² = 0.43; Chi² = 83.51, df = 12 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 4.31 (P < 0.0001)								
Total (95% CI)			**545**			**393**	**100.0%**	**-0.87 [-1.24 , -0.50]**
Heterogeneity: Tau² = 0.41; Chi² = 83.66, df = 13 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 4.57 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%								

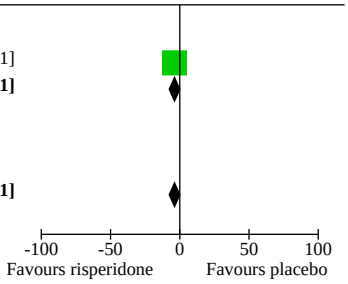


Footnotes

(1) 20mg/day
(2) 60mg/day
(3) 15mg/day aripiprazole
(4) 10mg/day aripiprazole
(5) 5mg/day aripiprazole

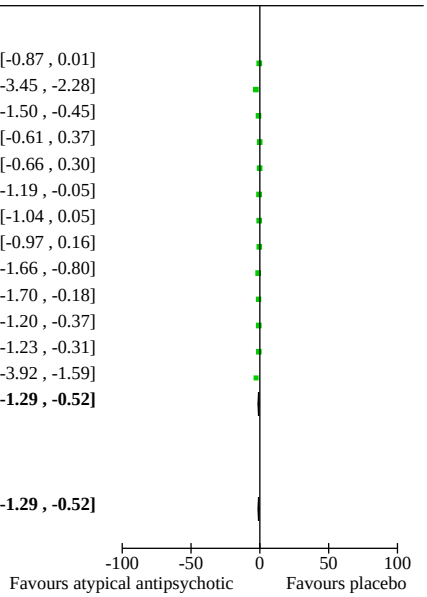
Analysis 1.20. Comparison 1: Atypical antipsychotic vs placebo, Outcome 20: Subgroup analysis: age - aggression

Study or Subgroup	Risperidone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.20.1 Children only								
Shea 2004	-10.4	7.4	39	-6.6	9.5	38	100.0%	-3.80 [-7.61 , 0.01]
Subtotal (95% CI)			**39**			**38**	**100.0%**	**-3.80 [-7.61 , 0.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.95 (P = 0.05)								
Total (95% CI)			**39**			**38**	**100.0%**	**-3.80 [-7.61 , 0.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.95 (P = 0.05)								
Test for subgroup differences: Not applicable								



Analysis 1.21. Comparison 1: Atypical antipsychotic vs placebo, Outcome 21: Subgroup analysis: cognitive ability - irritability

Study or Subgroup	Atypical antipsychotic Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.21.1 Mixed IQ								
Findling 2014	5.2	10.05	39	9.6	10.23	43	8.3%	-0.43 [-0.87 , 0.01]
Ichikawa 2017	-11.4	1.3	47	-7.5	1.4	45	7.6%	-2.87 [-3.45 , -2.28]
Kent 2013	-12.4	6.52	29	-3.5	10.67	34	7.9%	-0.98 [-1.50 , -0.45]
Loebel 2016 (1)	-8.8	10.39	48	-7.5	10.64	24	8.1%	-0.12 [-0.61 , 0.37]
Loebel 2016 (2)	-9.4	10.21	51	-7.5	10.64	25	8.1%	-0.18 [-0.66 , 0.30]
Marcus 2009 (3)	-14.4	9.54	53	-8.4	9.73	16	7.7%	-0.62 [-1.19 , -0.05]
Marcus 2009 (4)	-13.2	9.6	59	-8.4	9.73	17	7.8%	-0.49 [-1.04 , 0.05]
Marcus 2009 (5)	-12.4	9.81	52	-8.4	9.73	16	7.7%	-0.40 [-0.97 , 0.16]
McCracken 2002	11.3	7.4	49	21.9	9.5	51	8.3%	-1.23 [-1.66 , -0.80]
McDougle 1998	0.35	0.37	14	0.82	0.57	16	6.8%	-0.94 [-1.70 , -0.18]
Owen 2009	-12.9	9.77	46	-5	10.11	50	8.4%	-0.79 [-1.20 , -0.37]
Shea 2004	-12.1	5.8	39	-6.5	8.4	38	8.2%	-0.77 [-1.23 , -0.31]
Troost 2005	1.5	1.7	12	7.6	2.5	12	5.0%	-2.76 [-3.92 , -1.59]
Subtotal (95% CI)			**538**			**387**	**100.0%**	**-0.91 [-1.29 , -0.52]**
Heterogeneity: Tau² = 0.42; Chi² = 82.49, df = 12 (P < 0.00001); I² = 85%								
Test for overall effect: Z = 4.61 (P < 0.00001)								
Total (95% CI)			**538**			**387**	**100.0%**	**-0.91 [-1.29 , -0.52]**
Heterogeneity: Tau² = 0.42; Chi² = 82.49, df = 12 (P < 0.00001); I² = 85%								
Test for overall effect: Z = 4.61 (P < 0.00001)								
Test for subgroup differences: Not applicable								



Footnotes
(1) 20mg/day
(2) 60mg/day
(3) 15mg/day aripiprazole
(4) 10mg/day aripiprazole
(5) 5mg/day aripiprazole

Comparison 2. Neurohormone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Irritability	8	466	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.37, -0.00]
2.1.1 Secretin	3	69	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.46, 0.49]
2.1.2 ACTH	1	14	Std. Mean Difference (IV, Random, 95% CI)	0.40 [-0.66, 1.46]
2.1.3 Oxytocin	3	353	Std. Mean Difference (IV, Random, 95% CI)	-0.24 [-0.45, -0.03]
2.1.4 Vasopressin	1	30	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-1.02, 0.43]
2.2 Self-injury	1	100	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.74, 0.05]
2.2.1 Endpoint	1	50	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.93, 0.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2.2 Three month follow-up	1	50	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.88, 0.23]
2.3 Adverse effects: cardiovascular	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.3.1 Cardiac disorders	3	456	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.23, 9.05]
2.3.2 Vascular disorders	1	106	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.06, 15.57]
2.3.3 Palpitations	1	290	Risk Ratio (M-H, Random, 95% CI)	2.96 [0.12, 72.04]
2.4 Adverse effects: gastrointestinal	6		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.4.1 Abdominal pain or discomfort	1	290	Risk Ratio (IV, Random, 95% CI)	0.42 [0.17, 1.07]
2.4.2 Constipation	3	361	Risk Ratio (IV, Random, 95% CI)	0.89 [0.46, 1.73]
2.4.3 Diarrhoea	5	450	Risk Ratio (IV, Random, 95% CI)	0.71 [0.39, 1.28]
2.4.4 Dry mouth	2	350	Risk Ratio (IV, Random, 95% CI)	0.43 [0.06, 2.88]
2.4.5 Encopresis	1	290	Risk Ratio (IV, Random, 95% CI)	0.74 [0.17, 3.25]
2.4.6 Gastrointestinal disorders	2	166	Risk Ratio (IV, Random, 95% CI)	1.25 [0.35, 4.49]
2.4.7 Nausea	1	60	Risk Ratio (IV, Random, 95% CI)	0.14 [0.01, 2.65]
2.4.8 Salivary hypersecretion	2	319	Risk Ratio (IV, Random, 95% CI)	0.32 [0.03, 2.99]
2.4.9 Stomatitis	2	321	Risk Ratio (IV, Random, 95% CI)	0.13 [0.02, 1.11]
2.4.10 Vomiting	4	409	Risk Ratio (IV, Random, 95% CI)	0.45 [0.21, 0.97]
2.5 Adverse effects: immune system	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.5.1 infections and infestations	1	106	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.81, 4.93]
2.6 Adverse effects: metabolic (dichotomous)	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.6.1 Decreased appetite	4	409	Risk Ratio (IV, Random, 95% CI)	0.67 [0.37, 1.22]
2.6.2 Increased appetite	2	350	Risk Ratio (IV, Random, 95% CI)	1.74 [0.96, 3.16]
2.6.3 Metabolism and nutrition disorders	1	106	Risk Ratio (IV, Random, 95% CI)	0.50 [0.05, 5.35]
2.6.4 Thirst	2	319	Risk Ratio (IV, Random, 95% CI)	1.42 [0.35, 5.67]

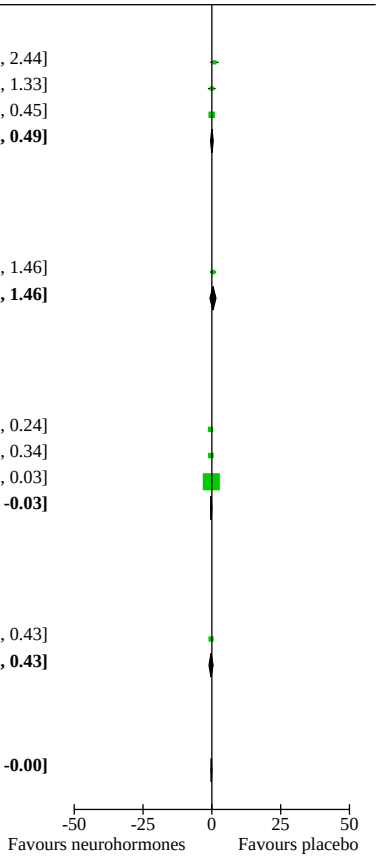
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.6.5 Weight gain	1	290	Risk Ratio (IV, Random, 95% CI)	1.21 [0.52, 2.82]
2.6.6 Weight loss	1	290	Risk Ratio (IV, Random, 95% CI)	1.97 [0.69, 5.63]
2.7 Adverse effects: metabolic (continuous)	1	24	Mean Difference (IV, Random, 95% CI)	-0.45 [-1.76, 0.86]
2.7.1 Mean change in weight (kg)	1	24	Mean Difference (IV, Random, 95% CI)	-0.45 [-1.76, 0.86]
2.8 Adverse effects: musculoskeletal	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.8.1 Muscle spasms	1	29	Risk Ratio (IV, Random, 95% CI)	2.81 [0.12, 63.83]
2.8.2 Musculoskeletal and connective tissue disorders	1	106	Risk Ratio (IV, Random, 95% CI)	3.00 [0.12, 72.02]
2.8.3 Rhabdomyolysis	1	220	Risk Ratio (IV, Random, 95% CI)	1.47 [0.06, 35.64]
2.9 Adverse effects: neurological	11		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.9.1 Absence seizures	1	19	Risk Ratio (IV, Random, 95% CI)	2.73 [0.12, 59.57]
2.9.2 Aggression	3	356	Risk Ratio (IV, Random, 95% CI)	0.91 [0.57, 1.44]
2.9.3 Agitation	3	344	Risk Ratio (IV, Random, 95% CI)	1.12 [0.65, 1.94]
2.9.4 Decreased attention	3	108	Risk Ratio (IV, Random, 95% CI)	1.46 [0.24, 8.84]
2.9.5 Dizziness	3	369	Risk Ratio (IV, Random, 95% CI)	0.65 [0.08, 5.27]
2.9.6 Dysphoria	1	290	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 8.00]
2.9.7 Excessive talking	1	29	Risk Ratio (IV, Random, 95% CI)	2.81 [0.12, 63.83]
2.9.8 Fatigue	3	120	Risk Ratio (IV, Random, 95% CI)	0.91 [0.50, 1.65]
2.9.9 Forgetfulness	1	19	Risk Ratio (IV, Random, 95% CI)	2.73 [0.12, 59.57]
2.9.10 Headache	7	689	Risk Ratio (IV, Random, 95% CI)	0.58 [0.38, 0.89]
2.9.11 Insomnia	6	477	Risk Ratio (IV, Random, 95% CI)	0.72 [0.50, 1.04]
2.9.12 Irritability	6	655	Risk Ratio (IV, Random, 95% CI)	0.86 [0.68, 1.10]
2.9.13 Leg shaking	1	19	Risk Ratio (IV, Random, 95% CI)	2.73 [0.12, 59.57]
2.9.14 Nervous systems disorders	1	106	Risk Ratio (IV, Random, 95% CI)	1.67 [0.42, 6.62]
2.9.15 Oppositional	1	25	Risk Ratio (IV, Random, 95% CI)	0.72 [0.14, 3.61]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.9.16 Restlessness	2	319	Risk Ratio (IV, Random, 95% CI)	1.64 [0.17, 15.47]
2.9.17 Seizure	1	29	Risk Ratio (IV, Random, 95% CI)	2.81 [0.12, 63.83]
2.9.18 Sedation	2	350	Risk Ratio (IV, Random, 95% CI)	1.69 [0.87, 3.27]
2.9.19 Somnolence	2	89	Risk Ratio (IV, Random, 95% CI)	3.81 [0.44, 32.96]
2.9.20 Tics	2	309	Risk Ratio (IV, Random, 95% CI)	0.63 [0.16, 2.38]
2.10 Adverse effects: psychological	6		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.10.1 Anxiety	2	97	Risk Ratio (IV, Random, 95% CI)	3.05 [0.50, 18.55]
2.10.2 Depression	4	427	Risk Ratio (IV, Random, 95% CI)	0.89 [0.29, 2.68]
2.10.3 Panic attack	1	19	Risk Ratio (IV, Random, 95% CI)	0.30 [0.01, 6.62]
2.10.4 Psychiatric	1	106	Risk Ratio (IV, Random, 95% CI)	4.00 [0.46, 34.61]
2.10.5 Self-injury	2	118	Risk Ratio (IV, Random, 95% CI)	1.00 [0.11, 9.35]
2.11 Adverse effects: respiratory	10		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.11.1 Cold symptoms	2	73	Risk Ratio (IV, Random, 95% CI)	0.65 [0.26, 1.65]
2.11.2 Cough	5	430	Risk Ratio (IV, Random, 95% CI)	1.35 [0.81, 2.25]
2.11.3 Croup	1	25	Risk Ratio (IV, Random, 95% CI)	3.23 [0.14, 72.46]
2.11.4 Epistaxis	3	379	Risk Ratio (IV, Random, 95% CI)	1.21 [0.63, 2.31]
2.11.5 Nasal congestion	5	468	Risk Ratio (IV, Random, 95% CI)	0.79 [0.59, 1.05]
2.11.6 Nasal irritation/runny nose	1	40	Risk Ratio (IV, Random, 95% CI)	0.55 [0.10, 2.92]
2.11.7 Nasopharyngitis	1	29	Risk Ratio (IV, Random, 95% CI)	0.93 [0.15, 5.76]
2.11.8 Respiratory, thoracic and mediastinal disorders	2	147	Risk Ratio (IV, Random, 95% CI)	0.49 [0.09, 2.56]
2.11.9 Sinusitis	1	29	Risk Ratio (IV, Random, 95% CI)	0.47 [0.05, 4.60]
2.11.10 Upper respiratory tract infection	2	273	Risk Ratio (IV, Random, 95% CI)	1.10 [0.35, 3.47]
2.12 Adverse effects: skin	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.12.1 General/systemic disorders and administration site conditions	1	106	Risk Ratio (IV, Random, 95% CI)	4.00 [0.46, 34.61]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.12.2 Skin rash	4	416	Risk Ratio (IV, Random, 95% CI)	1.12 [0.63, 1.97]
2.12.3 Skin and subcutaneous tissue disorders	1	106	Risk Ratio (IV, Random, 95% CI)	5.00 [0.25, 101.73]
2.13 Adverse effects: urinary	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.13.1 Renal and urinary disorders	1	106	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.12, 72.02]
2.13.2 Enuresis	1	290	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.06, 0.62]
2.14 Adverse effects: other	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.14.1 Injury, poisoning, and procedural complications	1	106	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.12, 72.02]
2.14.2 Investigations	1	106	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.05, 5.35]
2.14.3 Lymphadenopathy	1	60	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.87]
2.14.4 Neoplasms: benign, malignant, and unspecified	1	106	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.12, 72.02]
2.14.5 Troponin I increased	1	220	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.06, 35.64]
2.15 Quality of life	4	191	Std. Mean Difference (IV, Random, 95% CI)	0.70 [-0.12, 1.53]
2.15.1 Oxytocin	2	37	Std. Mean Difference (IV, Random, 95% CI)	0.24 [-0.74, 1.21]
2.15.2 Vasopressin	1	30	Std. Mean Difference (IV, Random, 95% CI)	0.55 [-0.19, 1.29]
2.15.3 Balovaptan	1	124	Std. Mean Difference (IV, Random, 95% CI)	1.54 [1.14, 1.95]
2.16 Tolerability/acceptability: loss to follow-up	14	1312	Risk Ratio (IV, Random, 95% CI)	1.10 [0.87, 1.40]
2.17 Subgroup analyses: gender - irritability	10	654	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.28, 0.03]
2.17.1 Male and female participants	8	563	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.30, 0.03]
2.17.2 Male participants only	2	91	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.76, 0.54]

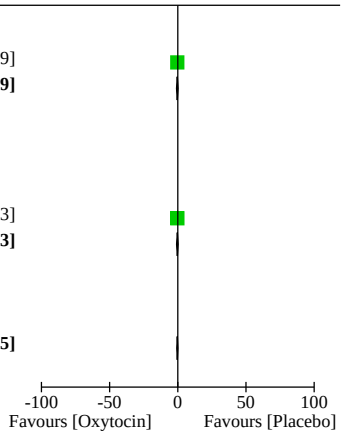
Analysis 2.1. Comparison 2: Neurohormone versus placebo, Outcome 1: Irritability

Study or Subgroup	Neurohormones Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.1.1 Secretin								
Carey 2002	23	12.7	4	12.5	6	4	1.4%	0.92 [-0.60 , 2.44]
Handen 2005	9.6	7.6	4	10	5.7	4	1.7%	-0.05 [-1.44 , 1.33]
Owley 2001	10.1	10.2	26	10.9	8.1	27	11.5%	-0.09 [-0.62 , 0.45]
Subtotal (95% CI)			**34**			**35**	**14.7%**	**0.02 [-0.46 , 0.49]**
Heterogeneity: Tau² = 0.00; Chi² = 1.50, df = 2 (P = 0.47); I² = 0%								
Test for overall effect: Z = 0.07 (P = 0.95)								
2.1.2 ACTH								
Buitelaar 1990	9.6	7.3	7	6.9	5.1	7	3.0%	0.40 [-0.66 , 1.46]
Subtotal (95% CI)			**7**			**7**	**3.0%**	**0.40 [-0.66 , 1.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.74 (P = 0.46)								
2.1.3 Oxytocin								
Munesue 2016	11.9	9.4	15	17.4	11.7	14	6.1%	-0.51 [-1.25 , 0.24]
Parker 2017	8.86	8.87	16	11.78	8.11	18	7.2%	-0.34 [-1.02 , 0.34]
Sikich 2021	8.7	6.04	146	9.9	6	144	62.7%	-0.20 [-0.43 , 0.03]
Subtotal (95% CI)			**177**			**176**	**76.0%**	**-0.24 [-0.45 , -0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 2 (P = 0.71); I² = 0%								
Test for overall effect: Z = 2.21 (P = 0.03)								
2.1.4 Vasopressin								
Parker 2019	6.24	7.05	17	8.38	7.23	13	6.3%	-0.29 [-1.02 , 0.43]
Subtotal (95% CI)			**17**			**13**	**6.3%**	**-0.29 [-1.02 , 0.43]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.79 (P = 0.43)								
Total (95% CI)			**235**			**231**	**100.0%**	**-0.18 [-0.37 , -0.00]**
Heterogeneity: Tau² = 0.00; Chi² = 4.36, df = 7 (P = 0.74); I² = 0%								
Test for overall effect: Z = 1.97 (P = 0.05)								
Test for subgroup differences: Chi² = 2.17, df = 3 (P = 0.54), I² = 0%								



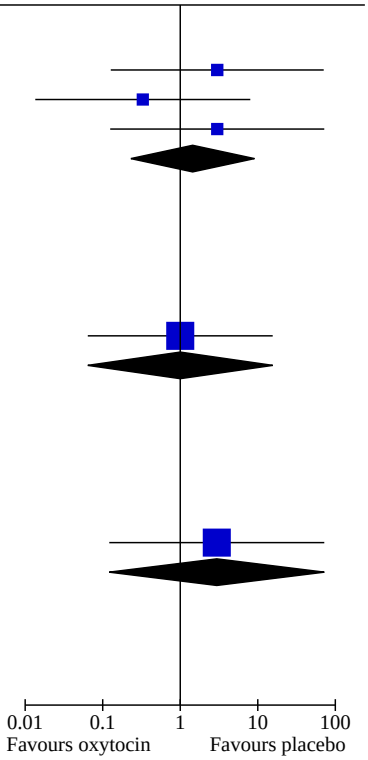
Analysis 2.2. Comparison 2: Neurohormone versus placebo, Outcome 2: Self-injury

Study or Subgroup	Oxytocin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.2.1 Endpoint								
Guastella 2015a	1.77	2.57	26	3.13	4.45	24	49.9%	-0.37 [-0.93 , 0.19]
Subtotal (95% CI)			**26**			**24**	**49.9%**	**-0.37 [-0.93 , 0.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.30 (P = 0.19)								
2.2.2 Three month follow-up								
Guastella 2015a	2.23	3.43	26	3.61	4.88	24	50.1%	-0.32 [-0.88 , 0.23]
Subtotal (95% CI)			**26**			**24**	**50.1%**	**-0.32 [-0.88 , 0.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.14 (P = 0.26)								
Total (95% CI)			**52**			**48**	**100.0%**	**-0.35 [-0.74 , 0.05]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%								
Test for overall effect: Z = 1.73 (P = 0.08)								
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%								



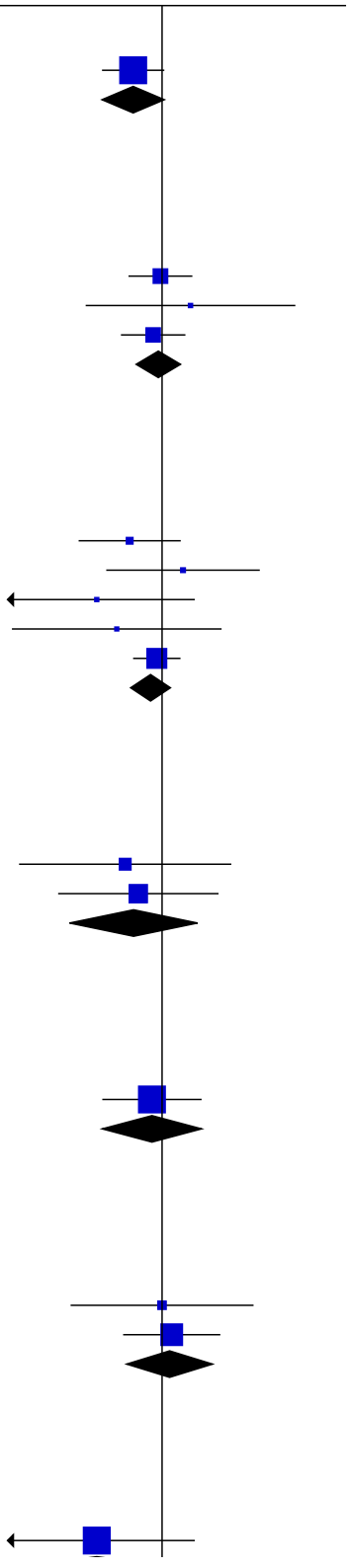
Analysis 2.3. Comparison 2: Neurohormone versus placebo, Outcome 3: Adverse effects: cardiovascular

Study or Subgroup	Oxytocin Events	Oxytocin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Cardiac disorders						
NCT01908205	1	30	0	30	33.7%	3.00 [0.13 , 70.83]
Sikich 2021	0	146	1	144	33.0%	0.33 [0.01 , 8.00]
Yamasue 2020	1	53	0	53	33.3%	3.00 [0.12 , 72.02]
Subtotal (95% CI)		**229**		**227**	**100.0%**	**1.45 [0.23 , 9.05]**
Total events:	2		1			
Heterogeneity: Tau² = 0.00; Chi² = 1.24, df = 2 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.39 (P = 0.69)						
2.3.2 Vascular disorders						
Yamasue 2020	1	53	1	53	100.0%	1.00 [0.06 , 15.57]
Subtotal (95% CI)		**53**		**53**	**100.0%**	**1.00 [0.06 , 15.57]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
2.3.3 Palpitations						
Sikich 2021	1	146	0	144	100.0%	2.96 [0.12 , 72.04]
Subtotal (95% CI)		**146**		**144**	**100.0%**	**2.96 [0.12 , 72.04]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.51)						
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%						



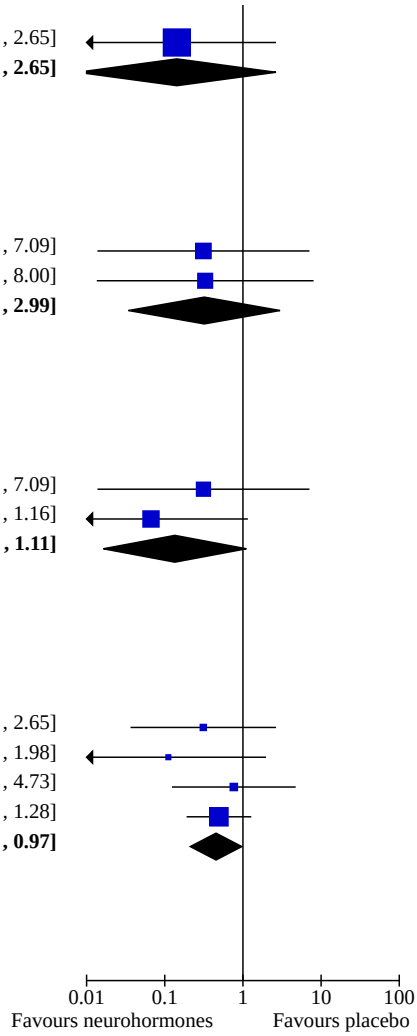
Analysis 2.4. Comparison 2: Neurohormone versus placebo, Outcome 4: Adverse effects: gastrointestinal

Study or Subgroup	Neurohormones Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.4.1 Abdominal pain or discomfort						
Sikich 2021	6	146	14	144	100.0%	0.42 [0.17 , 1.07]
Subtotal (95% CI)		**146**		**144**	**100.0%**	**0.42 [0.17 , 1.07]**
Total events:	6		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.82 (P = 0.07)						
2.4.2 Constipation						
Le 2022	6	21	6	20	48.2%	0.95 [0.37 , 2.47]
Parker 2019	1	17	0	13	4.5%	2.33 [0.10 , 53.03]
Sikich 2021	7	146	9	144	47.3%	0.77 [0.29 , 2.00]
Subtotal (95% CI)		**184**		**177**	**100.0%**	**0.89 [0.46 , 1.73]**
Total events:	14		15			
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 2 (P = 0.79); I² = 0%						
Test for overall effect: Z = 0.33 (P = 0.74)						
2.4.3 Diarrhoea						
Le 2022	2	21	5	20	15.2%	0.38 [0.08 , 1.74]
Munesue 2016	2	15	1	14	6.7%	1.87 [0.19 , 18.38]
NCT01908205	0	30	3	30	4.1%	0.14 [0.01 , 2.65]
Parker 2019	0	17	1	13	3.6%	0.26 [0.01 , 5.89]
Sikich 2021	13	146	15	144	70.4%	0.85 [0.42 , 1.73]
Subtotal (95% CI)		**229**		**221**	**100.0%**	**0.71 [0.39 , 1.28]**
Total events:	17		25			
Heterogeneity: Tau² = 0.00; Chi² = 3.15, df = 4 (P = 0.53); I² = 0%						
Test for overall effect: Z = 1.14 (P = 0.26)						
2.4.4 Dry mouth						
NCT01908205	0	30	1	30	36.4%	0.33 [0.01 , 7.87]
Sikich 2021	1	146	2	144	63.6%	0.49 [0.05 , 5.38]
Subtotal (95% CI)		**176**		**174**	**100.0%**	**0.43 [0.06 , 2.88]**
Total events:	1		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.87 (P = 0.38)						
2.4.5 Encopresis						
Sikich 2021	3	146	4	144	100.0%	0.74 [0.17 , 3.25]
Subtotal (95% CI)		**146**		**144**	**100.0%**	**0.74 [0.17 , 3.25]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
2.4.6 Gastrointestinal disorders						
NCT01908205	1	30	1	30	22.0%	1.00 [0.07 , 15.26]
Yamasue 2020	4	53	3	53	78.0%	1.33 [0.31 , 5.67]
Subtotal (95% CI)		**83**		**83**	**100.0%**	**1.25 [0.35 , 4.49]**
Total events:	5		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.34 (P = 0.73)						
2.4.7 Nausea						
NCT01908205	0	30	3	30	100.0%	0.14 [0.01 , 2.65]



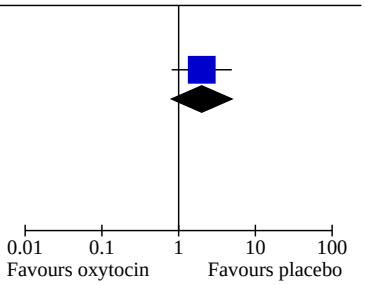
Analysis 2.4. (Continued)

2.4.7 Nausea						
NCT01908205	0	30	3	30	100.0%	0.14 [0.01 , 2.65]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**0.14 [0.01 , 2.65]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
2.4.8 Salivary hypersecretion						
Munesue 2016	0	15	1	14	51.1%	0.31 [0.01 , 7.09]
Sikich 2021	0	146	1	144	48.9%	0.33 [0.01 , 8.00]
Subtotal (95% CI)		**161**		**158**	**100.0%**	**0.32 [0.03 , 2.99]**
Total events:	0		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 1.00 (P = 0.32)						
2.4.9 Stomatitis						
Munesue 2016	0	15	1	14	45.5%	0.31 [0.01 , 7.09]
Sikich 2021	0	146	7	146	54.5%	0.07 [0.00 , 1.16]
Subtotal (95% CI)		**161**		**160**	**100.0%**	**0.13 [0.02 , 1.11]**
Total events:	0		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 1 (P = 0.47); I² = 0%						
Test for overall effect: Z = 1.87 (P = 0.06)						
2.4.10 Vomiting						
Munesue 2016	1	15	3	14	12.5%	0.31 [0.04 , 2.65]
NCT01908205	0	30	4	30	6.9%	0.11 [0.01 , 1.98]
Parker 2019	2	17	2	13	17.3%	0.76 [0.12 , 4.73]
Sikich 2021	6	146	12	144	63.3%	0.49 [0.19 , 1.28]
Subtotal (95% CI)		**208**		**201**	**100.0%**	**0.45 [0.21 , 0.97]**
Total events:	9		21			
Heterogeneity: Tau² = 0.00; Chi² = 1.38, df = 3 (P = 0.71); I² = 0%						
Test for overall effect: Z = 2.05 (P = 0.04)						
Test for subgroup differences: Chi² = 0.00, df = 9 (P < 0.00001), I² = 0%						



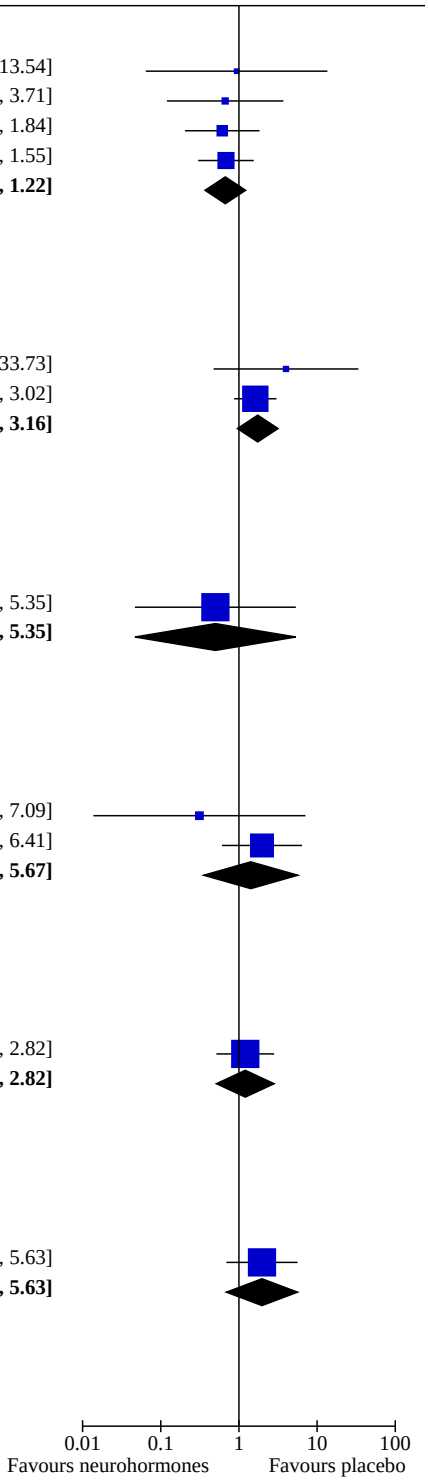
Analysis 2.5. Comparison 2: Neurohormone versus placebo, Outcome 5: Adverse effects: immune system

Study or Subgroup	Neurohormones Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 infections and infestations						
Yamasue 2020	12	53	6	53	100.0%	2.00 [0.81 , 4.93]
Subtotal (95% CI)		**53**		**53**	**100.0%**	**2.00 [0.81 , 4.93]**
Total events:	12		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
Test for subgroup differences: Not applicable						



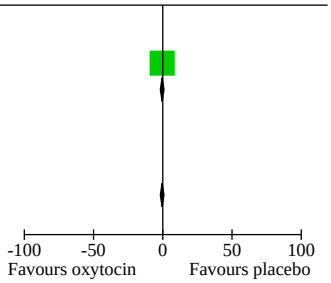
Analysis 2.6. Comparison 2: Neurohormone versus placebo, Outcome 6: Adverse effects: metabolic (dichotomous)

Study or Subgroup	Neurohormones Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.6.1 Decreased appetite						
Munesue 2016	1	15	1	14	5.0%	0.93 [0.06 , 13.54]
NCT01908205	2	30	3	30	12.1%	0.67 [0.12 , 3.71]
Parker 2019	4	17	5	13	29.6%	0.61 [0.20 , 1.84]
Sikich 2021	9	146	13	144	53.3%	0.68 [0.30 , 1.55]
Subtotal (95% CI)		**208**		**201**	**100.0%**	**0.67 [0.37 , 1.22]**
Total events:	16		22			
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 3 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.32 (P = 0.19)						
2.6.2 Increased appetite						
NCT01908205	4	30	1	30	7.9%	4.00 [0.47 , 33.73]
Sikich 2021	23	146	14	144	92.1%	1.62 [0.87 , 3.02]
Subtotal (95% CI)		**176**		**174**	**100.0%**	**1.74 [0.96 , 3.16]**
Total events:	27		15			
Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.81 (P = 0.07)						
2.6.3 Metabolism and nutrition disorders						
Yamasue 2020	1	53	2	53	100.0%	0.50 [0.05 , 5.35]
Subtotal (95% CI)		**53**		**53**	**100.0%**	**0.50 [0.05 , 5.35]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
2.6.4 Thirst						
Munesue 2016	0	15	1	14	17.9%	0.31 [0.01 , 7.09]
Sikich 2021	8	146	4	144	82.1%	1.97 [0.61 , 6.41]
Subtotal (95% CI)		**161**		**158**	**100.0%**	**1.42 [0.35 , 5.67]**
Total events:	8		5			
Heterogeneity: Tau² = 0.25; Chi² = 1.17, df = 1 (P = 0.28); I² = 15%						
Test for overall effect: Z = 0.49 (P = 0.62)						
2.6.5 Weight gain						
Sikich 2021	11	146	9	144	100.0%	1.21 [0.52 , 2.82]
Subtotal (95% CI)		**146**		**144**	**100.0%**	**1.21 [0.52 , 2.82]**
Total events:	11		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
2.6.6 Weight loss						
Sikich 2021	10	146	5	144	100.0%	1.97 [0.69 , 5.63]
Subtotal (95% CI)		**146**		**144**	**100.0%**	**1.97 [0.69 , 5.63]**
Total events:	10		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.27 (P = 0.20)						
Test for subgroup differences: Chi² = 0.00, df = 5 (P < 0.00001), I² = 0%						



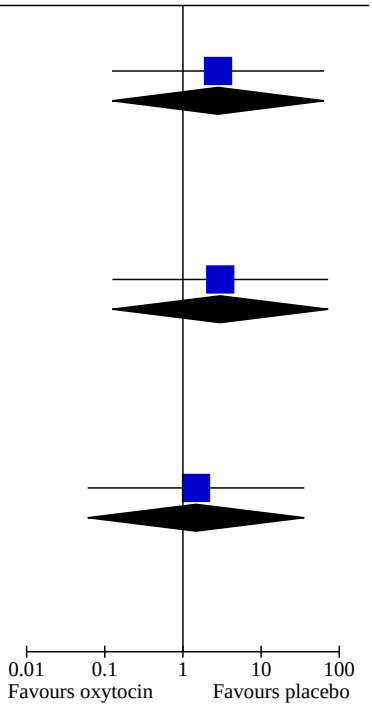
Analysis 2.7. Comparison 2: Neurohormone versus placebo, Outcome 7: Adverse effects: metabolic (continuous)

Study or Subgroup	Oxytocin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.7.1 Mean change in weight (kg)								
Sikich 2013	0.64	1.95	11	1.09	1.14	13	100.0%	-0.45 [-1.76 , 0.86]
Subtotal (95% CI)			**11**			**13**	**100.0%**	**-0.45 [-1.76 , 0.86]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.67 (P = 0.50)								
Total (95% CI)			**11**			**13**	**100.0%**	**-0.45 [-1.76 , 0.86]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.67 (P = 0.50)								
Test for subgroup differences: Not applicable								



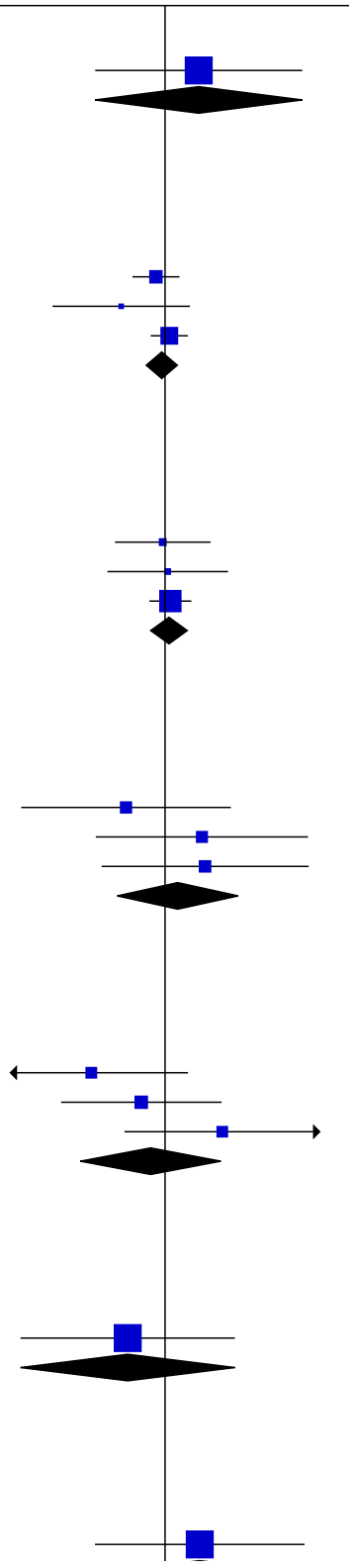
Analysis 2.8. Comparison 2: Neurohormone versus placebo, Outcome 8: Adverse effects: musculoskeletal

Study or Subgroup	Neurohormones Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.8.1 Muscle spasms						
Munesue 2016	1	15	0	14	100.0%	2.81 [0.12 , 63.83]
Subtotal (95% CI)		**15**		**14**	**100.0%**	**2.81 [0.12 , 63.83]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
2.8.2 Musculoskeletal and connective tissue disorders						
Yamasue 2020	1	53	0	53	100.0%	3.00 [0.12 , 72.02]
Subtotal (95% CI)		**53**		**53**	**100.0%**	**3.00 [0.12 , 72.02]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
2.8.3 Rhabdomyolysis						
Squassante 2018	1	148	0	72	100.0%	1.47 [0.06 , 35.64]
Subtotal (95% CI)		**148**		**72**	**100.0%**	**1.47 [0.06 , 35.64]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%						

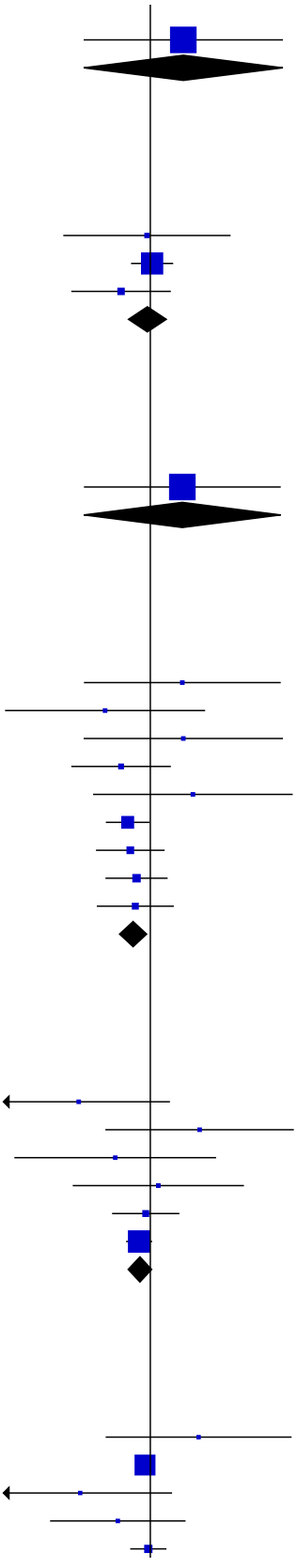


Analysis 2.9. Comparison 2: Neurohormone versus placebo, Outcome 9: Adverse effects: neurological

Study or Subgroup	Neurohormones Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.9.1 Absence seizures						
Anagnostou 2012	1	10	0	9	100.0%	2.73 [0.12 , 59.57]
Subtotal (95% CI)		**10**		**9**	**100.0%**	**2.73 [0.12 , 59.57]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
2.9.2 Aggression						
Le 2022	8	21	10	20	38.2%	0.76 [0.38 , 1.53]
Sikich 2013	1	12	4	13	5.0%	0.27 [0.04 , 2.10]
Sikich 2021	23	146	20	144	56.8%	1.13 [0.65 , 1.97]
Subtotal (95% CI)		**179**		**177**	**100.0%**	**0.91 [0.57 , 1.44]**
Total events:	32		34			
Heterogeneity: Tau² = 0.02; Chi² = 2.20, df = 2 (P = 0.33); I² = 9%						
Test for overall effect: Z = 0.42 (P = 0.68)						
2.9.3 Agitation						
Munesue 2016	3	15	3	14	14.6%	0.93 [0.22 , 3.88]
Sikich 2013	2	12	2	13	9.2%	1.08 [0.18 , 6.53]
Sikich 2021	19	146	16	144	76.2%	1.17 [0.63 , 2.19]
Subtotal (95% CI)		**173**		**171**	**100.0%**	**1.12 [0.65 , 1.94]**
Total events:	24		21			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 2 (P = 0.96); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.67)						
2.9.4 Decreased attention						
Munesue 2016	0	15	1	14	33.3%	0.31 [0.01 , 7.09]
NCT01908205	1	30	0	30	32.5%	3.00 [0.13 , 70.83]
Umbricht 2017	1	9	0	10	34.2%	3.30 [0.15 , 72.08]
Subtotal (95% CI)		**54**		**54**	**100.0%**	**1.46 [0.24 , 8.84]**
Total events:	2		1			
Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 2 (P = 0.50); I² = 0%						
Test for overall effect: Z = 0.41 (P = 0.68)						
2.9.5 Dizziness						
NCT01908205	0	30	4	30	31.1%	0.11 [0.01 , 1.98]
Sikich 2021	1	146	2	144	38.1%	0.49 [0.05 , 5.38]
Umbricht 2017	2	9	0	10	30.7%	5.50 [0.30 , 101.28]
Subtotal (95% CI)		**185**		**184**	**100.0%**	**0.65 [0.08 , 5.27]**
Total events:	3		6			
Heterogeneity: Tau² = 1.50; Chi² = 3.56, df = 2 (P = 0.17); I² = 44%						
Test for overall effect: Z = 0.40 (P = 0.69)						
2.9.6 Dysphoria						
Sikich 2021	0	146	1	144	100.0%	0.33 [0.01 , 8.00]
Subtotal (95% CI)		**146**		**144**	**100.0%**	**0.33 [0.01 , 8.00]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.49)						
2.9.7 Excessive talking						
Munesue 2016	1	15	0	14	100.0%	2.81 [0.12 , 63.83]



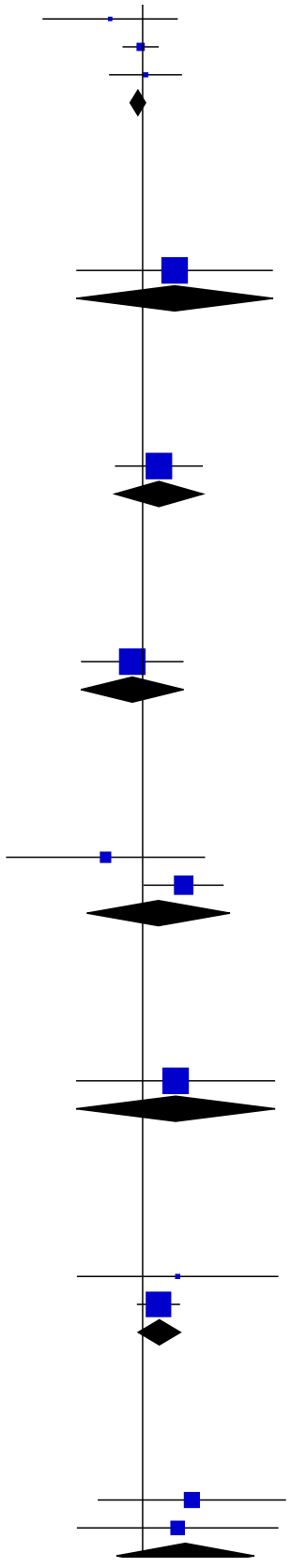
Analysis 2.9. (Continued)



2.9.7 Excessive talking						
Munesue 2016	1	15	0	14	100.0%	2.81 [0.12 , 63.83]
Subtotal (95% CI)		**15**		**14**	**100.0%**	**2.81 [0.12 , 63.83]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
2.9.8 Fatigue						
Anagnostou 2012	1	10	1	9	5.1%	0.90 [0.07 , 12.38]
Le 2022	10	21	9	20	80.5%	1.06 [0.55 , 2.05]
NCT01908205	2	30	5	30	14.4%	0.40 [0.08 , 1.90]
Subtotal (95% CI)		**61**		**59**	**100.0%**	**0.91 [0.50 , 1.65]**
Total events:	13		15			
Heterogeneity: Tau² = 0.00; Chi² = 1.27, df = 2 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.30 (P = 0.76)						
2.9.9 Forgetfulness						
NCT01337687	1	10	0	9	100.0%	2.73 [0.12 , 59.57]
Subtotal (95% CI)		**10**		**9**	**100.0%**	**2.73 [0.12 , 59.57]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
2.9.10 Headache						
Anagnostou 2012	1	10	0	9	1.9%	2.73 [0.12 , 59.57]
Le 2022	0	21	1	15	1.8%	0.24 [0.01 , 5.57]
Munesue 2016	1	15	0	14	1.8%	2.81 [0.12 , 63.83]
NCT01908205	2	30	5	30	7.4%	0.40 [0.08 , 1.90]
Parker 2017	1	14	0	18	1.8%	3.80 [0.17 , 86.76]
Sikich 2021	11	146	22	144	38.3%	0.49 [0.25 , 0.98]
Squassante 2018 (1)	5	39	6	25	15.6%	0.53 [0.18 , 1.57]
Squassante 2018 (2)	10	77	5	25	19.0%	0.65 [0.25 , 1.72]
Squassante 2018 (3)	4	32	5	25	12.4%	0.63 [0.19 , 2.09]
Subtotal (95% CI)		**384**		**305**	**100.0%**	**0.58 [0.38 , 0.89]**
Total events:	35		44			
Heterogeneity: Tau² = 0.00; Chi² = 4.16, df = 8 (P = 0.84); I² = 0%						
Test for overall effect: Z = 2.49 (P = 0.01)						
2.9.11 Insomnia						
Le 2022	0	21	4	20	1.7%	0.11 [0.01 , 1.85]
Munesue 2016	2	15	0	14	1.6%	4.69 [0.24 , 89.88]
NCT01908205	0	30	1	30	1.4%	0.33 [0.01 , 7.87]
Parker 2017	1	14	1	18	1.9%	1.29 [0.09 , 18.80]
Sikich 2013	4	12	5	13	12.2%	0.87 [0.30 , 2.49]
Sikich 2021	30	146	42	144	81.4%	0.70 [0.47 , 1.06]
Subtotal (95% CI)		**238**		**239**	**100.0%**	**0.72 [0.50 , 1.04]**
Total events:	37		53			
Heterogeneity: Tau² = 0.00; Chi² = 3.81, df = 5 (P = 0.58); I² = 0%						
Test for overall effect: Z = 1.73 (P = 0.08)						
2.9.12 Irritability						
Anagnostou 2012	2	10	0	9	0.7%	4.55 [0.25 , 83.70]
Le 2022	16	21	18	20	74.6%	0.85 [0.64 , 1.12]
NCT01908205	0	30	4	30	0.7%	0.11 [0.01 , 1.98]
Sikich 2013	1	12	3	13	1.3%	0.36 [0.04 , 3.02]
Sikich 2021	20	146	21	144	18.2%	0.94 [0.53 , 1.66]

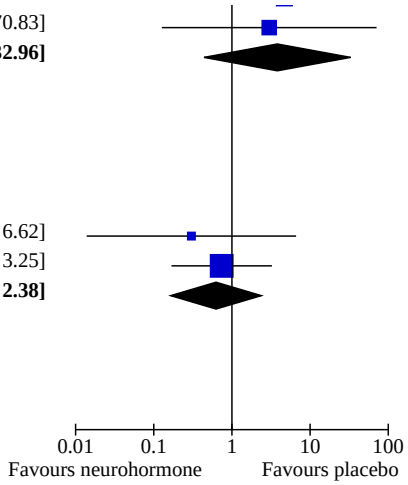
Analysis 2.9. (Continued)

Sikich 2013	1	12	3	13	1.3%	0.36 [0.04 , 3.02]
Sikich 2021	20	146	21	144	18.2%	0.94 [0.53 , 1.66]
Squassante 2018	9	148	4	72	4.5%	1.09 [0.35 , 3.43]
Subtotal (95% CI)		**367**		**288**	**100.0%**	**0.86 [0.68 , 1.10]**
Total events:	48		50			
Heterogeneity: Tau² = 0.00; Chi² = 4.11, df = 5 (P = 0.53); I² = 0%						
Test for overall effect: Z = 1.21 (P = 0.22)						
2.9.13 Leg shaking						
Anagnostou 2012	1	10	0	9	100.0%	2.73 [0.12 , 59.57]
Subtotal (95% CI)		**10**		**9**	**100.0%**	**2.73 [0.12 , 59.57]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
2.9.14 Nervous systems disorders						
Yamasue 2020	5	53	3	53	100.0%	1.67 [0.42 , 6.62]
Subtotal (95% CI)		**53**		**53**	**100.0%**	**1.67 [0.42 , 6.62]**
Total events:	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
2.9.15 Oppositional						
Sikich 2013	2	12	3	13	100.0%	0.72 [0.14 , 3.61]
Subtotal (95% CI)		**12**		**13**	**100.0%**	**0.72 [0.14 , 3.61]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
2.9.16 Restlessness						
Munesue 2016	0	15	1	14	32.3%	0.31 [0.01 , 7.09]
Sikich 2021	11	146	3	144	67.7%	3.62 [1.03 , 12.69]
Subtotal (95% CI)		**161**		**158**	**100.0%**	**1.64 [0.17 , 15.47]**
Total events:	11		4			
Heterogeneity: Tau² = 1.52; Chi² = 2.03, df = 1 (P = 0.15); I² = 51%						
Test for overall effect: Z = 0.43 (P = 0.67)						
2.9.17 Seizure						
Munesue 2016	1	15	0	14	100.0%	2.81 [0.12 , 63.83]
Subtotal (95% CI)		**15**		**14**	**100.0%**	**2.81 [0.12 , 63.83]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
2.9.18 Sedation						
NCT01908205	1	30	0	30	4.4%	3.00 [0.13 , 70.83]
Sikich 2021	20	146	12	144	95.6%	1.64 [0.83 , 3.24]
Subtotal (95% CI)		**176**		**174**	**100.0%**	**1.69 [0.87 , 3.27]**
Total events:	21		12			
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%						
Test for overall effect: Z = 1.55 (P = 0.12)						
2.9.19 Somnolence						
Munesue 2016	2	15	0	14	53.4%	4.69 [0.24 , 89.88]
NCT01908205	1	30	0	30	46.6%	3.00 [0.13 , 70.83]
Subtotal (95% CI)		**45**		**44**	**100.0%**	**3.81 [0.44 , 32.96]**



Analysis 2.9. (Continued)

NCT01908205	1	30	0	30	46.6%	3.00 [0.13 , 70.83]
Subtotal (95% CI)		**45**		**44**	**100.0%**	**3.81 [0.44 , 32.96]**
Total events:	3		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%						
Test for overall effect: Z = 1.21 (P = 0.22)						
2.9.20 Tics						
Anagnostou 2012	0	10	1	9	18.7%	0.30 [0.01 , 6.62]
Sikich 2021	3	146	4	144	81.3%	0.74 [0.17 , 3.25]
Subtotal (95% CI)		**156**		**153**	**100.0%**	**0.63 [0.16 , 2.38]**
Total events:	3		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Chi² = 0.00, df = 19 (P < 0.00001), I² = 0%						



Footnotes

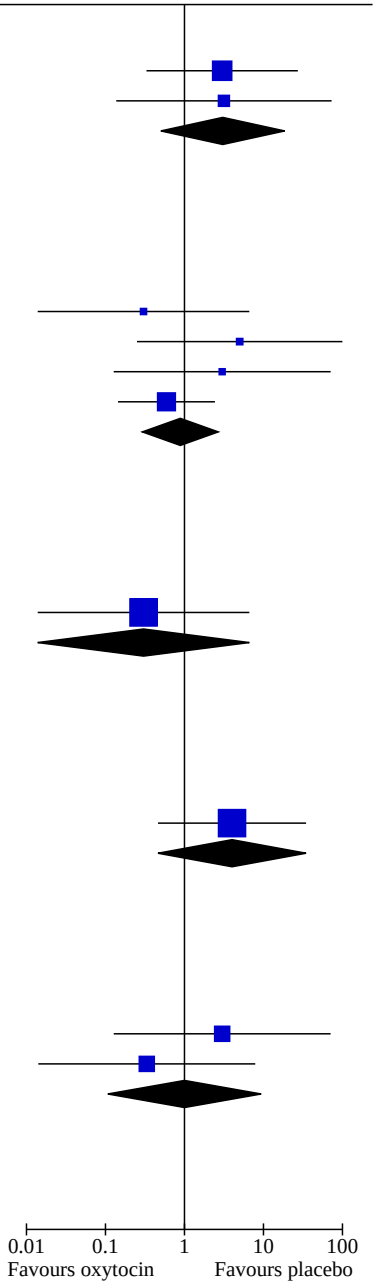
(1) Balovaptan 10mg

(2) Balovaptan 4mg

(3) Balovaptan 1.5 mg

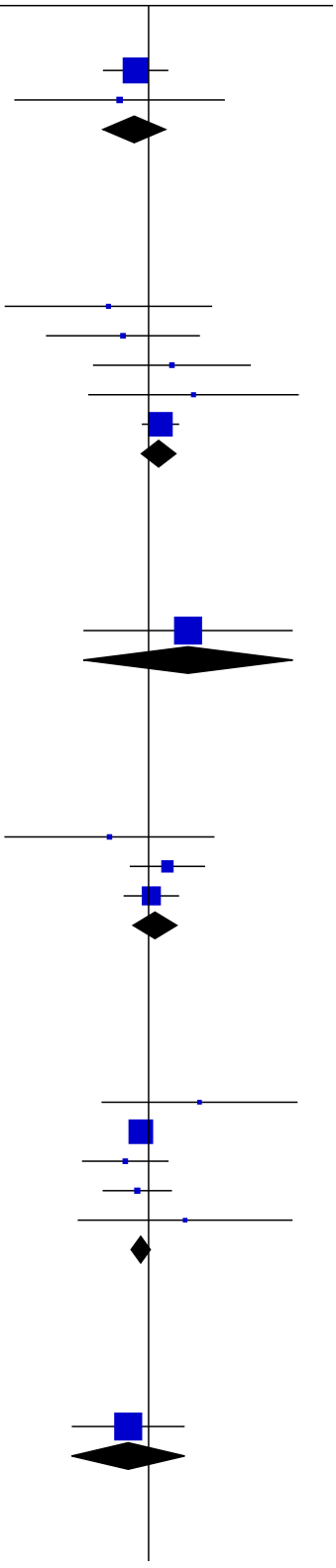
Analysis 2.10. Comparison 2: Neurohormone versus placebo, Outcome 10: Adverse effects: psychological

Study or Subgroup	Oxytocin Events	Oxytocin Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
2.10.1 Anxiety						
NCT01908205	3	30	1	30	66.9%	3.00 [0.33 , 27.23]
Umbricht 2017	1	18	0	19	33.1%	3.16 [0.14 , 72.84]
Subtotal (95% CI)		**48**		**49**	**100.0%**	**3.05 [0.50 , 18.55]**
Total events:	4		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 1.21 (P = 0.23)						
2.10.2 Depression						
Anagnostou 2012	0	10	1	9	12.9%	0.30 [0.01 , 6.62]
Munesue 2016	2	29	0	29	13.6%	5.00 [0.25 , 99.82]
NCT01908205	1	30	0	30	12.2%	3.00 [0.13 , 70.83]
Sikich 2021	3	146	5	144	61.3%	0.59 [0.14 , 2.43]
Subtotal (95% CI)		**215**		**212**	**100.0%**	**0.89 [0.29 , 2.68]**
Total events:	6		6			
Heterogeneity: Tau² = 0.00; Chi² = 2.63, df = 3 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.21 (P = 0.83)						
2.10.3 Panic attack						
Anagnostou 2012	0	10	1	9	100.0%	0.30 [0.01 , 6.62]
Subtotal (95% CI)		**10**		**9**	**100.0%**	**0.30 [0.01 , 6.62]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.76 (P = 0.45)						
2.10.4 Psychiatric						
Yamasue 2020	4	53	1	53	100.0%	4.00 [0.46 , 34.61]
Subtotal (95% CI)		**53**		**53**	**100.0%**	**4.00 [0.46 , 34.61]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.26 (P = 0.21)						
2.10.5 Self-injury						
Munesue 2016	1	29	0	29	50.0%	3.00 [0.13 , 70.74]
NCT01908205	0	30	1	30	50.0%	0.33 [0.01 , 7.87]
Subtotal (95% CI)		**59**		**59**	**100.0%**	**1.00 [0.11 , 9.35]**
Total events:	1		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.34); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Chi² = 0.00, df = 4 (P < 0.00001), I² = 0%						



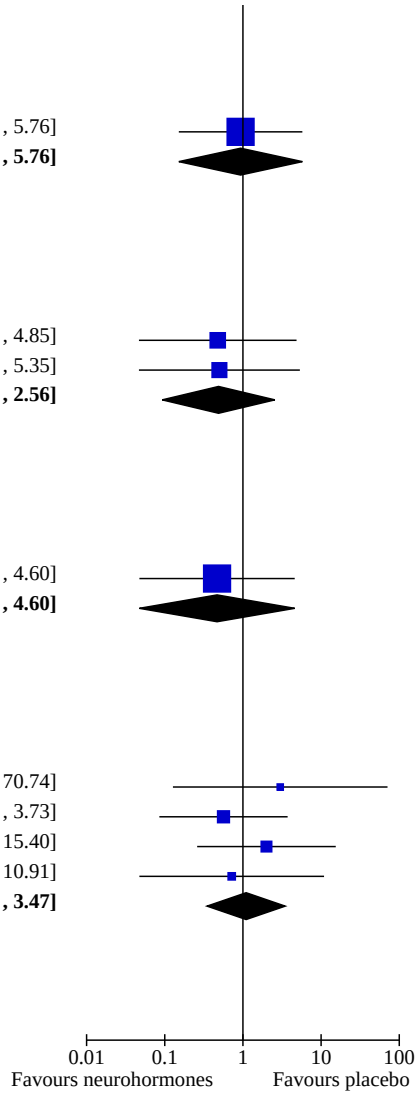
Analysis 2.11. Comparison 2: Neurohormone versus placebo, Outcome 11: Adverse effects: respiratory

Study or Subgroup	Neurohormones Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.11.1 Cold symptoms						
Le 2022	5	21	7	20	91.2%	0.68 [0.26 , 1.80]
Parker 2017	0	14	1	18	8.8%	0.42 [0.02 , 9.64]
Subtotal (95% CI)		**35**		**38**	**100.0%**	**0.65 [0.26 , 1.65]**
Total events:	5		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 0.90 (P = 0.37)						
2.11.2 Cough						
Anagnostou 2012	0	10	1	9	2.7%	0.30 [0.01 , 6.62]
Munesue 2016	1	15	2	14	5.0%	0.47 [0.05 , 4.60]
NCT01908205	2	30	1	30	4.7%	2.00 [0.19 , 20.90]
Parker 2017	1	14	0	18	2.7%	3.80 [0.17 , 86.76]
Sikich 2021	26	146	18	144	84.8%	1.42 [0.82 , 2.48]
Subtotal (95% CI)		**215**		**215**	**100.0%**	**1.35 [0.81 , 2.25]**
Total events:	30		22			
Heterogeneity: Tau² = 0.00; Chi² = 2.29, df = 4 (P = 0.68); I² = 0%						
Test for overall effect: Z = 1.14 (P = 0.25)						
2.11.3 Croup						
Sikich 2013	1	12	0	13	100.0%	3.23 [0.14 , 72.46]
Subtotal (95% CI)		**12**		**13**	**100.0%**	**3.23 [0.14 , 72.46]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						
2.11.4 Epistaxis						
Munesue 2016	0	15	1	14	4.3%	0.31 [0.01 , 7.09]
NCT01908205	7	30	4	30	33.7%	1.75 [0.57 , 5.36]
Sikich 2021	11	146	10	144	62.0%	1.08 [0.48 , 2.48]
Subtotal (95% CI)		**191**		**188**	**100.0%**	**1.21 [0.63 , 2.31]**
Total events:	18		15			
Heterogeneity: Tau² = 0.00; Chi² = 1.21, df = 2 (P = 0.55); I² = 0%						
Test for overall effect: Z = 0.57 (P = 0.57)						
2.11.5 Nasal congestion						
Anagnostou 2012	2	10	0	9	1.0%	4.55 [0.25 , 83.70]
Le 2022	15	21	18	20	85.7%	0.79 [0.58 , 1.08]
Munesue 2016	3	29	6	29	4.9%	0.50 [0.14 , 1.81]
NCT01908205	5	30	7	30	7.6%	0.71 [0.25 , 2.00]
Sikich 2021	1	146	0	144	0.8%	2.96 [0.12 , 72.04]
Subtotal (95% CI)		**236**		**232**	**100.0%**	**0.79 [0.59 , 1.05]**
Total events:	26		31			
Heterogeneity: Tau² = 0.00; Chi² = 2.57, df = 4 (P = 0.63); I² = 0%						
Test for overall effect: Z = 1.62 (P = 0.11)						
2.11.6 Nasal irritation/runny nose						
Bernaerts 2020	2	22	3	18	100.0%	0.55 [0.10 , 2.92]
Subtotal (95% CI)		**22**		**18**	**100.0%**	**0.55 [0.10 , 2.92]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						



Analysis 2.11. (Continued)

Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
2.11.7 Nasopharyngitis						
Munesue 2016	2	15	2	14	100.0%	0.93 [0.15 , 5.76]
Subtotal (95% CI)		**15**		**14**	**100.0%**	**0.93 [0.15 , 5.76]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.07 (P = 0.94)						
2.11.8 Respiratory, thoracic and mediastinal disorders						
Le 2022	1	21	2	20	51.0%	0.48 [0.05 , 4.85]
Yamasue 2020	1	53	2	53	49.0%	0.50 [0.05 , 5.35]
Subtotal (95% CI)		**74**		**73**	**100.0%**	**0.49 [0.09 , 2.56]**
Total events:	2		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.85 (P = 0.40)						
2.11.9 Sinusitis						
Munesue 2016	1	15	2	14	100.0%	0.47 [0.05 , 4.60]
Subtotal (95% CI)		**15**		**14**	**100.0%**	**0.47 [0.05 , 4.60]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.51)						
2.11.10 Upper respiratory tract infection						
Munesue 2016	1	29	0	29	13.3%	3.00 [0.13 , 70.74]
Squassante 2018 (1)	2	39	2	22	37.1%	0.56 [0.09 , 3.73]
Squassante 2018 (2)	7	77	1	22	31.8%	2.00 [0.26 , 15.40]
Squassante 2018 (3)	1	32	1	23	17.9%	0.72 [0.05 , 10.91]
Subtotal (95% CI)		**177**		**96**	**100.0%**	**1.10 [0.35 , 3.47]**
Total events:	11		4			
Heterogeneity: Tau² = 0.00; Chi² = 1.29, df = 3 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.16 (P = 0.87)						
Test for subgroup differences: Chi² = 0.00, df = 9 (P < 0.00001), I² = 0%						

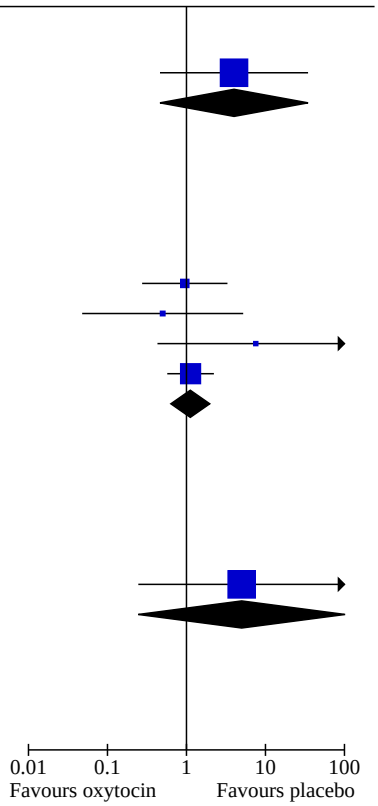


Footnotes

(1) Balovaptan 10mg
(2) Balovaptan 4mg
(3) Balovaptan 1.5mg

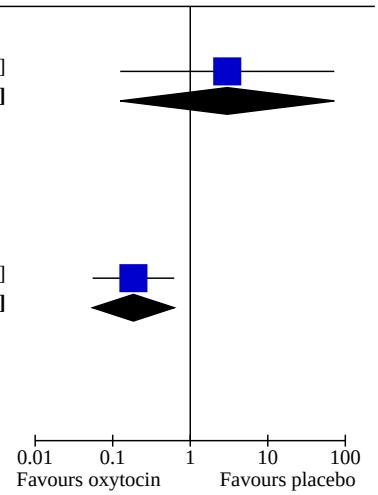
Analysis 2.12. Comparison 2: Neurohormone versus placebo, Outcome 12: Adverse effects: skin

Study or Subgroup	Oxytocin Events	Oxytocin Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
2.12.1 General/systemic disorders and administration site conditions						
Yamasue 2020	4	53	1	53	100.0%	4.00 [0.46 , 34.61]
Subtotal (95% CI)		**53**		**53**	**100.0%**	**4.00 [0.46 , 34.61]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.26 (P = 0.21)						
2.12.2 Skin rash						
Le 2022	4	21	4	20	20.8%	0.95 [0.27 , 3.30]
NCT01908205	1	30	2	30	5.8%	0.50 [0.05 , 5.22]
Sikich 2013	3	12	0	13	3.9%	7.54 [0.43 , 132.35]
Sikich 2021	16	146	14	144	69.5%	1.13 [0.57 , 2.22]
Subtotal (95% CI)		**209**		**207**	**100.0%**	**1.12 [0.63 , 1.97]**
Total events:	24		20			
Heterogeneity: Tau² = 0.00; Chi² = 2.22, df = 3 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.39 (P = 0.70)						
2.12.3 Skin and subcutaneous tissue disorders						
Yamasue 2020	2	53	0	53	100.0%	5.00 [0.25 , 101.73]
Subtotal (95% CI)		**53**		**53**	**100.0%**	**5.00 [0.25 , 101.73]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.30)						
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%						



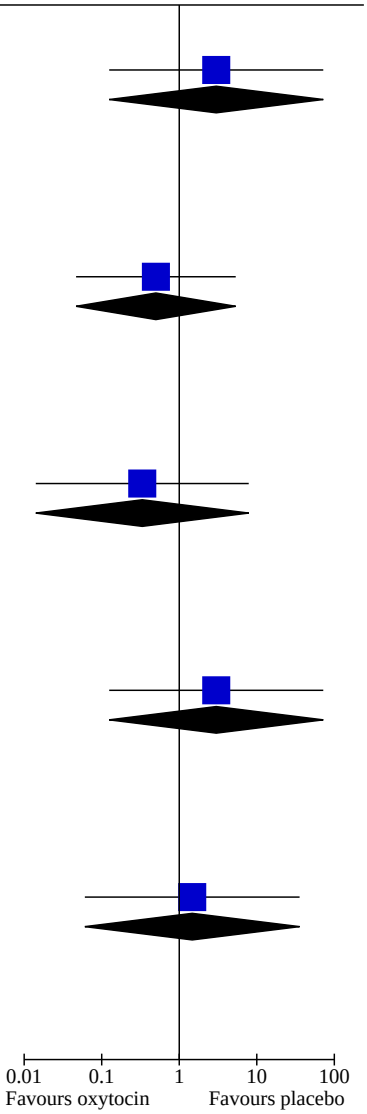
Analysis 2.13. Comparison 2: Neurohormone versus placebo, Outcome 13: Adverse effects: urinary

Study or Subgroup	Oxytocin Events	Oxytocin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.13.1 Renal and urinary disorders						
Yamasue 2020	1	53	0	53	100.0%	3.00 [0.12 , 72.02]
Subtotal (95% CI)		**53**		**53**	**100.0%**	**3.00 [0.12 , 72.02]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
2.13.2 Enuresis						
Sikich 2021	3	146	16	144	100.0%	0.18 [0.06 , 0.62]
Subtotal (95% CI)		**146**		**144**	**100.0%**	**0.18 [0.06 , 0.62]**
Total events:	3		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.73 (P = 0.006)						

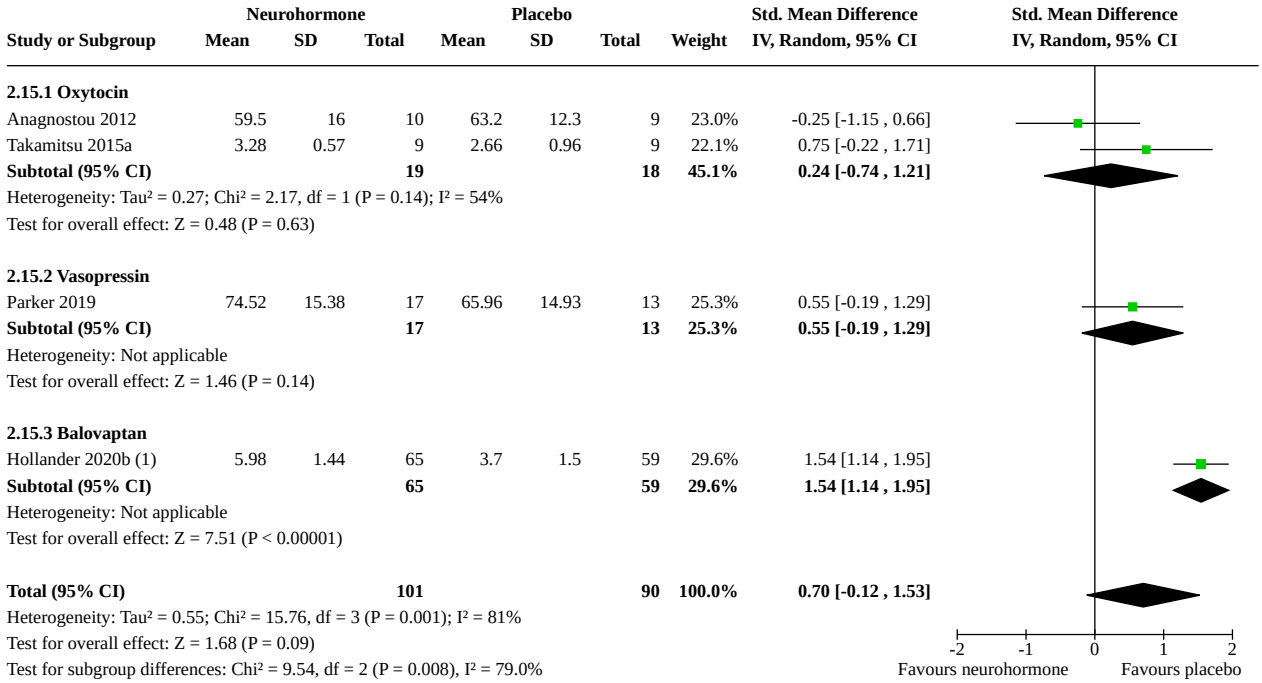


Analysis 2.14. Comparison 2: Neurohormone versus placebo, Outcome 14: Adverse effects: other

Study or Subgroup	Oxytocin Events	Oxytocin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.14.1 Injury, poisoning, and procedural complications						
Yamasue 2020	1	53	0	53	100.0%	3.00 [0.12 , 72.02]
Subtotal (95% CI)		**53**		**53**	**100.0%**	**3.00 [0.12 , 72.02]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
2.14.2 Investigations						
Yamasue 2020	1	53	2	53	100.0%	0.50 [0.05 , 5.35]
Subtotal (95% CI)		**53**		**53**	**100.0%**	**0.50 [0.05 , 5.35]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
2.14.3 Lymphadenopathy						
NCT01908205	0	30	1	30	100.0%	0.33 [0.01 , 7.87]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**0.33 [0.01 , 7.87]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
2.14.4 Neoplasms: benign, malignant, and unspecified						
Yamasue 2020	1	53	0	53	100.0%	3.00 [0.12 , 72.02]
Subtotal (95% CI)		**53**		**53**	**100.0%**	**3.00 [0.12 , 72.02]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
2.14.5 Troponin I increased						
Squassante 2018	1	148	0	72	100.0%	1.47 [0.06 , 35.64]
Subtotal (95% CI)		**148**		**72**	**100.0%**	**1.47 [0.06 , 35.64]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						
Test for subgroup differences: $Chi^2 = 0.00$, df = 4 (P < 0.00001), $I^2 = 0\%$						



Analysis 2.15. Comparison 2: Neurohormone versus placebo, Outcome 15: Quality of life

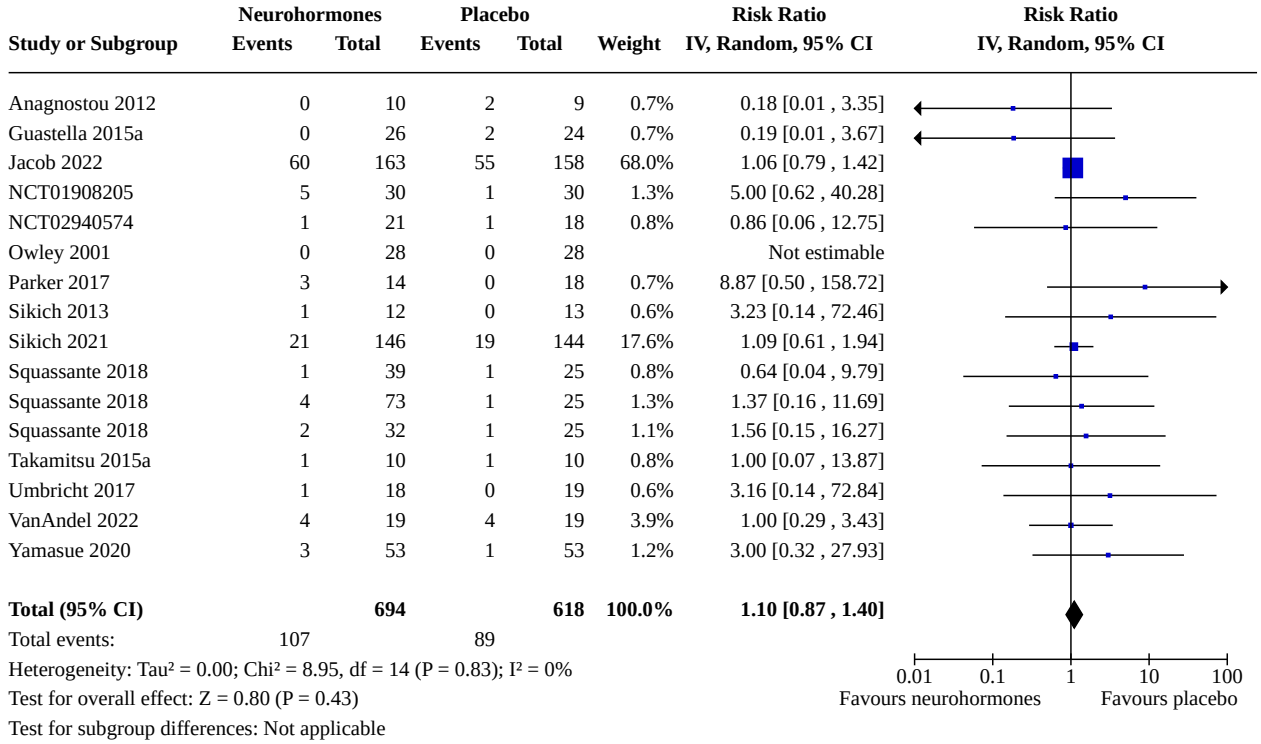


Study or Subgroup	Neurohormone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.15.1 Oxytocin								
Anagnostou 2012	59.5	16	10	63.2	12.3	9	23.0%	-0.25 [-1.15 , 0.66]
Takamitsu 2015a	3.28	0.57	9	2.66	0.96	9	22.1%	0.75 [-0.22 , 1.71]
Subtotal (95% CI)			**19**			**18**	**45.1%**	**0.24 [-0.74 , 1.21]**
Heterogeneity: Tau² = 0.27; Chi² = 2.17, df = 1 (P = 0.14); I² = 54%								
Test for overall effect: Z = 0.48 (P = 0.63)								
2.15.2 Vasopressin								
Parker 2019	74.52	15.38	17	65.96	14.93	13	25.3%	0.55 [-0.19 , 1.29]
Subtotal (95% CI)			**17**			**13**	**25.3%**	**0.55 [-0.19 , 1.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.46 (P = 0.14)								
2.15.3 Balovaptan								
Hollander 2020b (1)	5.98	1.44	65	3.7	1.5	59	29.6%	1.54 [1.14 , 1.95]
Subtotal (95% CI)			**65**			**59**	**29.6%**	**1.54 [1.14 , 1.95]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.51 (P < 0.00001)								
Total (95% CI)			**101**			**90**	**100.0%**	**0.70 [-0.12 , 1.53]**
Heterogeneity: Tau² = 0.55; Chi² = 15.76, df = 3 (P = 0.001); I² = 81%								
Test for overall effect: Z = 1.68 (P = 0.09)								
Test for subgroup differences: Chi² = 9.54, df = 2 (P = 0.008), I² = 79.0%								

Footnotes

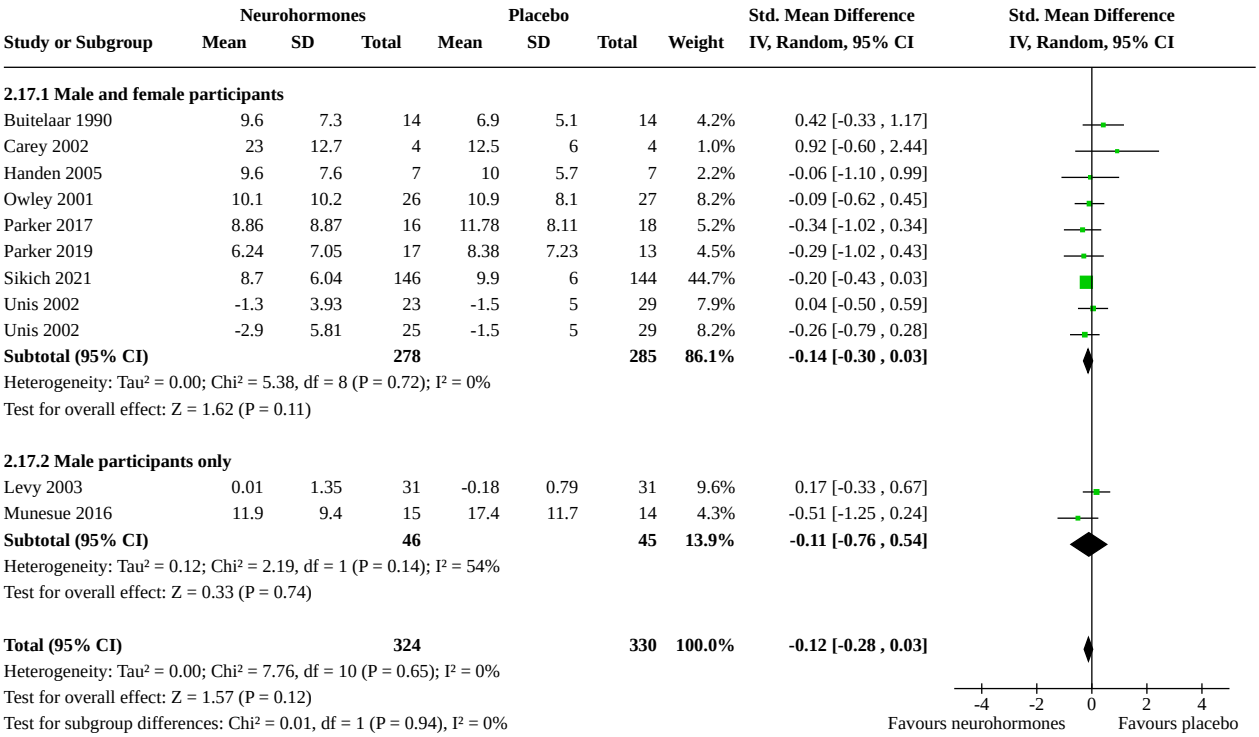
(1) Change from baseline (higher scores indicate higher quality of life)

Analysis 2.16. Comparison 2: Neurohormone versus placebo, Outcome 16: Tolerability/acceptability: loss to follow-up



Study or Subgroup	Neurohormones Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Anagnostou 2012	0	10	2	9	0.7%	0.18 [0.01 , 3.35]
Guastella 2015a	0	26	2	24	0.7%	0.19 [0.01 , 3.67]
Jacob 2022	60	163	55	158	68.0%	1.06 [0.79 , 1.42]
NCT01908205	5	30	1	30	1.3%	5.00 [0.62 , 40.28]
NCT02940574	1	21	1	18	0.8%	0.86 [0.06 , 12.75]
Owley 2001	0	28	0	28		Not estimable
Parker 2017	3	14	0	18	0.7%	8.87 [0.50 , 158.72]
Sikich 2013	1	12	0	13	0.6%	3.23 [0.14 , 72.46]
Sikich 2021	21	146	19	144	17.6%	1.09 [0.61 , 1.94]
Squassante 2018	1	39	1	25	0.8%	0.64 [0.04 , 9.79]
Squassante 2018	4	73	1	25	1.3%	1.37 [0.16 , 11.69]
Squassante 2018	2	32	1	25	1.1%	1.56 [0.15 , 16.27]
Takamitsu 2015a	1	10	1	10	0.8%	1.00 [0.07 , 13.87]
Umbricht 2017	1	18	0	19	0.6%	3.16 [0.14 , 72.84]
VanAndel 2022	4	19	4	19	3.9%	1.00 [0.29 , 3.43]
Yamasue 2020	3	53	1	53	1.2%	3.00 [0.32 , 27.93]
Total (95% CI)		**694**		**618**	**100.0%**	**1.10 [0.87 , 1.40]**
Total events:	107		89			
Heterogeneity: Tau² = 0.00; Chi² = 8.95, df = 14 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.80 (P = 0.43)						
Test for subgroup differences: Not applicable						

Analysis 2.17. Comparison 2: Neurohormone versus placebo, Outcome 17: Subgroup analyses: gender - irritability



Comparison 3. ADHD-related medications vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Irritability	10	400	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.40, -0.01]
3.1.1 Irritability: non-stimulant ADHD-related drugs	8	342	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.38, 0.05]
3.1.2 Irritability: stimulant ADHD-related drugs	2	58	Std. Mean Difference (IV, Random, 95% CI)	-0.45 [-0.97, 0.08]
3.2 Self-injury	1	16	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-1.63, 0.39]
3.3 Adverse effects: cardiovascular	3	114	Risk Ratio (IV, Random, 95% CI)	0.64 [0.16, 2.54]
3.3.1 Bradycardia	1	66	Risk Ratio (IV, Random, 95% CI)	0.36 [0.09, 1.37]
3.3.2 Tachycardia	2	48	Risk Ratio (IV, Random, 95% CI)	3.52 [0.44, 27.85]
3.4 Adverse effects: gastrointestinal	9		Risk Ratio (IV, Random, 95% CI)	Subtotals only

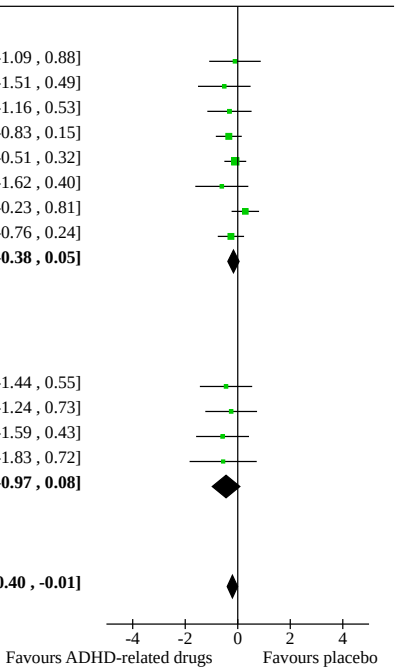
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.4.1 Constipation	5	220	Risk Ratio (IV, Random, 95% CI)	2.68 [1.61, 4.45]
3.4.2 Diarrhoea	6	426	Risk Ratio (IV, Random, 95% CI)	0.81 [0.46, 1.40]
3.4.3 Dry mouth	3	102	Risk Ratio (IV, Random, 95% CI)	5.92 [1.86, 18.81]
3.4.4 Nausea	5	239	Risk Ratio (IV, Random, 95% CI)	3.08 [1.51, 6.29]
3.4.5 Stomachache	2	86	Risk Ratio (IV, Random, 95% CI)	2.58 [1.10, 6.06]
3.4.6 Stomach or abdominal discomfort	6	504	Risk Ratio (IV, Random, 95% CI)	2.26 [1.41, 3.63]
3.4.7 Vomiting	4	347	Risk Ratio (IV, Random, 95% CI)	1.35 [0.81, 2.25]
3.5 Adverse effects: immune system	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.5.1 Fever	3	183	Risk Ratio (IV, Random, 95% CI)	0.27 [0.06, 1.27]
3.5.2 Influenza	1	97	Risk Ratio (IV, Random, 95% CI)	7.14 [0.38, 134.69]
3.5.3 Myalgia	2	115	Risk Ratio (IV, Random, 95% CI)	4.72 [0.56, 39.55]
3.5.4 Weakness	1	62	Risk Ratio (IV, Random, 95% CI)	3.20 [0.35, 29.10]
3.6 Adverse effects: metabolic (dichotomous)	9		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.6.1 Decreased appetite	9	511	Risk Ratio (IV, Random, 95% CI)	2.15 [1.55, 2.99]
3.6.2 Increased appetite	2	122	Risk Ratio (IV, Random, 95% CI)	0.67 [0.14, 3.34]
3.6.3 Increased energy	1	62	Risk Ratio (IV, Random, 95% CI)	1.60 [0.65, 3.95]
3.7 Adverse effects: neurological (dichotomous)	9		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.7.1 Aggression	5	365	Risk Ratio (IV, Random, 95% CI)	0.95 [0.58, 1.53]
3.7.2 Agitation	1	128	Risk Ratio (IV, Random, 95% CI)	0.95 [0.56, 1.60]
3.7.3 Dizziness	3	175	Risk Ratio (IV, Random, 95% CI)	2.17 [0.63, 7.53]
3.7.4 Drowsiness	4	186	Risk Ratio (IV, Random, 95% CI)	3.42 [1.54, 7.59]
3.7.5 Emotional / tearful	2	128	Risk Ratio (IV, Random, 95% CI)	6.32 [2.47, 16.18]
3.7.6 Fatigue	4	235	Risk Ratio (IV, Random, 95% CI)	3.73 [1.98, 7.03]
3.7.7 Headache	8	383	Risk Ratio (IV, Random, 95% CI)	1.63 [1.09, 2.44]
3.7.8 Hyperactivity	2	115	Risk Ratio (IV, Random, 95% CI)	0.68 [0.06, 7.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.7.9 Increased motor activity	1	66	Risk Ratio (IV, Random, 95% CI)	1.89 [0.48, 7.47]
3.7.10 Insomnia	7	411	Risk Ratio (IV, Random, 95% CI)	1.58 [1.01, 2.47]
3.7.11 Irritability	6	336	Risk Ratio (IV, Random, 95% CI)	1.61 [1.25, 2.07]
3.7.12 Motor tics	3	118	Risk Ratio (IV, Random, 95% CI)	2.33 [0.51, 10.69]
3.7.13 Nightmares	2	122	Risk Ratio (IV, Random, 95% CI)	1.48 [0.38, 5.75]
3.7.14 Repetitive behaviour	2	128	Risk Ratio (IV, Random, 95% CI)	1.59 [0.74, 3.39]
3.7.15 Restless	2	76	Risk Ratio (IV, Random, 95% CI)	1.52 [0.06, 40.44]
3.7.16 Sleep disturbance	2	84	Risk Ratio (IV, Random, 95% CI)	1.12 [0.54, 2.31]
3.7.17 Talking excessively	1	62	Risk Ratio (IV, Random, 95% CI)	0.24 [0.06, 1.01]
3.7.18 Waking	1	62	Risk Ratio (IV, Random, 95% CI)	1.60 [0.29, 8.92]
3.7.19 Tremor	1	16	Risk Ratio (IV, Random, 95% CI)	3.00 [0.14, 64.26]
3.8 Adverse effects: neurological (continuous)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.8.1 Drowsiness	1	8	Mean Difference (IV, Random, 95% CI)	4.80 [0.55, 9.05]
3.8.2 Decreased activity	1	8	Mean Difference (IV, Random, 95% CI)	2.00 [-2.66, 6.66]
3.9 Adverse effects: psychological (dichotomous)	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.9.1 Anxiety	5	252	Risk Ratio (IV, Random, 95% CI)	1.39 [0.74, 2.62]
3.9.2 Depression	3	152	Risk Ratio (IV, Random, 95% CI)	2.45 [1.12, 5.36]
3.9.3 Mood change	1	40	Risk Ratio (IV, Random, 95% CI)	13.00 [0.78, 216.39]
3.9.4 Self-injury	3	188	Risk Ratio (IV, Random, 95% CI)	1.67 [0.78, 3.58]
3.9.5 Silly behaviour	1	62	Risk Ratio (IV, Random, 95% CI)	0.64 [0.17, 2.45]
3.9.6 Social withdrawal	2	126	Risk Ratio (IV, Random, 95% CI)	2.28 [0.39, 13.37]
3.10 Adverse effects: respiratory	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.10.1 Cough	2	122	Risk Ratio (IV, Random, 95% CI)	0.81 [0.26, 2.46]
3.11 Adverse effects: skin	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.11.1 Rash	3	102	Risk Ratio (IV, Random, 95% CI)	2.21 [0.79, 6.16]
3.11.2 Skin picking	1	62	Risk Ratio (IV, Random, 95% CI)	0.36 [0.04, 3.23]
3.12 Adverse effects: urinary	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.12.1 Enuresis	2	122	Risk Ratio (IV, Random, 95% CI)	0.81 [0.19, 3.55]
3.13 Quality of life	1	54	Std. Mean Difference (IV, Random, 95% CI)	0.21 [-0.33, 0.75]
3.14 Tolerability/acceptability: loss to follow-up	9	380	Risk Ratio (IV, Random, 95% CI)	0.91 [0.50, 1.69]
3.14.1 ADHD-related drugs: loss to follow-up	9	380	Risk Ratio (IV, Random, 95% CI)	0.91 [0.50, 1.69]
3.15 Subgroup analyses: gender - irritability	9	291	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.48, -0.01]
3.15.1 Male participants only	2	17	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-1.50, 0.47]
3.15.2 Male and female participants	7	274	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.47, 0.01]
3.16 Subgroup analyses: age - irritability	9	293	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.48, -0.02]
3.16.1 Adults and children	1	9	Std. Mean Difference (IV, Random, 95% CI)	-0.48 [-1.83, 0.87]
3.16.2 Children only	8	284	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.48, -0.01]

Analysis 3.1. Comparison 3: ADHD-related medications vs placebo, Outcome 1: Irritability

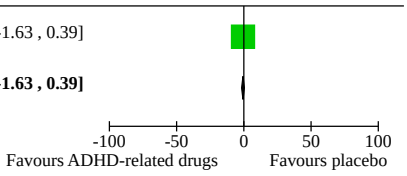
Study or Subgroup	Stimulant ADHD-related drugs Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.1.1 Irritability: non-stimulant ADHD-related drugs								
Arnold 2006	13.06	9.28	8	14.13	9.89	8	4.1%	-0.11 [-1.09 , 0.88]
Fankhauser 1992	0.36	0.37	8	0.55	0.33	8	3.9%	-0.51 [-1.51 , 0.49]
Handen 2008	16.36	9.3	11	19.27	8.4	11	5.5%	-0.32 [-1.16 , 0.53]
Handen 2015	10.31	7.87	32	12.95	7.43	32	16.0%	-0.34 [-0.83 , 0.15]
Harfterkamp 2014	14.5	9.26	43	15.4	9.8	46	22.6%	-0.09 [-0.51 , 0.32]
Jaselskis 1992	10.9	7.9	8	16.2	8.6	8	3.8%	-0.61 [-1.62 , 0.40]
NCT00498173	15.6	6.1	27	13.8	6.19	30	14.3%	0.29 [-0.23 , 0.81]
Scahill 2015	13.5	9.85	30	16.1	9.9	32	15.6%	-0.26 [-0.76 , 0.24]
Subtotal (95% CI)			**167**			**175**	**85.8%**	**-0.16 [-0.38 , 0.05]**
Heterogeneity: Tau² = 0.00; Chi² = 4.97, df = 7 (P = 0.66); I² = 0%								
Test for overall effect: Z = 1.50 (P = 0.13)								
3.1.2 Irritability: stimulant ADHD-related drugs								
Pearson 2013 (1)	8.2	8.1	8	12.6	10.4	8	3.9%	-0.45 [-1.44 , 0.55]
Pearson 2013 (2)	10	9.2	8	12.6	10.4	8	4.0%	-0.25 [-1.24 , 0.73]
Pearson 2013 (3)	7.2	6.9	8	12.6	10.4	8	3.9%	-0.58 [-1.59 , 0.43]
Quintana 1995	4	3.8	5	7.2	6.3	5	2.4%	-0.56 [-1.83 , 0.72]
Subtotal (95% CI)			**29**			**29**	**14.2%**	**-0.45 [-0.97 , 0.08]**
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 3 (P = 0.97); I² = 0%								
Test for overall effect: Z = 1.66 (P = 0.10)								
Total (95% CI)			**196**			**204**	**100.0%**	**-0.20 [-0.40 , -0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 6.17, df = 11 (P = 0.86); I² = 0%								
Test for overall effect: Z = 2.01 (P = 0.04)								
Test for subgroup differences: Chi² = 0.95, df = 1 (P = 0.33), I² = 0%								



Footnotes
(1) 0.35mg/kg Methylphenidate
(2) 0.21mg/kg Methylphenidate
(3) 0.48mg/kg Methylphenidate

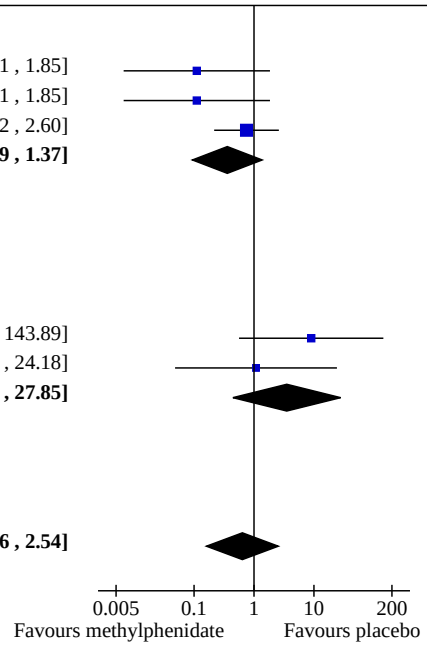
Analysis 3.2. Comparison 3: ADHD-related medications vs placebo, Outcome 2: Self-injury

Study or Subgroup	ADHD-related medications Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Arnold 2006	1.88	0.63	8	2.38	0.88	8	100.0%	-0.62 [-1.63 , 0.39]
Total (95% CI)			**8**			**8**	**100.0%**	**-0.62 [-1.63 , 0.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.20 (P = 0.23)								
Test for subgroup differences: Not applicable								



Analysis 3.3. Comparison 3: ADHD-related medications vs placebo, Outcome 3: Adverse effects: cardiovascular

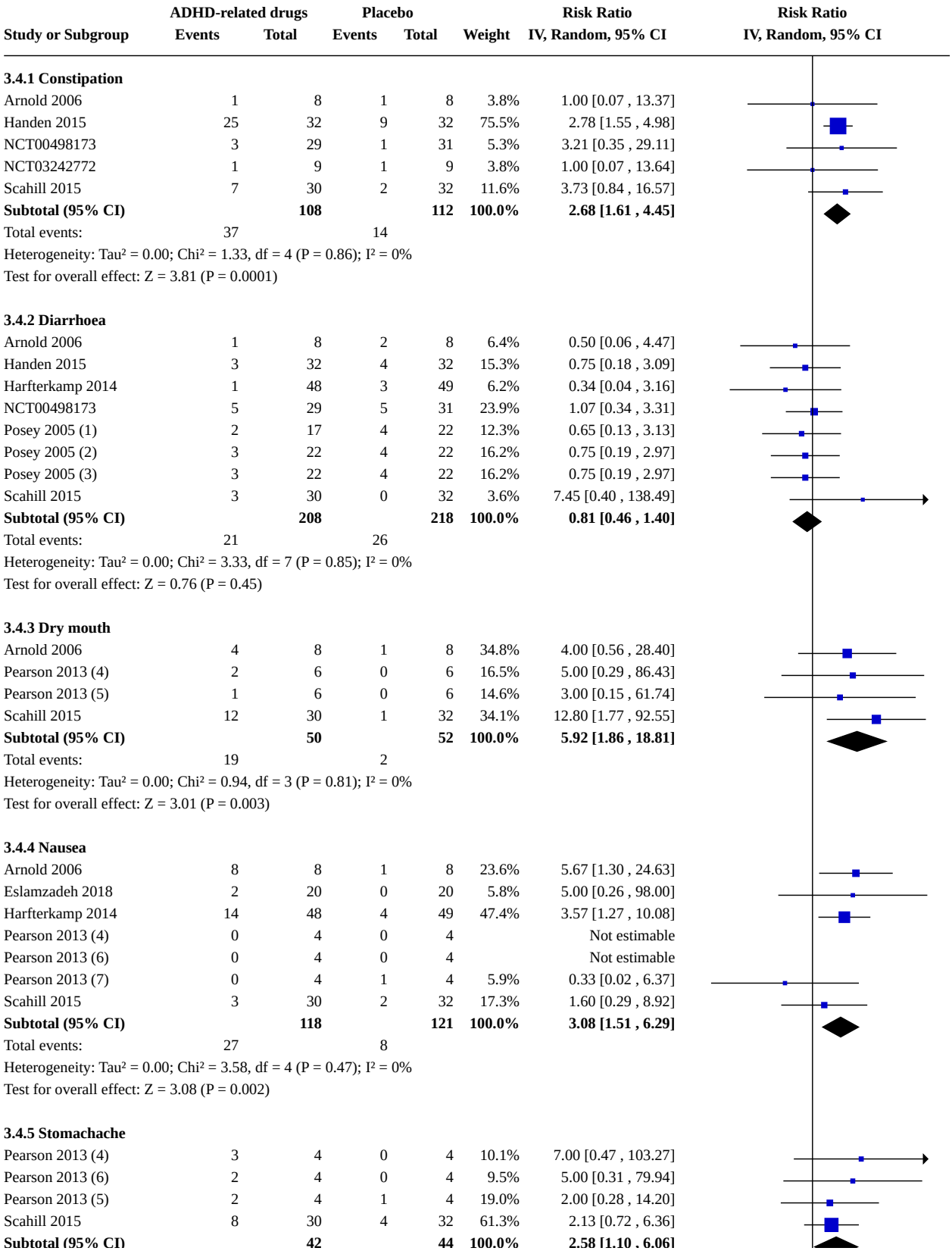
Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
3.3.1 Bradycardia						
Posey 2005 (1)	0	11	4	11	16.4%	0.11 [0.01 , 1.85]
Posey 2005 (2)	0	11	4	11	16.4%	0.11 [0.01 , 1.85]
Posey 2005 (3)	3	11	4	11	36.3%	0.75 [0.22 , 2.60]
Subtotal (95% CI)		**33**		**33**	**69.1%**	**0.36 [0.09 , 1.37]**
Total events:	3		12			
Heterogeneity: Tau² = 0.36; Chi² = 2.55, df = 2 (P = 0.28); I² = 22%						
Test for overall effect: Z = 1.50 (P = 0.13)						
3.3.2 Tachycardia						
Arnold 2006	4	8	0	8	16.7%	9.00 [0.56 , 143.89]
Pearson 2013 (4)	1	24	0	8	14.2%	1.08 [0.05 , 24.18]
Subtotal (95% CI)		**32**		**16**	**30.9%**	**3.52 [0.44 , 27.85]**
Total events:	5		0			
Heterogeneity: Tau² = 0.00; Chi² = 1.00, df = 1 (P = 0.32); I² = 0%						
Test for overall effect: Z = 1.19 (P = 0.23)						
Total (95% CI)		**65**		**49**	**100.0%**	**0.64 [0.16 , 2.54]**
Total events:	8		12			
Heterogeneity: Tau² = 0.96; Chi² = 6.64, df = 4 (P = 0.16); I² = 40%						
Test for overall effect: Z = 0.64 (P = 0.53)						
Test for subgroup differences: Chi² = 3.30, df = 1 (P = 0.07), I² = 69.7%						



Footnotes

(1) 0.500mg/kg Methylphenidate
(2) 0.250mg/kg Methylphenidate
(3) 0.125mg/kg Methylphenidate
(4) 0.35mg/kg Methylphenidate

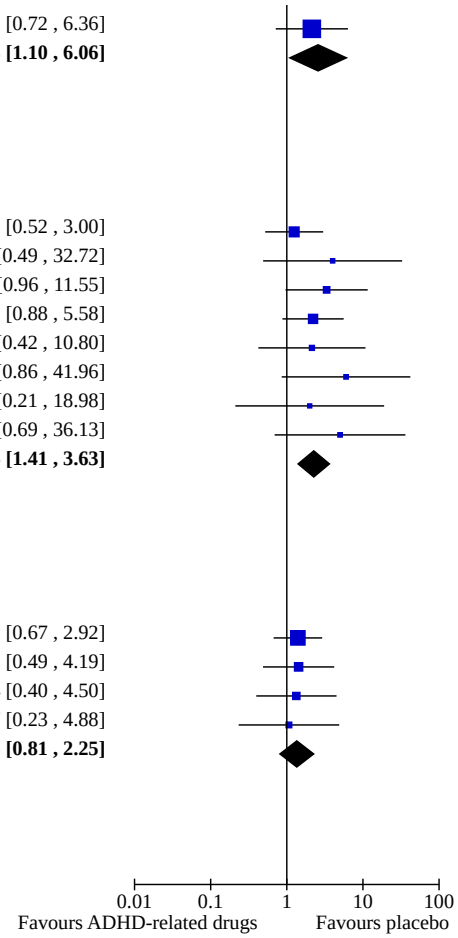
Analysis 3.4. Comparison 3: ADHD-related medications vs placebo, Outcome 4: Adverse effects: gastrointestinal



Study or Subgroup	ADHD-related drugs Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
3.4.1 Constipation						
Arnold 2006	1	8	1	8	3.8%	1.00 [0.07 , 13.37]
Handen 2015	25	32	9	32	75.5%	2.78 [1.55 , 4.98]
NCT00498173	3	29	1	31	5.3%	3.21 [0.35 , 29.11]
NCT03242772	1	9	1	9	3.8%	1.00 [0.07 , 13.64]
Scahill 2015	7	30	2	32	11.6%	3.73 [0.84 , 16.57]
Subtotal (95% CI)		**108**		**112**	**100.0%**	**2.68 [1.61 , 4.45]**
Total events:	37		14			
Heterogeneity: Tau² = 0.00; Chi² = 1.33, df = 4 (P = 0.86); I² = 0%						
Test for overall effect: Z = 3.81 (P = 0.0001)						
3.4.2 Diarrhoea						
Arnold 2006	1	8	2	8	6.4%	0.50 [0.06 , 4.47]
Handen 2015	3	32	4	32	15.3%	0.75 [0.18 , 3.09]
Harfterkamp 2014	1	48	3	49	6.2%	0.34 [0.04 , 3.16]
NCT00498173	5	29	5	31	23.9%	1.07 [0.34 , 3.31]
Posey 2005 (1)	2	17	4	22	12.3%	0.65 [0.13 , 3.13]
Posey 2005 (2)	3	22	4	22	16.2%	0.75 [0.19 , 2.97]
Posey 2005 (3)	3	22	4	22	16.2%	0.75 [0.19 , 2.97]
Scahill 2015	3	30	0	32	3.6%	7.45 [0.40 , 138.49]
Subtotal (95% CI)		**208**		**218**	**100.0%**	**0.81 [0.46 , 1.40]**
Total events:	21		26			
Heterogeneity: Tau² = 0.00; Chi² = 3.33, df = 7 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.76 (P = 0.45)						
3.4.3 Dry mouth						
Arnold 2006	4	8	1	8	34.8%	4.00 [0.56 , 28.40]
Pearson 2013 (4)	2	6	0	6	16.5%	5.00 [0.29 , 86.43]
Pearson 2013 (5)	1	6	0	6	14.6%	3.00 [0.15 , 61.74]
Scahill 2015	12	30	1	32	34.1%	12.80 [1.77 , 92.55]
Subtotal (95% CI)		**50**		**52**	**100.0%**	**5.92 [1.86 , 18.81]**
Total events:	19		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.94, df = 3 (P = 0.81); I² = 0%						
Test for overall effect: Z = 3.01 (P = 0.003)						
3.4.4 Nausea						
Arnold 2006	8	8	1	8	23.6%	5.67 [1.30 , 24.63]
Eslamzadeh 2018	2	20	0	20	5.8%	5.00 [0.26 , 98.00]
Harfterkamp 2014	14	48	4	49	47.4%	3.57 [1.27 , 10.08]
Pearson 2013 (4)	0	4	0	4		Not estimable
Pearson 2013 (6)	0	4	0	4		Not estimable
Pearson 2013 (7)	0	4	1	4	5.9%	0.33 [0.02 , 6.37]
Scahill 2015	3	30	2	32	17.3%	1.60 [0.29 , 8.92]
Subtotal (95% CI)		**118**		**121**	**100.0%**	**3.08 [1.51 , 6.29]**
Total events:	27		8			
Heterogeneity: Tau² = 0.00; Chi² = 3.58, df = 4 (P = 0.47); I² = 0%						
Test for overall effect: Z = 3.08 (P = 0.002)						
3.4.5 Stomachache						
Pearson 2013 (4)	3	4	0	4	10.1%	7.00 [0.47 , 103.27]
Pearson 2013 (6)	2	4	0	4	9.5%	5.00 [0.31 , 79.94]
Pearson 2013 (5)	2	4	1	4	19.0%	2.00 [0.28 , 14.20]
Scahill 2015	8	30	4	32	61.3%	2.13 [0.72 , 6.36]
Subtotal (95% CI)		**42**		**44**	**100.0%**	**2.58 [1.10 , 6.06]**

Analysis 3.4. (Continued)

Scahill 2015	8	30	4	32	61.3%	2.13 [0.72 , 6.36]
Subtotal (95% CI)		**42**		**44**	**100.0%**	**2.58 [1.10 , 6.06]**
Total events:	15		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 3 (P = 0.82); I² = 0%						
Test for overall effect: Z = 2.17 (P = 0.03)						
3.4.6 Stomach or abdominal discomfort						
Arnold 2006	5	8	4	8	29.3%	1.25 [0.52 , 3.00]
Eslamzadeh 2018	4	20	1	20	5.1%	4.00 [0.49 , 32.72]
Handen 2015	10	64	3	64	14.6%	3.33 [0.96 , 11.55]
Harfterkamp 2014	13	96	6	98	26.3%	2.21 [0.88 , 5.58]
NCT00498173	4	29	2	31	8.6%	2.14 [0.42 , 10.80]
Posey 2005 (1)	6	11	1	11	6.0%	6.00 [0.86 , 41.96]
Posey 2005 (2)	2	11	1	11	4.4%	2.00 [0.21 , 18.98]
Posey 2005 (3)	5	11	1	11	5.8%	5.00 [0.69 , 36.13]
Subtotal (95% CI)		**250**		**254**	**100.0%**	**2.26 [1.41 , 3.63]**
Total events:	49		19			
Heterogeneity: Tau² = 0.00; Chi² = 4.02, df = 7 (P = 0.78); I² = 0%						
Test for overall effect: Z = 3.37 (P = 0.0008)						
3.4.7 Vomiting						
Handen 2015	14	64	10	64	48.5%	1.40 [0.67 , 2.92]
Harfterkamp 2014	7	48	5	49	22.5%	1.43 [0.49 , 4.19]
NCT00498173	5	29	4	31	17.7%	1.34 [0.40 , 4.50]
Scahill 2015	3	30	3	32	11.3%	1.07 [0.23 , 4.88]
Subtotal (95% CI)		**171**		**176**	**100.0%**	**1.35 [0.81 , 2.25]**
Total events:	29		22			
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 3 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.16 (P = 0.25)						
Test for subgroup differences: Chi² = 0.00, df = 6 (P < 0.00001), I² = 0%						

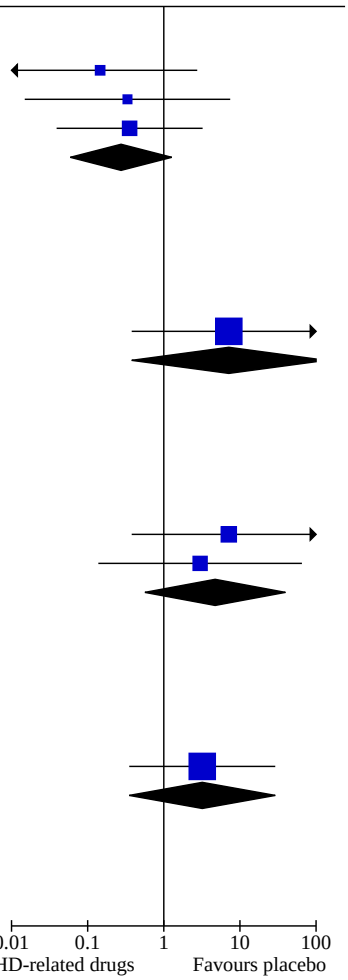


Footnotes

(1) 0.500mg/kg Methylphenidate
(2) 0.125mg/kg Methylphenidate
(3) 0.250mg/kg Methylphenidate
(4) 0.35mg/kg Methylphenidate
(5) 0.21mg/kg Methylphenidate
(6) 0.48mg/kg Methylphenidate
(7) 0.21mg/kg methylphenidate

Analysis 3.5. Comparison 3: ADHD-related medications vs placebo, Outcome 5: Adverse effects: immune system

Study or Subgroup	ADHD-related drugs Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
3.5.1 Fever						
Harfterkamp 2014	0	48	3	49	27.3%	0.15 [0.01 , 2.75]
Pearson 2013 (1)	0	12	1	12	24.4%	0.33 [0.01 , 7.45]
Scahill 2015	1	30	3	32	48.3%	0.36 [0.04 , 3.23]
Subtotal (95% CI)		**90**		**93**	**100.0%**	**0.27 [0.06 , 1.27]**
Total events:	1		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 2 (P = 0.88); I² = 0%						
Test for overall effect: Z = 1.65 (P = 0.10)						
3.5.2 Influenza						
Harfterkamp 2014	3	48	0	49	100.0%	7.14 [0.38 , 134.69]
Subtotal (95% CI)		**48**		**49**	**100.0%**	**7.14 [0.38 , 134.69]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
3.5.3 Myalgia						
Harfterkamp 2014	3	48	0	49	52.3%	7.14 [0.38 , 134.69]
NCT03242772	1	9	0	9	47.7%	3.00 [0.14 , 65.16]
Subtotal (95% CI)		**57**		**58**	**100.0%**	**4.72 [0.56 , 39.55]**
Total events:	4		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%						
Test for overall effect: Z = 1.43 (P = 0.15)						
3.5.4 Weakness						
Scahill 2015	3	30	1	32	100.0%	3.20 [0.35 , 29.10]
Subtotal (95% CI)		**30**		**32**	**100.0%**	**3.20 [0.35 , 29.10]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						

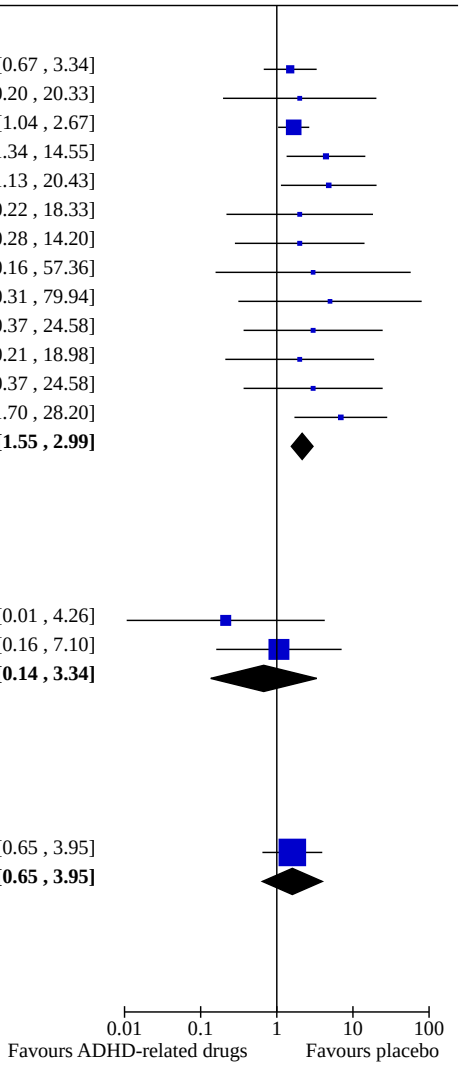


Footnotes

(1) 0.21mg/kg Methylphenidate

Analysis 3.6. Comparison 3: ADHD-related medications vs placebo, Outcome 6: Adverse effects: metabolic (dichotomous)

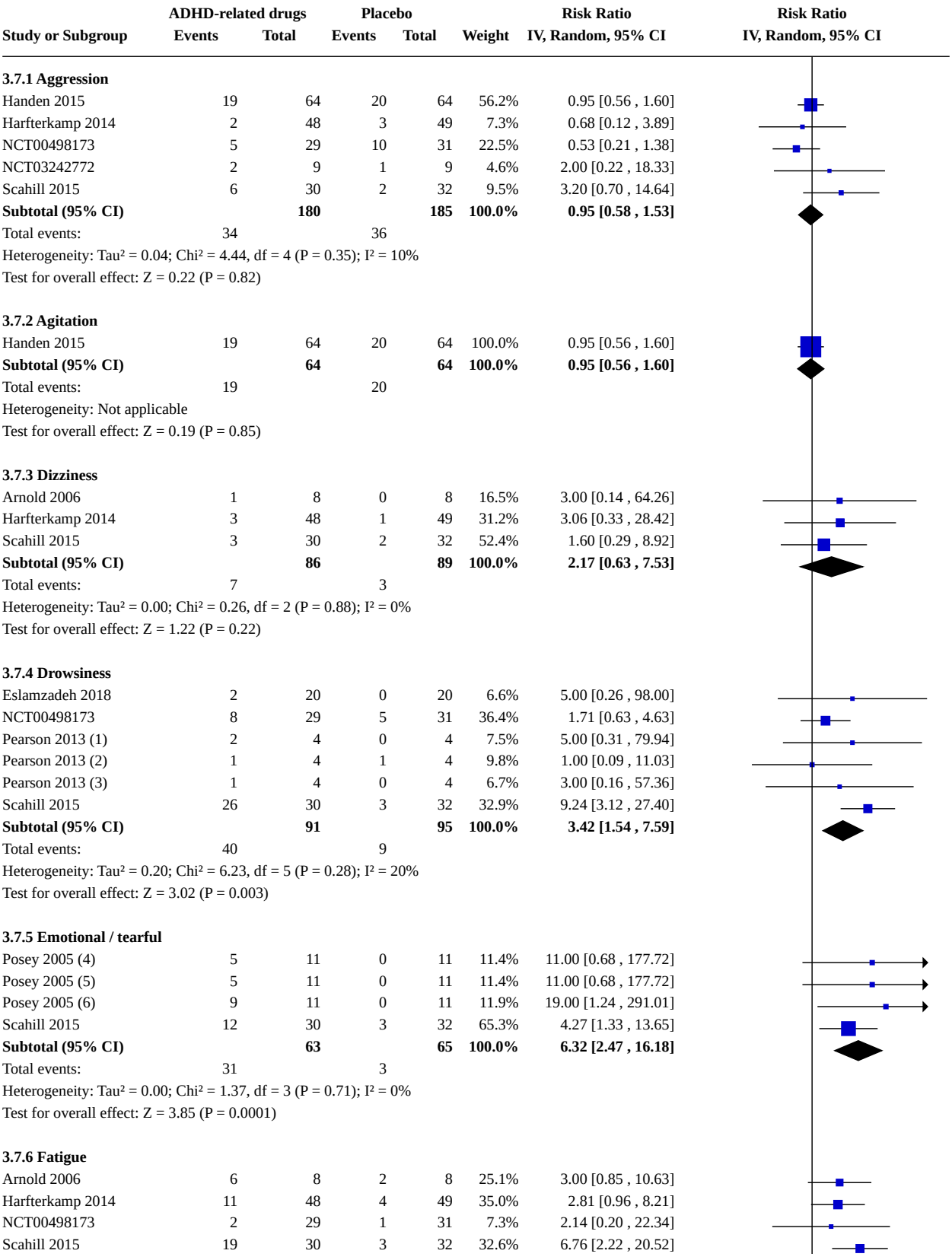
Study or Subgroup	ADHD-related drugs Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
3.6.1 Decreased appetite						
Arnold 2006	6	8	4	8	16.8%	1.50 [0.67 , 3.34]
Eslamzadeh 2018	2	20	1	20	2.0%	2.00 [0.20 , 20.33]
Handen 2015	30	64	18	64	48.5%	1.67 [1.04 , 2.67]
Harfterkamp 2014	13	48	3	49	7.6%	4.42 [1.34 , 14.55]
NCT00498173	9	29	2	31	5.1%	4.81 [1.13 , 20.43]
NCT03242772	2	9	1	9	2.2%	2.00 [0.22 , 18.33]
Pearson 2013 (1)	2	4	1	4	2.8%	2.00 [0.28 , 14.20]
Pearson 2013 (2)	1	4	0	4	1.2%	3.00 [0.16 , 57.36]
Pearson 2013 (3)	2	4	0	4	1.4%	5.00 [0.31 , 79.94]
Posey 2005 (4)	3	11	1	11	2.4%	3.00 [0.37 , 24.58]
Posey 2005 (5)	2	11	1	11	2.1%	2.00 [0.21 , 18.98]
Posey 2005 (6)	3	11	1	11	2.4%	3.00 [0.37 , 24.58]
Scahill 2015	13	30	2	32	5.5%	6.93 [1.70 , 28.20]
Subtotal (95% CI)		**253**		**258**	**100.0%**	**2.15 [1.55 , 2.99]**
Total events:	88		35			
Heterogeneity: Tau² = 0.00; Chi² = 7.80, df = 12 (P = 0.80); I² = 0%						
Test for overall effect: Z = 4.59 (P < 0.00001)						
3.6.2 Increased appetite						
NCT00498173	0	29	2	31	28.6%	0.21 [0.01 , 4.26]
Scahill 2015	2	30	2	32	71.4%	1.07 [0.16 , 7.10]
Subtotal (95% CI)		**59**		**63**	**100.0%**	**0.67 [0.14 , 3.34]**
Total events:	2		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 1 (P = 0.37); I² = 0%						
Test for overall effect: Z = 0.48 (P = 0.63)						
3.6.3 Increased energy						
Scahill 2015	9	30	6	32	100.0%	1.60 [0.65 , 3.95]
Subtotal (95% CI)		**30**		**32**	**100.0%**	**1.60 [0.65 , 3.95]**
Total events:	9		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%						



Footnotes

(1) 0.48mg/kg methylphenidate
(2) 0.35mg/kg Methylphenidate
(3) 0.21mg/kg Methylphenidate
(4) 0.125mg/kg Methylphenidate
(5) 0.500mg/kg Methylphenidate
(6) 0.250mg/kg Methylphenidate

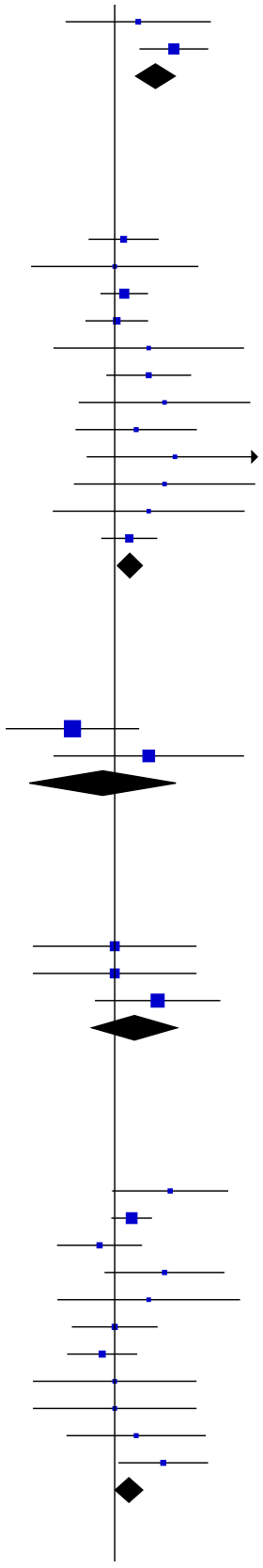
Analysis 3.7. Comparison 3: ADHD-related medications vs placebo, Outcome 7: Adverse effects: neurological (dichotomous)



Study or Subgroup	ADHD-related drugs Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
3.7.1 Aggression						
Handen 2015	19	64	20	64	56.2%	0.95 [0.56 , 1.60]
Harfterkamp 2014	2	48	3	49	7.3%	0.68 [0.12 , 3.89]
NCT00498173	5	29	10	31	22.5%	0.53 [0.21 , 1.38]
NCT03242772	2	9	1	9	4.6%	2.00 [0.22 , 18.33]
Scahill 2015	6	30	2	32	9.5%	3.20 [0.70 , 14.64]
Subtotal (95% CI)		**180**		**185**	**100.0%**	**0.95 [0.58 , 1.53]**
Total events:	34		36			
Heterogeneity: Tau² = 0.04; Chi² = 4.44, df = 4 (P = 0.35); I² = 10%						
Test for overall effect: Z = 0.22 (P = 0.82)						
3.7.2 Agitation						
Handen 2015	19	64	20	64	100.0%	0.95 [0.56 , 1.60]
Subtotal (95% CI)		**64**		**64**	**100.0%**	**0.95 [0.56 , 1.60]**
Total events:	19		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.19 (P = 0.85)						
3.7.3 Dizziness						
Arnold 2006	1	8	0	8	16.5%	3.00 [0.14 , 64.26]
Harfterkamp 2014	3	48	1	49	31.2%	3.06 [0.33 , 28.42]
Scahill 2015	3	30	2	32	52.4%	1.60 [0.29 , 8.92]
Subtotal (95% CI)		**86**		**89**	**100.0%**	**2.17 [0.63 , 7.53]**
Total events:	7		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 2 (P = 0.88); I² = 0%						
Test for overall effect: Z = 1.22 (P = 0.22)						
3.7.4 Drowsiness						
Eslamzadeh 2018	2	20	0	20	6.6%	5.00 [0.26 , 98.00]
NCT00498173	8	29	5	31	36.4%	1.71 [0.63 , 4.63]
Pearson 2013 (1)	2	4	0	4	7.5%	5.00 [0.31 , 79.94]
Pearson 2013 (2)	1	4	1	4	9.8%	1.00 [0.09 , 11.03]
Pearson 2013 (3)	1	4	0	4	6.7%	3.00 [0.16 , 57.36]
Scahill 2015	26	30	3	32	32.9%	9.24 [3.12 , 27.40]
Subtotal (95% CI)		**91**		**95**	**100.0%**	**3.42 [1.54 , 7.59]**
Total events:	40		9			
Heterogeneity: Tau² = 0.20; Chi² = 6.23, df = 5 (P = 0.28); I² = 20%						
Test for overall effect: Z = 3.02 (P = 0.003)						
3.7.5 Emotional / tearful						
Posey 2005 (4)	5	11	0	11	11.4%	11.00 [0.68 , 177.72]
Posey 2005 (5)	5	11	0	11	11.4%	11.00 [0.68 , 177.72]
Posey 2005 (6)	9	11	0	11	11.9%	19.00 [1.24 , 291.01]
Scahill 2015	12	30	3	32	65.3%	4.27 [1.33 , 13.65]
Subtotal (95% CI)		**63**		**65**	**100.0%**	**6.32 [2.47 , 16.18]**
Total events:	31		3			
Heterogeneity: Tau² = 0.00; Chi² = 1.37, df = 3 (P = 0.71); I² = 0%						
Test for overall effect: Z = 3.85 (P = 0.0001)						
3.7.6 Fatigue						
Arnold 2006	6	8	2	8	25.1%	3.00 [0.85 , 10.63]
Harfterkamp 2014	11	48	4	49	35.0%	2.81 [0.96 , 8.21]
NCT00498173	2	29	1	31	7.3%	2.14 [0.20 , 22.34]
Scahill 2015	19	30	3	32	32.6%	6.76 [2.22 , 20.52]

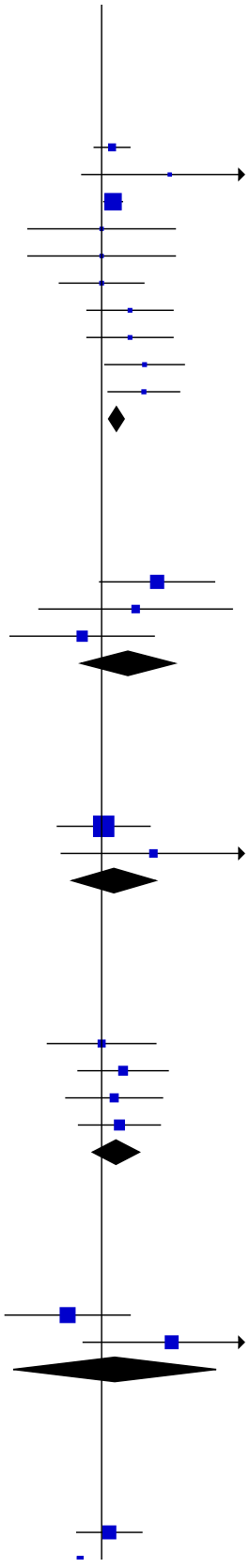
Analysis 3.7. (Continued)

NCT00498173	2	29	1	31	7.3%	2.14 [0.20 , 22.34]
Scahill 2015	19	30	3	32	32.6%	6.76 [2.22 , 20.52]
Subtotal (95% CI)		**115**		**120**	**100.0%**	**3.73 [1.98 , 7.03]**
Total events:	38		10			
Heterogeneity: Tau² = 0.00; Chi² = 1.70, df = 3 (P = 0.64); I² = 0%						
Test for overall effect: Z = 4.06 (P < 0.0001)						
3.7.7 Headache						
Arnold 2006	4	8	3	8	12.6%	1.33 [0.43 , 4.13]
Eslamzadeh 2018	1	20	1	20	2.2%	1.00 [0.07 , 14.90]
Harfterkamp 2014	12	48	9	49	27.5%	1.36 [0.63 , 2.93]
NCT00498173	6	29	6	31	15.8%	1.07 [0.39 , 2.94]
NCT03242772	1	9	0	9	1.7%	3.00 [0.14 , 65.16]
Pearson 2013 (3)	4	4	1	4	8.6%	3.00 [0.76 , 11.81]
Pearson 2013 (2)	2	4	0	4	2.1%	5.00 [0.31 , 79.94]
Pearson 2013 (1)	2	4	1	4	4.2%	2.00 [0.28 , 14.20]
Posey 2005 (5)	3	11	0	11	2.0%	7.00 [0.40 , 121.39]
Posey 2005 (4)	2	11	0	11	1.9%	5.00 [0.27 , 93.55]
Posey 2005 (6)	1	11	0	11	1.7%	3.00 [0.14 , 66.53]
Scahill 2015	9	30	6	32	19.7%	1.60 [0.65 , 3.95]
Subtotal (95% CI)		**189**		**194**	**100.0%**	**1.63 [1.09 , 2.44]**
Total events:	47		27			
Heterogeneity: Tau² = 0.00; Chi² = 4.42, df = 11 (P = 0.96); I² = 0%						
Test for overall effect: Z = 2.38 (P = 0.02)						
3.7.8 Hyperactivity						
Harfterkamp 2014	1	48	4	49	60.4%	0.26 [0.03 , 2.20]
NCT03242772	1	9	0	9	39.6%	3.00 [0.14 , 65.16]
Subtotal (95% CI)		**57**		**58**	**100.0%**	**0.68 [0.06 , 7.20]**
Total events:	2		4			
Heterogeneity: Tau² = 1.20; Chi² = 1.65, df = 1 (P = 0.20); I² = 39%						
Test for overall effect: Z = 0.32 (P = 0.75)						
3.7.9 Increased motor activity						
Posey 2005 (5)	1	11	1	11	27.0%	1.00 [0.07 , 14.05]
Posey 2005 (6)	1	11	1	11	27.0%	1.00 [0.07 , 14.05]
Posey 2005 (4)	4	11	1	11	46.0%	4.00 [0.53 , 30.33]
Subtotal (95% CI)		**33**		**33**	**100.0%**	**1.89 [0.48 , 7.47]**
Total events:	6		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 2 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.91 (P = 0.36)						
3.7.10 Insomnia						
Arnold 2006	6	8	1	8	5.4%	6.00 [0.92 , 39.18]
Handen 2015	19	64	11	64	35.6%	1.73 [0.90 , 3.33]
Harfterkamp 2014	3	48	5	49	9.8%	0.61 [0.15 , 2.42]
NCT03242772	5	9	1	9	5.1%	5.00 [0.72 , 34.73]
Pearson 2013 (2)	1	4	0	4	2.2%	3.00 [0.16 , 57.36]
Pearson 2013 (1)	2	4	2	4	9.6%	1.00 [0.25 , 4.00]
Pearson 2013 (3)	2	4	3	4	14.0%	0.67 [0.22 , 2.07]
Posey 2005 (5)	1	11	1	11	2.8%	1.00 [0.07 , 14.05]
Posey 2005 (4)	1	11	1	11	2.8%	1.00 [0.07 , 14.05]
Posey 2005 (6)	2	11	1	11	3.8%	2.00 [0.21 , 18.98]
Scahill 2015	9	30	2	32	8.9%	4.80 [1.13 , 20.44]
Subtotal (95% CI)		**204**		**207**	**100.0%**	**1.58 [1.01 , 2.47]**
Total events:	51		28			
Heterogeneity: Tau² = 0.03; Chi² = 10.56, df = 10 (P = 0.39); I² = 5%						



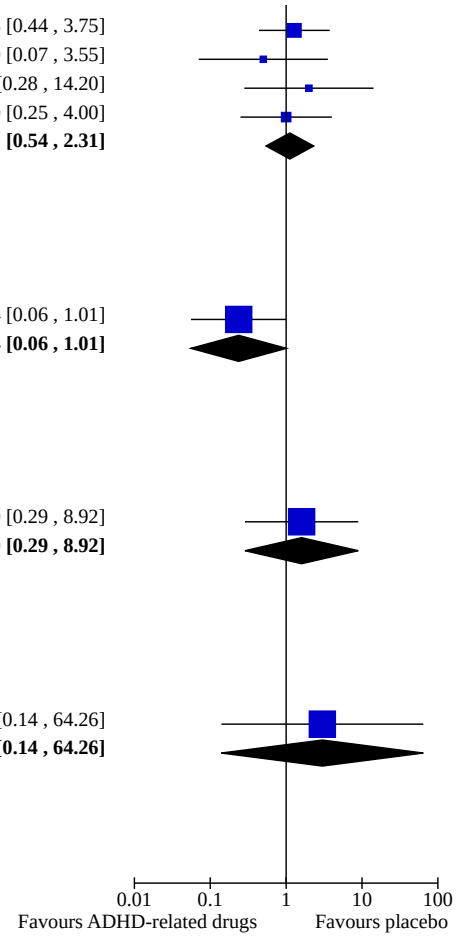
Analysis 3.7. (Continued)

Total events:	51		28			
Heterogeneity: Tau² = 0.03; Chi² = 10.56, df = 10 (P = 0.39); I² = 5%						
Test for overall effect: Z = 2.02 (P = 0.04)						
3.7.11 Irritability						
Arnold 2006	7	8	5	8	17.8%	1.40 [0.77 , 2.54]
Eslamzadeh 2018	4	20	0	20	0.8%	9.00 [0.52 , 156.91]
Handen 2015	42	64	29	64	61.2%	1.45 [1.05 , 2.00]
Pearson 2013 (3)	1	4	1	4	1.1%	1.00 [0.09 , 11.03]
Pearson 2013 (1)	1	4	1	4	1.1%	1.00 [0.09 , 11.03]
Pearson 2013 (2)	2	4	2	4	3.3%	1.00 [0.25 , 4.00]
Posey 2005 (4)	5	11	2	11	3.2%	2.50 [0.61 , 10.25]
Posey 2005 (5)	5	11	2	11	3.2%	2.50 [0.61 , 10.25]
Posey 2005 (6)	8	11	2	11	3.7%	4.00 [1.08 , 14.75]
Scahill 2015	11	30	3	32	4.6%	3.91 [1.21 , 12.67]
Subtotal (95% CI)		**167**		**169**	**100.0%**	**1.61 [1.25 , 2.07]**
Total events:	86		47			
Heterogeneity: Tau² = 0.00; Chi² = 7.58, df = 9 (P = 0.58); I² = 0%						
Test for overall effect: Z = 3.71 (P = 0.0002)						
3.7.12 Motor tics						
Arnold 2006	6	8	1	8	46.4%	6.00 [0.92 , 39.18]
Eslamzadeh 2018	1	20	0	20	20.4%	3.00 [0.13 , 69.52]
Scahill 2015	1	30	2	32	33.2%	0.53 [0.05 , 5.58]
Subtotal (95% CI)		**58**		**60**	**100.0%**	**2.33 [0.51 , 10.69]**
Total events:	8		3			
Heterogeneity: Tau² = 0.38; Chi² = 2.51, df = 2 (P = 0.28); I² = 20%						
Test for overall effect: Z = 1.09 (P = 0.28)						
3.7.13 Nightmares						
NCT00498173	3	29	3	31	79.6%	1.07 [0.23 , 4.88]
Scahill 2015	2	30	0	32	20.4%	5.32 [0.27 , 106.54]
Subtotal (95% CI)		**59**		**63**	**100.0%**	**1.48 [0.38 , 5.75]**
Total events:	5		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 0.57 (P = 0.57)						
3.7.14 Repetitive behaviour						
Posey 2005 (4)	2	11	2	11	18.4%	1.00 [0.17 , 5.89]
Posey 2005 (6)	4	11	2	11	26.5%	2.00 [0.46 , 8.76]
Posey 2005 (5)	3	11	2	11	23.1%	1.50 [0.31 , 7.30]
Scahill 2015	5	30	3	32	32.1%	1.78 [0.46 , 6.80]
Subtotal (95% CI)		**63**		**65**	**100.0%**	**1.59 [0.74 , 3.39]**
Total events:	14		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.39, df = 3 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.19 (P = 0.23)						
3.7.15 Restless						
Arnold 2006	1	8	3	8	54.8%	0.33 [0.04 , 2.56]
NCT00498173	4	29	0	31	45.2%	9.60 [0.54 , 170.84]
Subtotal (95% CI)		**37**		**39**	**100.0%**	**1.52 [0.06 , 40.44]**
Total events:	5		3			
Heterogeneity: Tau² = 4.03; Chi² = 3.48, df = 1 (P = 0.06); I² = 71%						
Test for overall effect: Z = 0.25 (P = 0.80)						
3.7.16 Sleep disturbance						
NCT00498173	6	29	5	31	45.5%	1.28 [0.44 , 3.75]
Pearson 2013 (2)	1	4	2	4	13.6%	0.50 [0.07 , 3.55]



Analysis 3.7. (Continued)

NCT00498173	6	29	5	31	45.5%	1.28 [0.44 , 3.75]
Pearson 2013 (2)	1	4	2	4	13.6%	0.50 [0.07 , 3.55]
Pearson 2013 (3)	2	4	1	4	13.6%	2.00 [0.28 , 14.20]
Pearson 2013 (1)	2	4	2	4	27.3%	1.00 [0.25 , 4.00]
Subtotal (95% CI)		**41**		**43**	**100.0%**	**1.12 [0.54 , 2.31]**
Total events:	11		10			
Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 3 (P = 0.78); I² = 0%						
Test for overall effect: Z = 0.31 (P = 0.76)						
3.7.17 Talking excessively						
Scahill 2015	2	30	9	32	100.0%	0.24 [0.06 , 1.01]
Subtotal (95% CI)		**30**		**32**	**100.0%**	**0.24 [0.06 , 1.01]**
Total events:	2		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.95 (P = 0.05)						
3.7.18 Waking						
Scahill 2015	3	30	2	32	100.0%	1.60 [0.29 , 8.92]
Subtotal (95% CI)		**30**		**32**	**100.0%**	**1.60 [0.29 , 8.92]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
3.7.19 Tremor						
Arnold 2006	1	8	0	8	100.0%	3.00 [0.14 , 64.26]
Subtotal (95% CI)		**8**		**8**	**100.0%**	**3.00 [0.14 , 64.26]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
Test for subgroup differences: Chi² = 0.00, df = 18 (P < 0.00001), I² = 0%						

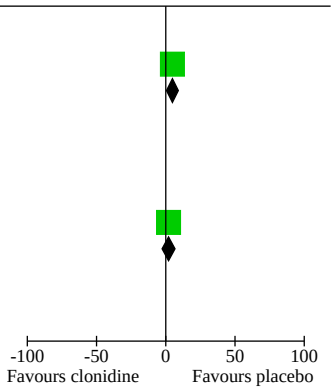


Footnotes

(1) 0.48mg/kg Methylphenidate
(2) 0.21mg/kg Methylphenidate
(3) 0.35mg/kg Methylphenidate
(4) 0.125mg/kg Methylphenidate
(5) 0.500mg/kg Methylphenidate
(6) 0.250mg/kg Methylphenidate

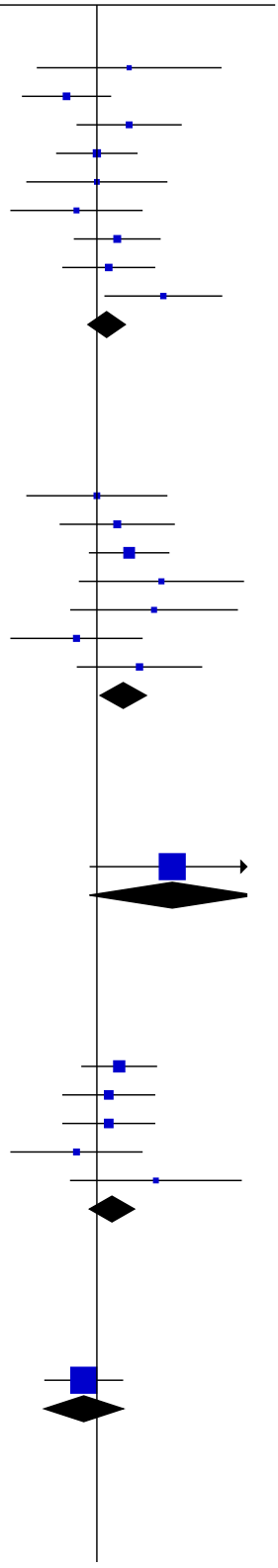
Analysis 3.8. Comparison 3: ADHD-related medications vs placebo, Outcome 8: Adverse effects: neurological (continuous)

Study or Subgroup	Clonidine Mean	Clonidine SD	Clonidine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
3.8.1 Drowsiness								
Jaselskis 1992	5.4	4.2	4	0.6	1.1	4	100.0%	4.80 [0.55 , 9.05]
Subtotal (95% CI)			**4**			**4**	**100.0%**	**4.80 [0.55 , 9.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.21 (P = 0.03)								
3.8.2 Decreased activity								
Jaselskis 1992	4.6	3.6	4	2.6	3.1	4	100.0%	2.00 [-2.66 , 6.66]
Subtotal (95% CI)			**4**			**4**	**100.0%**	**2.00 [-2.66 , 6.66]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.84 (P = 0.40)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%								



Analysis 3.9. Comparison 3: ADHD-related medications vs placebo, Outcome 9: Adverse effects: psychological (dichotomous)

Study or Subgroup	ADHD-related drugs Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
3.9.1 Anxiety						
Eslamzadeh 2018	1	20	0	20	3.9%	3.00 [0.13 , 69.52]
NCT00498173	2	29	6	31	14.9%	0.36 [0.08 , 1.63]
Pearson 2013 (1)	3	4	1	4	11.2%	3.00 [0.50 , 17.95]
Pearson 2013 (2)	2	4	2	4	17.4%	1.00 [0.25 , 4.00]
Pearson 2013 (3)	1	4	1	4	6.5%	1.00 [0.09 , 11.03]
Posey 2005 (4)	1	11	2	11	7.4%	0.50 [0.05 , 4.75]
Posey 2005 (5)	4	11	2	11	15.6%	2.00 [0.46 , 8.76]
Posey 2005 (6)	3	11	2	11	13.9%	1.50 [0.31 , 7.30]
Scahill 2015	9	30	1	32	9.1%	9.60 [1.29 , 71.29]
Subtotal (95% CI)		**124**		**128**	**100.0%**	**1.39 [0.74 , 2.62]**
Total events:	26		17			
Heterogeneity: Tau² = 0.10; Chi² = 8.92, df = 8 (P = 0.35); I² = 10%						
Test for overall effect: Z = 1.03 (P = 0.30)						
3.9.2 Depression						
Pearson 2013 (7)	1	4	1	4	10.6%	1.00 [0.09 , 11.03]
Pearson 2013 (2)	2	4	1	4	15.9%	2.00 [0.28 , 14.20]
Pearson 2013 (1)	4	4	1	4	32.6%	3.00 [0.76 , 11.81]
Posey 2005 (5)	4	11	0	11	7.8%	9.00 [0.54 , 149.50]
Posey 2005 (4)	3	11	0	11	7.5%	7.00 [0.40 , 121.39]
Posey 2005 (6)	1	11	2	11	12.1%	0.50 [0.05 , 4.75]
Scahill 2015	4	30	1	32	13.4%	4.27 [0.51 , 36.05]
Subtotal (95% CI)		**75**		**77**	**100.0%**	**2.45 [1.12 , 5.36]**
Total events:	19		6			
Heterogeneity: Tau² = 0.00; Chi² = 4.18, df = 6 (P = 0.65); I² = 0%						
Test for overall effect: Z = 2.25 (P = 0.02)						
3.9.3 Mood change						
Eslamzadeh 2018	6	20	0	20	100.0%	13.00 [0.78 , 216.39]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**13.00 [0.78 , 216.39]**
Total events:	6		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.79 (P = 0.07)						
3.9.4 Self-injury						
NCT00498173	6	29	3	31	35.0%	2.14 [0.59 , 7.77]
Posey 2005 (5)	3	11	2	11	23.3%	1.50 [0.31 , 7.30]
Posey 2005 (4)	3	11	2	11	23.3%	1.50 [0.31 , 7.30]
Posey 2005 (6)	1	11	2	11	11.5%	0.50 [0.05 , 4.75]
Scahill 2015	3	30	0	32	6.8%	7.45 [0.40 , 138.49]
Subtotal (95% CI)		**92**		**96**	**100.0%**	**1.67 [0.78 , 3.58]**
Total events:	16		9			
Heterogeneity: Tau² = 0.00; Chi² = 2.29, df = 4 (P = 0.68); I² = 0%						
Test for overall effect: Z = 1.32 (P = 0.19)						
3.9.5 Silly behaviour						
Scahill 2015	3	30	5	32	100.0%	0.64 [0.17 , 2.45]
Subtotal (95% CI)		**30**		**32**	**100.0%**	**0.64 [0.17 , 2.45]**
Total events:	3		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.51)						
3.9.6 Social withdrawal						



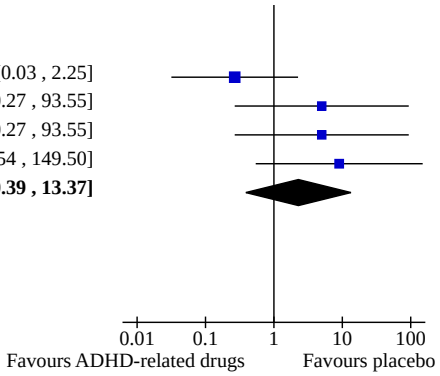
Analysis 3.9. (Continued)

3.9.6 Social withdrawal						
NCT00498173	1	29	4	31	31.6%	0.27 [0.03 , 2.25]
Posey 2005 (6)	2	11	0	11	22.4%	5.00 [0.27 , 93.55]
Posey 2005 (5)	2	11	0	11	22.4%	5.00 [0.27 , 93.55]
Posey 2005 (4)	4	11	0	11	23.6%	9.00 [0.54 , 149.50]
Subtotal (95% CI)		**62**		**64**	**100.0%**	**2.28 [0.39 , 13.37]**
Total events:	9		4			

Heterogeneity: Tau² = 1.40; Chi² = 5.27, df = 3 (P = 0.15); I² = 43%

Test for overall effect: Z = 0.91 (P = 0.36)

Test for subgroup differences: Chi² = 0.00, df = 5 (P < 0.00001), I² = 0%



Footnotes

(1) 0.35mg/kg Methylphenidate
(2) 0.21mg/kg Methylphenidate
(3) 0.48mg/kg Methylphenidate
(4) 0.250mg/kg Methylphenidate
(5) 0.500mg/kg Methylphenidate
(6) 0.125mg/kg Methylphenidate
(7) 0.48mg/kg Methylphenidate

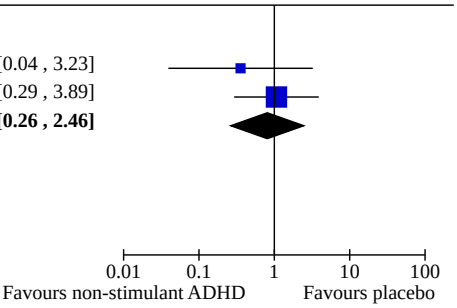
Analysis 3.10. Comparison 3: ADHD-related medications vs placebo, Outcome 10: Adverse effects: respiratory

	Non-stimulant ADHD		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
3.10.1 Cough							
NCT00498173 (1)	1	29	3	31	25.6%	0.36 [0.04 , 3.23]	
Scahill 2015 (2)	4	30	4	32	74.4%	1.07 [0.29 , 3.89]	
Subtotal (95% CI)		**59**		**63**	**100.0%**	**0.81 [0.26 , 2.46]**	
Total events:	5		7				

Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 1 (P = 0.40); I² = 0%

Test for overall effect: Z = 0.38 (P = 0.70)

Test for subgroup differences: Not applicable

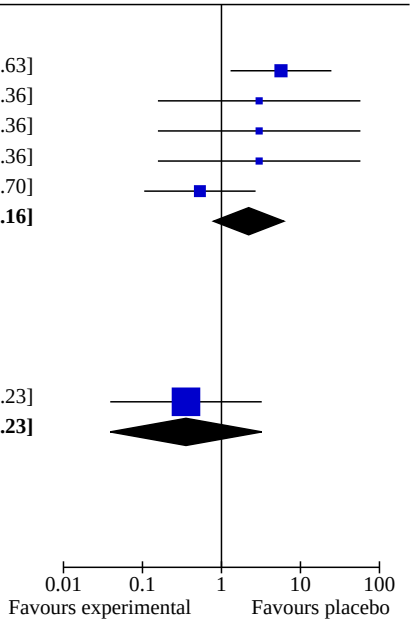


Footnotes

(1) Atomoxetine vs placebo
(2) Guanfacine vs placebo

Analysis 3.11. Comparison 3: ADHD-related medications vs placebo, Outcome 11: Adverse effects: skin

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
3.11.1 Rash						
Arnold 2006	8	8	1	8	35.9%	5.67 [1.30 , 24.63]
Pearson 2013 (1)	1	4	0	4	11.1%	3.00 [0.16 , 57.36]
Pearson 2013 (2)	1	4	0	4	11.1%	3.00 [0.16 , 57.36]
Pearson 2013 (3)	1	4	0	4	11.1%	3.00 [0.16 , 57.36]
Scahill 2015 (4)	2	30	4	32	30.9%	0.53 [0.11 , 2.70]
Subtotal (95% CI)		**50**		**52**	**100.0%**	**2.21 [0.79 , 6.16]**
Total events:	13		5			
Heterogeneity: Tau² = 0.20; Chi² = 4.65, df = 4 (P = 0.33); I² = 14%						
Test for overall effect: Z = 1.52 (P = 0.13)						
3.11.2 Skin picking						
Scahill 2015	1	30	3	32	100.0%	0.36 [0.04 , 3.23]
Subtotal (95% CI)		**30**		**32**	**100.0%**	**0.36 [0.04 , 3.23]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						

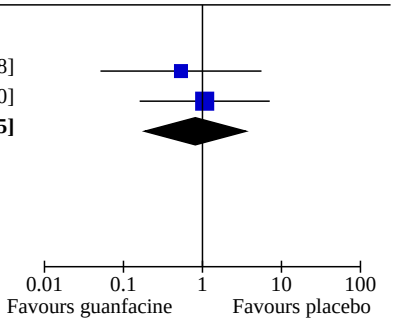


Footnotes

(1) 0.21mg/kg Methylphenidate
(2) 0.35mg/kg Methylphenidate
(3) 0.48mg/kg Methylphenidate
(4) Guanfacine vs placebo

Analysis 3.12. Comparison 3: ADHD-related medications vs placebo, Outcome 12: Adverse effects: urinary

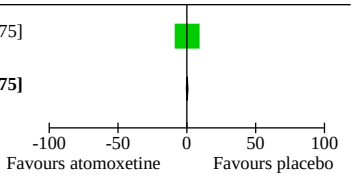
Study or Subgroup	Guanfacine Events	Guanfacine Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
3.12.1 Enuresis						
NCT00498173	1	29	2	31	39.5%	0.53 [0.05 , 5.58]
Scahill 2015	2	30	2	32	60.5%	1.07 [0.16 , 7.10]
Subtotal (95% CI)		**59**		**63**	**100.0%**	**0.81 [0.19 , 3.55]**
Total events:	3		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.28 (P = 0.78)						
Test for subgroup differences: Not applicable						



Analysis 3.13. Comparison 3: ADHD-related medications vs placebo, Outcome 13: Quality of life

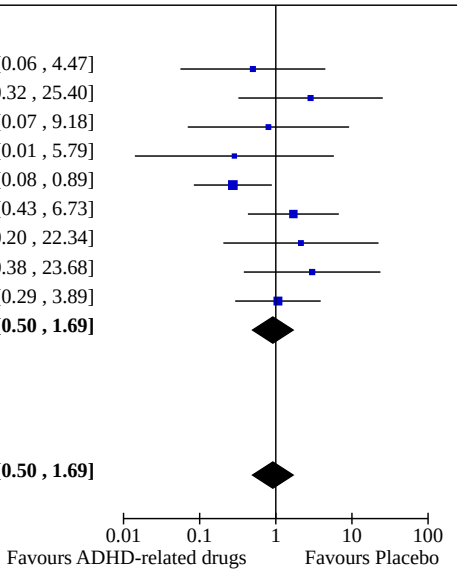
Study or Subgroup	Atomoxetine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
NCT00498173	64.2	9.24	25	62.2	9.58	29	100.0%	0.21 [-0.33 , 0.75]
Total (95% CI)			**25**			**29**	**100.0%**	**0.21 [-0.33 , 0.75]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.44)
Test for subgroup differences: Not applicable



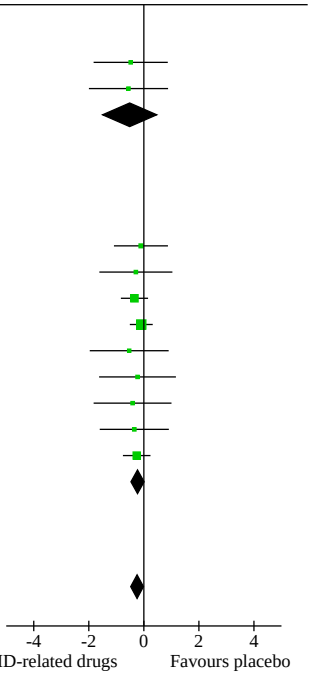
Analysis 3.14. Comparison 3: ADHD-related medications vs placebo, Outcome 14: Tolerability/acceptability: loss to follow-up

Study or Subgroup	ADHD-related drugs Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
3.14.1 ADHD-related drugs: loss to follow-up						
Arnold 2006	1	8	2	8	7.4%	0.50 [0.06 , 4.47]
Eslamzadeh 2018	3	22	1	21	7.5%	2.86 [0.32 , 25.40]
Fankhauser 1992	1	5	1	4	6.0%	0.80 [0.07 , 9.18]
Handen 2008	0	6	1	5	4.0%	0.29 [0.01 , 5.79]
Handen 2015	3	32	11	32	23.0%	0.27 [0.08 , 0.89]
Harfterkamp 2014	5	48	3	49	17.6%	1.70 [0.43 , 6.73]
NCT00498173	2	29	1	31	6.5%	2.14 [0.20 , 22.34]
NCT03242772	3	9	1	9	8.3%	3.00 [0.38 , 23.68]
Scahill 2015	4	30	4	32	19.6%	1.07 [0.29 , 3.89]
Subtotal (95% CI)		**189**		**191**	**100.0%**	**0.91 [0.50 , 1.69]**
Total events:	22		25			
Heterogeneity: Tau² = 0.06; Chi² = 8.58, df = 8 (P = 0.38); I² = 7%						
Test for overall effect: Z = 0.29 (P = 0.78)						
Total (95% CI)		**189**		**191**	**100.0%**	**0.91 [0.50 , 1.69]**
Total events:	22		25			
Heterogeneity: Tau² = 0.06; Chi² = 8.58, df = 8 (P = 0.38); I² = 7%						
Test for overall effect: Z = 0.29 (P = 0.78)						
Test for subgroup differences: Not applicable						



Analysis 3.15. Comparison 3: ADHD-related medications vs placebo, Outcome 15: Subgroup analyses: gender - irritability

Study or Subgroup	ADHD-related drugs Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.15.1 Male participants only								
Fankhauser 1992	0.36	0.37	5	0.55	0.33	4	3.0%	-0.48 [-1.83 , 0.87]
Jaselskis 1992	10.9	7.9	4	16.2	8.6	4	2.6%	-0.56 [-2.00 , 0.88]
Subtotal (95% CI)			**9**			**8**	**5.5%**	**-0.52 [-1.50 , 0.47]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%								
Test for overall effect: Z = 1.03 (P = 0.30)								
3.15.2 Male and female participants								
Arnold 2006	13.06	9.26	8	14.13	9.89	8	5.6%	-0.11 [-1.09 , 0.88]
Handen 2008	16.36	9.3	5	19.27	8.4	4	3.0%	-0.29 [-1.62 , 1.04]
Handen 2015	10.31	7.87	32	12.95	7.43	32	22.0%	-0.34 [-0.83 , 0.15]
Harfterkamp 2014	14.5	9.26	43	15.4	9.8	46	31.0%	-0.09 [-0.51 , 0.32]
Pearson 2013 (1)	7.2	6.9	4	12.6	10.4	4	2.6%	-0.53 [-1.97 , 0.90]
Pearson 2013 (2)	10	9.2	4	12.6	10.4	4	2.8%	-0.23 [-1.63 , 1.16]
Pearson 2013 (3)	8.2	8.1	4	12.6	10.4	4	2.7%	-0.41 [-1.82 , 1.00]
Quintana 1995	4	3.8	5	6	6.3	5	3.4%	-0.35 [-1.60 , 0.91]
Scahill 2015	13.5	9.85	30	16.1	9.9	32	21.4%	-0.26 [-0.76 , 0.24]
Subtotal (95% CI)			**135**			**139**	**94.5%**	**-0.23 [-0.47 , 0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 8 (P = 1.00); I² = 0%								
Test for overall effect: Z = 1.89 (P = 0.06)								
Total (95% CI)			**144**			**147**	**100.0%**	**-0.25 [-0.48 , -0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 1.27, df = 10 (P = 1.00); I² = 0%								
Test for overall effect: Z = 2.08 (P = 0.04)								
Test for subgroup differences: Chi² = 0.31, df = 1 (P = 0.58), I² = 0%								

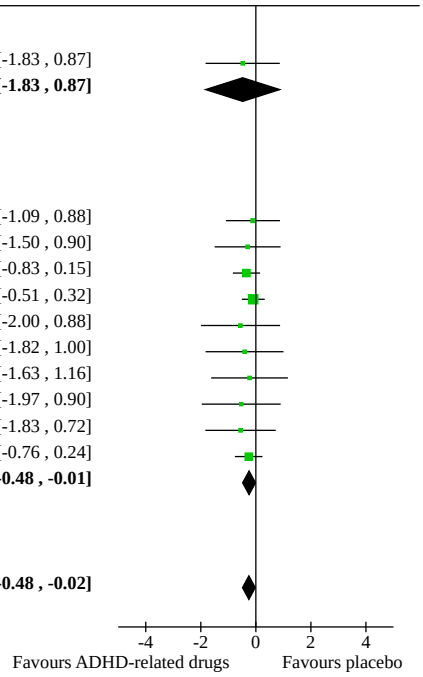


Footnotes

(1) 0.48mg/kg Methylphenidate
(2) 0.21mg/kg/day
(3) 0.35mg/kg Methylphenidate

Analysis 3.16. Comparison 3: ADHD-related medications vs placebo, Outcome 16: Subgroup analyses: age - irritability

Study or Subgroup	ADHD-related drugs Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.16.1 Adults and children								
Fankhauser 1992	0.36	0.37	5	0.55	0.33	4	2.9%	-0.48 [-1.83 , 0.87]
Subtotal (95% CI)			**5**			**4**	**2.9%**	**-0.48 [-1.83 , 0.87]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.70 (P = 0.49)								
3.16.2 Children only								
Arnold 2006	13.06	9.28	8	14.13	9.89	8	5.5%	-0.11 [-1.09 , 0.88]
Handen 2008	16.36	9.3	6	19.27	8.4	5	3.7%	-0.30 [-1.50 , 0.90]
Handen 2015	10.31	7.87	32	12.95	7.43	32	21.9%	-0.34 [-0.83 , 0.15]
Harfterkamp 2014	14.5	9.26	43	15.4	9.8	46	30.8%	-0.09 [-0.51 , 0.32]
Jaselskis 1992	10.9	7.9	4	16.2	8.6	4	2.6%	-0.56 [-2.00 , 0.88]
Pearson 2013 (1)	8.2	8.1	4	12.6	10.4	4	2.7%	-0.41 [-1.82 , 1.00]
Pearson 2013 (2)	10	9.2	4	12.6	10.4	4	2.7%	-0.23 [-1.63 , 1.16]
Pearson 2013 (3)	7.2	6.9	4	12.6	10.4	4	2.6%	-0.53 [-1.97 , 0.90]
Quintana 1995	4	3.8	5	7.2	6.3	5	3.3%	-0.56 [-1.83 , 0.72]
Scahill 2015	13.5	9.85	30	16.1	9.9	32	21.3%	-0.26 [-0.76 , 0.24]
Subtotal (95% CI)			**140**			**144**	**97.1%**	**-0.25 [-0.48 , -0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 1.36, df = 9 (P = 1.00); I² = 0%								
Test for overall effect: Z = 2.06 (P = 0.04)								
Total (95% CI)			**145**			**148**	**100.0%**	**-0.25 [-0.48 , -0.02]**
Heterogeneity: Tau² = 0.00; Chi² = 1.47, df = 10 (P = 1.00); I² = 0%								
Test for overall effect: Z = 2.15 (P = 0.03)								
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%								



Footnotes
(1) 0.35mg/kg Methylphenidate
(2) 0.21mg/kg Methylphenidate
(3) 0.48mg/kg Methylphenidate

Comparison 4. Antidepressant vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Irritability	3	267	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.30, 0.18]
4.1.1 SSRIs	2	255	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.29, 0.20]
4.1.2 Dibenzoxazepine	1	12	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-1.37, 0.91]
4.2 Adverse effects: cardiovascular	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.2.1 Flushing	1	12	Risk Ratio (IV, Random, 95% CI)	2.00 [0.24, 16.61]
4.2.2 Tachycardia	2	35	Risk Ratio (IV, Random, 95% CI)	2.67 [0.31, 23.25]
4.3 Adverse effects: gastrointestinal	10		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3.1 Constipation	2	70	Risk Ratio (IV, Random, 95% CI)	0.95 [0.09, 10.03]
4.3.2 Diarrhoea	4	409	Risk Ratio (IV, Random, 95% CI)	0.94 [0.33, 2.64]
4.3.3 Dry mouth	1	12	Risk Ratio (IV, Random, 95% CI)	2.00 [0.24, 16.61]
4.3.4 Gastrointestinal disturbance	3	341	Risk Ratio (IV, Random, 95% CI)	1.41 [0.97, 2.05]
4.3.5 Nausea/abdominal pain	5	251	Risk Ratio (IV, Random, 95% CI)	1.67 [0.85, 3.27]
4.3.6 Vomiting	5	400	Risk Ratio (IV, Random, 95% CI)	1.49 [0.76, 2.92]
4.4 Adverse effect: immune system	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.4.1 Allergies	1	149	Risk Ratio (IV, Random, 95% CI)	1.42 [0.70, 2.88]
4.4.2 Cold, flu or other systemic infection	1	149	Risk Ratio (IV, Random, 95% CI)	1.24 [0.82, 1.87]
4.4.3 Infections	3	472	Risk Ratio (IV, Random, 95% CI)	1.15 [0.85, 1.56]
4.5 Adverse effects: metabolic	7		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.5.1 Appetite disturbance	1	165	Risk Ratio (IV, Random, 95% CI)	0.55 [0.14, 2.23]
4.5.2 Decreased appetite	4	242	Risk Ratio (IV, Random, 95% CI)	1.35 [0.68, 2.69]
4.5.3 Decreased energy	1	149	Risk Ratio (IV, Random, 95% CI)	1.94 [1.13, 3.33]
4.5.4 Increased appetite	1	149	Risk Ratio (IV, Random, 95% CI)	0.91 [0.35, 2.38]
4.5.5 Weight gain	2	93	Risk Ratio (IV, Random, 95% CI)	1.47 [0.08, 27.39]
4.6 Adverse effect: musculoskeletal	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.6.1 Motor disturbance	1	165	Risk Ratio (IV, Random, 95% CI)	0.31 [0.03, 2.88]
4.6.2 Neck pain	1	37	Risk Ratio (IV, Random, 95% CI)	2.09 [0.09, 48.04]
4.7 Adverse effects: neurological	10		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.7.1 Activation syndrome	1	158	Risk Ratio (IV, Random, 95% CI)	0.80 [0.31, 2.04]
4.7.2 Agitation	2	197	Risk Ratio (IV, Random, 95% CI)	1.01 [0.59, 1.75]
4.7.3 Aggression or hostility	3	225	Risk Ratio (IV, Random, 95% CI)	1.07 [0.59, 1.95]
4.7.4 Anger/irritability	2	167	Risk Ratio (IV, Random, 95% CI)	1.31 [0.75, 2.29]

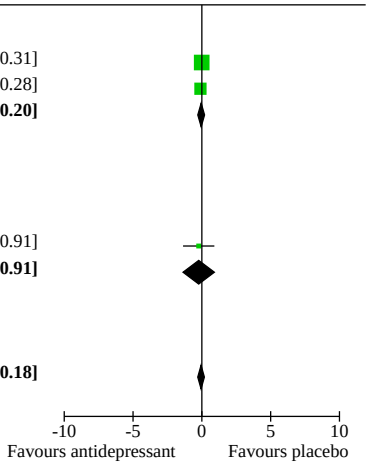
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.7.5 Autonomic disturbance	1	165	Risk Ratio (IV, Random, 95% CI)	1.15 [0.32, 4.12]
4.7.6 CNS disturbance	1	165	Risk Ratio (IV, Random, 95% CI)	0.75 [0.33, 1.72]
4.7.7 Decreased attention	2	207	Risk Ratio (IV, Random, 95% CI)	4.16 [1.07, 16.11]
4.7.8 Diaphoresis (sweating)	1	36	Risk Ratio (IV, Random, 95% CI)	3.00 [0.13, 69.09]
4.7.9 Drowsiness/fatigue	4	282	Risk Ratio (IV, Random, 95% CI)	1.25 [0.65, 2.41]
4.7.10 Headache	3	244	Risk Ratio (IV, Random, 95% CI)	1.53 [0.77, 3.07]
4.7.11 Hyperactivity	2	207	Risk Ratio (IV, Random, 95% CI)	1.93 [0.47, 7.82]
4.7.12 Increased speech	1	149	Risk Ratio (IV, Random, 95% CI)	2.08 [0.66, 6.62]
4.7.13 Insomnia	7	449	Risk Ratio (IV, Random, 95% CI)	1.19 [0.87, 1.63]
4.7.14 Mood disturbance	1	165	Risk Ratio (IV, Random, 95% CI)	1.32 [0.75, 2.31]
4.7.15 Mood lability	2	167	Risk Ratio (IV, Random, 95% CI)	0.69 [0.27, 1.74]
4.7.16 Numbness	1	37	Risk Ratio (IV, Random, 95% CI)	2.09 [0.09, 48.04]
4.7.17 Restlessness	1	149	Risk Ratio (IV, Random, 95% CI)	1.93 [0.82, 4.57]
4.7.18 Sedation	3	117	Risk Ratio (IV, Random, 95% CI)	1.91 [0.77, 4.72]
4.7.19 Sleep disturbance	2	223	Risk Ratio (IV, Random, 95% CI)	1.24 [0.31, 4.92]
4.7.20 Tremor	3	85	Risk Ratio (IV, Random, 95% CI)	2.56 [0.57, 11.60]
4.7.21 Twitching	1	12	Risk Ratio (IV, Random, 95% CI)	7.00 [0.44, 111.91]
4.7.22 Vertigo	1	37	Risk Ratio (IV, Random, 95% CI)	2.09 [0.09, 48.04]
4.8 Adverse effects: psychological	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.8.1 Anorexia	1	39	Risk Ratio (IV, Random, 95% CI)	1.58 [0.53, 4.74]
4.8.2 Anxiety/nervousness	2	188	Risk Ratio (IV, Random, 95% CI)	0.66 [0.37, 1.18]
4.8.3 Depression	1	37	Risk Ratio (IV, Random, 95% CI)	1.36 [0.14, 13.72]
4.8.4 Impulsive/intrusive behaviour	1	149	Risk Ratio (IV, Random, 95% CI)	2.92 [1.11, 7.68]
4.8.5 Self-injury	1	18	Risk Ratio (IV, Random, 95% CI)	1.25 [0.09, 17.02]
4.8.6 Silliness	1	149	Risk Ratio (IV, Random, 95% CI)	0.94 [0.40, 2.17]
4.8.7 Stereotypy	1	149	Risk Ratio (IV, Random, 95% CI)	8.33 [1.07, 64.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.8.8 Suicidal ideation	1	37	Risk Ratio (IV, Random, 95% CI)	2.09 [0.09, 48.04]
4.8.9 Unstable mood	1	149	Risk Ratio (IV, Random, 95% CI)	0.81 [0.32, 2.06]
4.8.10 Verbal aggression	1	37	Risk Ratio (IV, Random, 95% CI)	0.23 [0.01, 5.34]
4.8.11 Vivid or bad dreams	1	37	Risk Ratio (IV, Random, 95% CI)	4.87 [0.27, 87.94]
4.9 Adverse effects: respiratory	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.9.1 Cough	1	18	Risk Ratio (IV, Random, 95% CI)	1.67 [0.52, 5.39]
4.9.2 Respiratory	2	314	Risk Ratio (IV, Random, 95% CI)	2.19 [0.86, 5.55]
4.9.3 Upper respiratory infection (URI)	2	216	Risk Ratio (IV, Random, 95% CI)	0.98 [0.73, 1.31]
4.10 Adverse effects: skin	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.10.1 Rash or skin irritation	3	332	Risk Ratio (IV, Random, 95% CI)	1.00 [0.36, 2.78]
4.11 Adverse effects: urinary	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.11.1 Enuresis	1	18	Risk Ratio (IV, Random, 95% CI)	3.12 [0.81, 12.06]
4.11.2 Polyuria	1	37	Risk Ratio (IV, Random, 95% CI)	2.09 [0.09, 48.04]
4.11.3 Urinary tract infection (UTI)	1	39	Risk Ratio (IV, Random, 95% CI)	0.60 [0.21, 1.73]
4.12 Adverse effects: other	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.12.1 Salty taste	1	37	Risk Ratio (IV, Random, 95% CI)	2.09 [0.09, 48.04]
4.12.2 Trembling (mild)	1	37	Risk Ratio (IV, Random, 95% CI)	2.09 [0.09, 48.04]
4.13 Tolerability/acceptability: loss to follow-up	7	564	Risk Ratio (IV, Random, 95% CI)	1.22 [0.93, 1.59]
4.14 Subgroup analyses: gender - irritability	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.14.1 Male and female participants	2	255	Mean Difference (IV, Random, 95% CI)	-0.44 [-2.79, 1.90]
4.14.2 Male participants only	1	12	Mean Difference (IV, Random, 95% CI)	-1.50 [-8.37, 5.37]
4.15 Serious adverse events	2	76	Risk Ratio (IV, Random, 95% CI)	0.98 [0.11, 8.85]
4.15.1 Hospitalisation for dehydration	1	58	Risk Ratio (IV, Random, 95% CI)	2.45 [0.10, 57.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.15.2 Severe diarrhoea	1	18	Risk Ratio (IV, Random, 95% CI)	0.41 [0.02, 8.84]

Analysis 4.1. Comparison 4: Antidepressant vs placebo, Outcome 1: Irritability

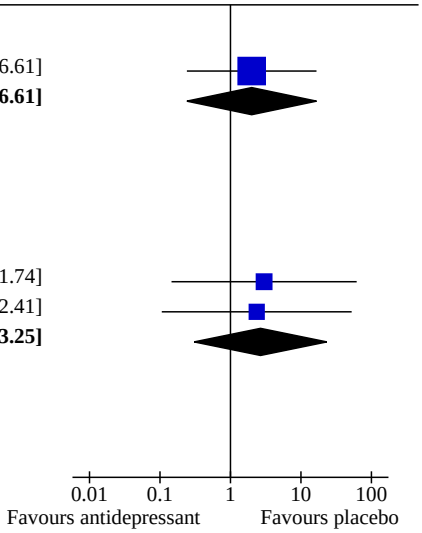
Study or Subgroup	Antidepressant Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.1.1 SSRIs								
King 2009 (1)	10.1	9.3	73	10.2	8.9	76	55.8%	-0.01 [-0.33 , 0.31]
Mouti 2014 (2)	12.28	9.19	53	13.34	11.29	53	39.7%	-0.10 [-0.48 , 0.28]
Subtotal (95% CI)			**126**			**129**	**95.5%**	**-0.05 [-0.29 , 0.20]**
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%								
Test for overall effect: Z = 0.39 (P = 0.70)								
4.1.2 Dibenzoxazepine								
Niederhofer 2003 (3)	12.3	6.9	6	13.8	5.1	6	4.5%	-0.23 [-1.37 , 0.91]
Subtotal (95% CI)			**6**			**6**	**4.5%**	**-0.23 [-1.37 , 0.91]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.39 (P = 0.69)								
Total (95% CI)			**132**			**135**	**100.0%**	**-0.06 [-0.30 , 0.18]**
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 2 (P = 0.90); I² = 0%								
Test for overall effect: Z = 0.46 (P = 0.64)								
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.76), I² = 0%								



Footnotes
(1) Citalopram
(2) Fluoxetine
(3) Tianeptine

Analysis 4.2. Comparison 4: Antidepressant vs placebo, Outcome 2: Adverse effects: cardiovascular

Study or Subgroup	Antidepressant Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
4.2.1 Flushing						
Gordon 1993	2	6	1	6	100.0%	2.00 [0.24 , 16.61]
Subtotal (95% CI)		**6**		**6**	**100.0%**	**2.00 [0.24 , 16.61]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
4.2.2 Tachycardia						
Gordon 1993	1	6	0	6	51.3%	3.00 [0.15 , 61.74]
Remington 2001	1	13	0	10	48.7%	2.36 [0.11 , 52.41]
Subtotal (95% CI)		**19**		**16**	**100.0%**	**2.67 [0.31 , 23.25]**
Total events:	2		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.89 (P = 0.37)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						



Analysis 4.3. Comparison 4: Antidepressant vs placebo, Outcome 3: Adverse effects: gastrointestinal

Study or Subgroup	Antidepressant Events	Antidepressant Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
4.3.1 Constipation						
Gordon 1993	3	6	1	6	52.3%	3.00 [0.42 , 21.30]
Hagerman 2018	1	32	3	26	47.7%	0.27 [0.03 , 2.45]
Subtotal (95% CI)		**38**		**32**	**100.0%**	**0.95 [0.09 , 10.03]**
Total events:	4		4			
Heterogeneity: Tau² = 1.76; Chi² = 2.55, df = 1 (P = 0.11); I² = 61%						
Test for overall effect: Z = 0.04 (P = 0.97)						
4.3.2 Diarrhoea						
Hagerman 2018	8	32	15	26	28.1%	0.43 [0.22 , 0.86]
Herscu 2020	11	78	5	80	24.6%	2.26 [0.82 , 6.20]
Hollander 2005	2	22	7	22	19.6%	0.29 [0.07 , 1.23]
King 2009	19	73	9	76	27.7%	2.20 [1.06 , 4.54]
Subtotal (95% CI)		**205**		**204**	**100.0%**	**0.94 [0.33 , 2.64]**
Total events:	40		36			
Heterogeneity: Tau² = 0.87; Chi² = 15.60, df = 3 (P = 0.001); I² = 81%						
Test for overall effect: Z = 0.12 (P = 0.91)						
4.3.3 Dry mouth						
Gordon 1993	2	6	1	6	100.0%	2.00 [0.24 , 16.61]
Subtotal (95% CI)		**6**		**6**	**100.0%**	**2.00 [0.24 , 16.61]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
4.3.4 Gastrointestinal disturbance						
Herscu 2020	26	78	17	80	50.2%	1.57 [0.93 , 2.65]
Mouti 2014	10	86	7	79	16.5%	1.31 [0.52 , 3.28]
NCT00183339	6	8	6	10	33.3%	1.25 [0.66 , 2.38]
Subtotal (95% CI)		**172**		**169**	**100.0%**	**1.41 [0.97 , 2.05]**
Total events:	42		30			
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 2 (P = 0.85); I² = 0%						
Test for overall effect: Z = 1.82 (P = 0.07)						
4.3.5 Nausea/abdominal pain						
Gordon 1993	1	6	1	6	7.1%	1.00 [0.08 , 12.56]
Hollander 2012	2	22	0	15	5.1%	3.48 [0.18 , 67.70]
King 2009	13	73	9	76	73.2%	1.50 [0.68 , 3.30]
McDougle 1996	3	15	1	15	9.8%	3.00 [0.35 , 25.68]
Remington 2001	1	13	0	10	4.7%	2.36 [0.11 , 52.41]
Subtotal (95% CI)		**129**		**122**	**100.0%**	**1.67 [0.85 , 3.27]**
Total events:	20		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 4 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.49 (P = 0.14)						
4.3.6 Vomiting						
Gordon 1993	1	6	0	6	4.7%	3.00 [0.15 , 61.74]
Hagerman 2018	7	32	3	26	23.1%	1.90 [0.54 , 6.61]
Herscu 2020	5	78	9	80	30.3%	0.57 [0.20 , 1.62]
King 2009	14	73	6	76	37.5%	2.43 [0.99 , 5.98]
Remington 2001	1	13	0	10	4.5%	2.36 [0.11 , 52.41]
Subtotal (95% CI)		**202**		**198**	**100.0%**	**1.49 [0.76 , 2.92]**

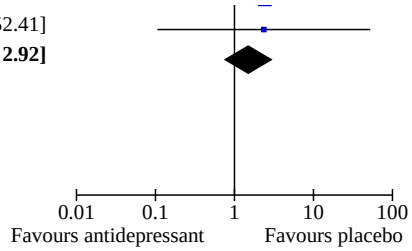
Analysis 4.3. (Continued)

Remington 2001	1	13	0	10	4.5%	2.36 [0.11 , 52.41]
Subtotal (95% CI)		**202**		**198**	**100.0%**	**1.49 [0.76 , 2.92]**
Total events:	28		18			

Heterogeneity: Tau² = 0.10; Chi² = 4.80, df = 4 (P = 0.31); I² = 17%

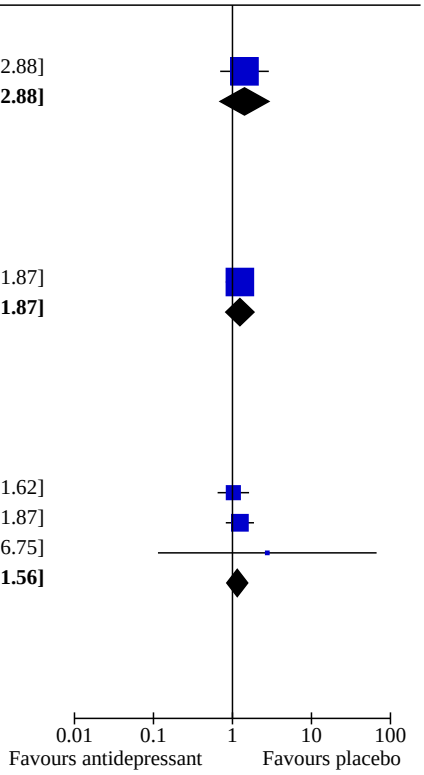
Test for overall effect: Z = 1.17 (P = 0.24)

Test for subgroup differences: Chi² = 0.00, df = 5 (P < 0.00001), I² = 0%



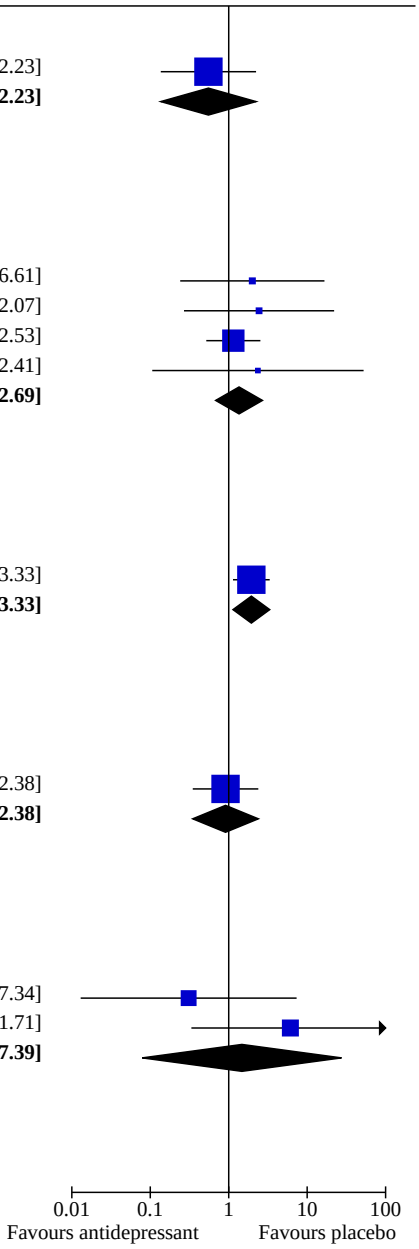
Analysis 4.4. Comparison 4: Antidepressant vs placebo, Outcome 4: Adverse effect: immune system

Study or Subgroup	Antidepressant Events	Antidepressant Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
4.4.1 Allergies						
King 2009	15	73	11	76	100.0%	1.42 [0.70 , 2.88]
Subtotal (95% CI)		**73**		**76**	**100.0%**	**1.42 [0.70 , 2.88]**
Total events:	15		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
4.4.2 Cold, flu or other systemic infection						
King 2009	31	73	26	76	100.0%	1.24 [0.82 , 1.87]
Subtotal (95% CI)		**73**		**76**	**100.0%**	**1.24 [0.82 , 1.87]**
Total events:	31		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						
4.4.3 Infections						
Herscu 2020	25	78	25	80	44.1%	1.03 [0.65 , 1.62]
King 2009	31	73	26	76	55.0%	1.24 [0.82 , 1.87]
Mouti 2014	1	86	0	79	0.9%	2.76 [0.11 , 66.75]
Subtotal (95% CI)		**237**		**235**	**100.0%**	**1.15 [0.85 , 1.56]**
Total events:	57		51			
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 2 (P = 0.72); I² = 0%						
Test for overall effect: Z = 0.90 (P = 0.37)						
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%						



Analysis 4.5. Comparison 4: Antidepressant vs placebo, Outcome 5: Adverse effects: metabolic

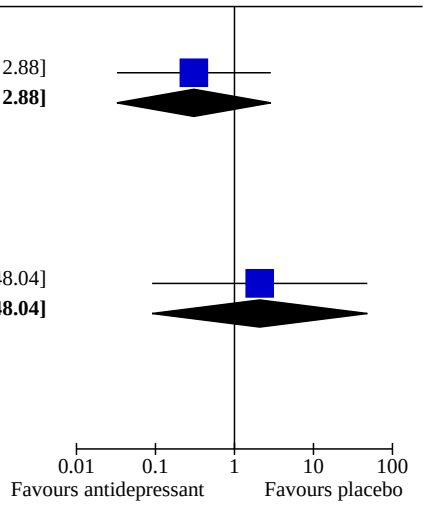
Study or Subgroup	Antidepressants Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
4.5.1 Appetite disturbance						
Mouti 2014	3	86	5	79	100.0%	0.55 [0.14 , 2.23]
Subtotal (95% CI)		**86**		**79**	**100.0%**	**0.55 [0.14 , 2.23]**
Total events:	3		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.40)						
4.5.2 Decreased appetite						
Gordon 1993	2	6	1	6	10.5%	2.00 [0.24 , 16.61]
Hagerman 2018	3	32	1	26	9.7%	2.44 [0.27 , 22.07]
King 2009	11	73	10	76	74.9%	1.15 [0.52 , 2.53]
Remington 2001	1	13	0	10	4.9%	2.36 [0.11 , 52.41]
Subtotal (95% CI)		**124**		**118**	**100.0%**	**1.35 [0.68 , 2.69]**
Total events:	17		12			
Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 3 (P = 0.87); I² = 0%						
Test for overall effect: Z = 0.86 (P = 0.39)						
4.5.3 Decreased energy						
King 2009	28	73	15	76	100.0%	1.94 [1.13 , 3.33]
Subtotal (95% CI)		**73**		**76**	**100.0%**	**1.94 [1.13 , 3.33]**
Total events:	28		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.42 (P = 0.02)						
4.5.4 Increased appetite						
King 2009	7	73	8	76	100.0%	0.91 [0.35 , 2.38]
Subtotal (95% CI)		**73**		**76**	**100.0%**	**0.91 [0.35 , 2.38]**
Total events:	7		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.19 (P = 0.85)						
4.5.5 Weight gain						
Hollander 2005	0	39	1	36	47.7%	0.31 [0.01 , 7.34]
NCT00183339	2	8	0	10	52.3%	6.11 [0.33 , 111.71]
Subtotal (95% CI)		**47**		**46**	**100.0%**	**1.47 [0.08 , 27.39]**
Total events:	2		1			
Heterogeneity: Tau² = 2.05; Chi² = 1.85, df = 1 (P = 0.17); I² = 46%						
Test for overall effect: Z = 0.26 (P = 0.80)						
Test for subgroup differences: Chi² = 0.00, df = 4 (P < 0.00001), I² = 0%						



Analysis 4.6. Comparison 4: Antidepressant vs placebo, Outcome 6: Adverse effect: musculoskeletal

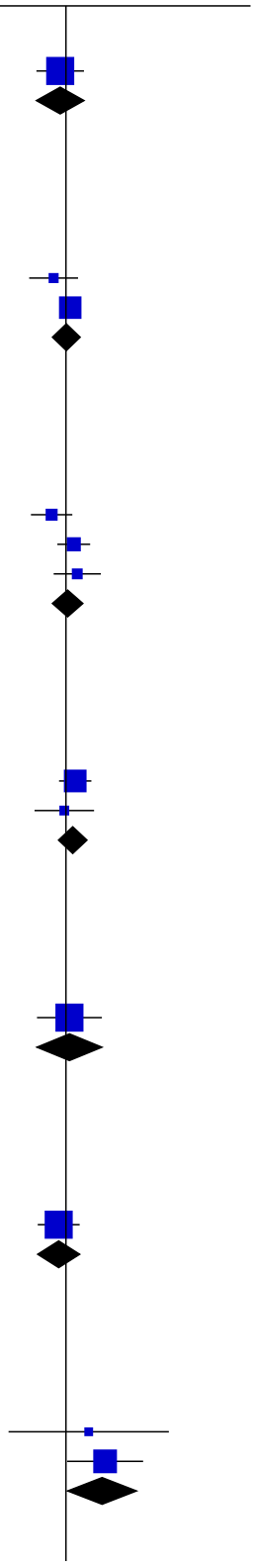
Study or Subgroup	Antidepressant Events	Antidepressant Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
4.6.1 Motor disturbance						
Mouti 2014	1	86	3	79	100.0%	0.31 [0.03 , 2.88]
Subtotal (95% CI)		**86**		**79**	**100.0%**	**0.31 [0.03 , 2.88]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						
4.6.2 Neck pain						
Hollander 2012	1	22	0	15	100.0%	2.09 [0.09 , 48.04]
Subtotal (95% CI)		**22**		**15**	**100.0%**	**2.09 [0.09 , 48.04]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						

Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%



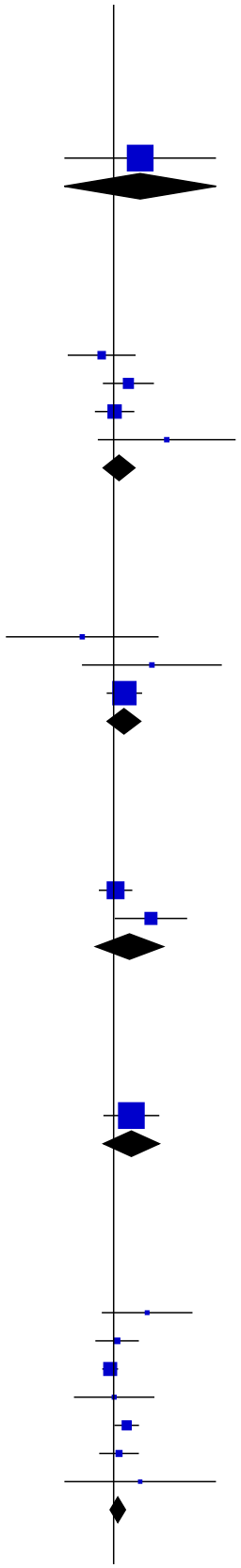
Analysis 4.7. Comparison 4: Antidepressant vs placebo, Outcome 7: Adverse effects: neurological

Study or Subgroup	Antidepressants Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
4.7.1 Activation syndrome						
Herscu 2020	7	78	9	80	100.0%	0.80 [0.31 , 2.04]
Subtotal (95% CI)		**78**		**80**	**100.0%**	**0.80 [0.31 , 2.04]**
Total events:	7		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
4.7.2 Agitation						
Herscu 2020	6	78	10	80	23.6%	0.62 [0.23 , 1.61]
Hollander 2005	18	19	16	20	76.4%	1.18 [0.93 , 1.51]
Subtotal (95% CI)		**97**		**100**	**100.0%**	**1.01 [0.59 , 1.75]**
Total events:	24		26			
Heterogeneity: Tau² = 0.09; Chi² = 1.67, df = 1 (P = 0.20); I² = 40%						
Test for overall effect: Z = 0.05 (P = 0.96)						
4.7.3 Aggression or hostility						
Hagerman 2018	7	32	10	26	31.9%	0.57 [0.25 , 1.29]
King 2009	17	73	13	76	40.9%	1.36 [0.71 , 2.60]
NCT00183339	5	8	4	10	27.1%	1.56 [0.62 , 3.96]
Subtotal (95% CI)		**113**		**112**	**100.0%**	**1.07 [0.59 , 1.95]**
Total events:	29		27			
Heterogeneity: Tau² = 0.12; Chi² = 3.47, df = 2 (P = 0.18); I² = 42%						
Test for overall effect: Z = 0.22 (P = 0.83)						
4.7.4 Anger/irritability						
King 2009	18	73	13	76	77.2%	1.44 [0.76 , 2.73]
NCT00183339	3	8	4	10	22.8%	0.94 [0.29 , 3.03]
Subtotal (95% CI)		**81**		**86**	**100.0%**	**1.31 [0.75 , 2.29]**
Total events:	21		17			
Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.94 (P = 0.35)						
4.7.5 Autonomic disturbance						
Mouti 2014	5	86	4	79	100.0%	1.15 [0.32 , 4.12]
Subtotal (95% CI)		**86**		**79**	**100.0%**	**1.15 [0.32 , 4.12]**
Total events:	5		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.83)						
4.7.6 CNS disturbance						
Mouti 2014	9	86	11	79	100.0%	0.75 [0.33 , 1.72]
Subtotal (95% CI)		**86**		**79**	**100.0%**	**0.75 [0.33 , 1.72]**
Total events:	9		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
4.7.7 Decreased attention						
Hagerman 2018	1	32	0	26	18.4%	2.45 [0.10 , 57.85]
King 2009	9	73	2	76	81.6%	4.68 [1.05 , 20.96]
Subtotal (95% CI)		**105**		**102**	**100.0%**	**4.16 [1.07 , 16.11]**
Total events:	10		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%						



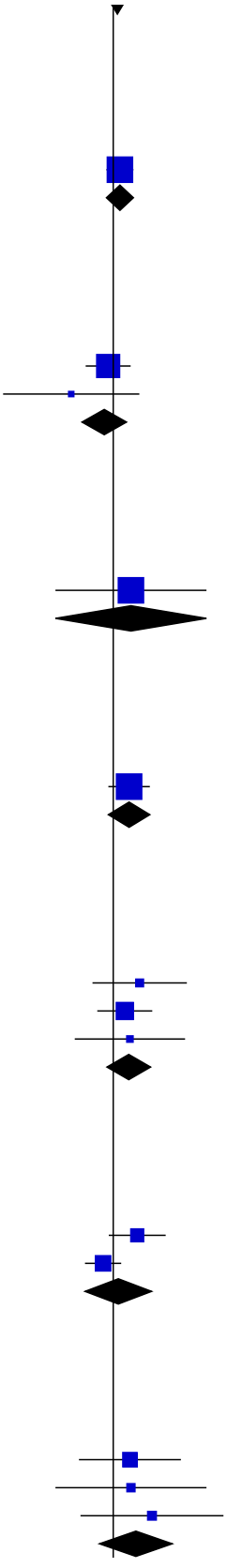
Analysis 4.7. (Continued)

Total events:	10		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%						
Test for overall effect: Z = 2.06 (P = 0.04)						
4.7.8 Diaphoresis (sweating)						
Remington 2001	1	18	0	18	100.0%	3.00 [0.13 , 69.09]
Subtotal (95% CI)		**18**		**18**	**100.0%**	**3.00 [0.13 , 69.09]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
4.7.9 Drowsiness/fatigue						
Hagerman 2018	3	32	4	26	19.0%	0.61 [0.15 , 2.48]
Hollander 2005	7	19	4	20	30.7%	1.84 [0.64 , 5.30]
King 2009	10	73	10	76	45.2%	1.04 [0.46 , 2.35]
Remington 2001	4	18	0	18	5.1%	9.00 [0.52 , 155.86]
Subtotal (95% CI)		**142**		**140**	**100.0%**	**1.25 [0.65 , 2.41]**
Total events:	24		18			
Heterogeneity: Tau² = 0.07; Chi² = 3.55, df = 3 (P = 0.31); I² = 16%						
Test for overall effect: Z = 0.67 (P = 0.50)						
4.7.10 Headache						
Hagerman 2018	0	32	1	26	4.8%	0.27 [0.01 , 6.43]
Hollander 2012	3	22	0	15	5.7%	4.87 [0.27 , 87.94]
King 2009	15	73	10	76	89.5%	1.56 [0.75 , 3.25]
Subtotal (95% CI)		**127**		**117**	**100.0%**	**1.53 [0.77 , 3.07]**
Total events:	18		11			
Heterogeneity: Tau² = 0.00; Chi² = 1.76, df = 2 (P = 0.41); I² = 0%						
Test for overall effect: Z = 1.21 (P = 0.23)						
4.7.11 Hyperactivity						
Hagerman 2018	12	32	9	26	60.7%	1.08 [0.54 , 2.16]
King 2009	9	73	2	76	39.3%	4.68 [1.05 , 20.96]
Subtotal (95% CI)		**105**		**102**	**100.0%**	**1.93 [0.47 , 7.82]**
Total events:	21		11			
Heterogeneity: Tau² = 0.72; Chi² = 3.02, df = 1 (P = 0.08); I² = 67%						
Test for overall effect: Z = 0.92 (P = 0.36)						
4.7.12 Increased speech						
King 2009	8	73	4	76	100.0%	2.08 [0.66 , 6.62]
Subtotal (95% CI)		**73**		**76**	**100.0%**	**2.08 [0.66 , 6.62]**
Total events:	8		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.24 (P = 0.21)						
4.7.13 Insomnia						
Gordon 1993	4	6	1	6	2.7%	4.00 [0.61 , 26.12]
Herscu 2020	9	78	8	80	10.7%	1.15 [0.47 , 2.84]
Hollander 2005	14	19	17	20	43.4%	0.87 [0.63 , 1.20]
Hollander 2012	3	22	2	15	3.5%	1.02 [0.19 , 5.40]
King 2009	28	73	17	76	26.1%	1.71 [1.03 , 2.86]
NCT00183339	5	8	5	10	12.6%	1.25 [0.55 , 2.84]
Remington 2001	1	18	0	18	1.0%	3.00 [0.13 , 69.09]
Subtotal (95% CI)		**224**		**225**	**100.0%**	**1.19 [0.87 , 1.63]**
Total events:	64		50			
Heterogeneity: Tau² = 0.03; Chi² = 7.28, df = 6 (P = 0.30); I² = 18%						



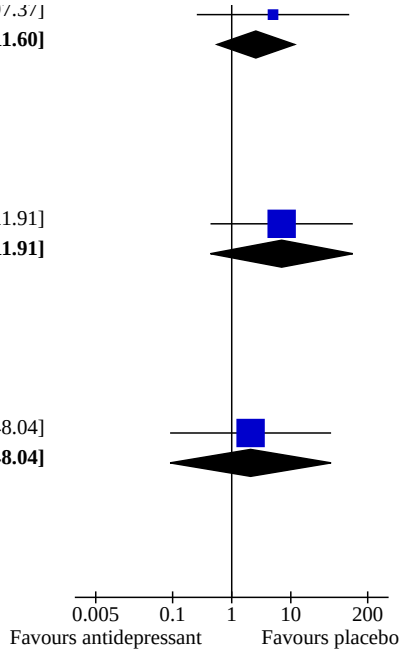
Analysis 4.7. (Continued)

Total events:	64		50			
Heterogeneity: Tau² = 0.03; Chi² = 7.28, df = 6 (P = 0.30); I² = 18%						
Test for overall effect: Z = 1.06 (P = 0.29)						
4.7.14 Mood disturbance						
Mouti 2014	23	86	16	79	100.0%	1.32 [0.75 , 2.31]
Subtotal (95% CI)		**86**		**79**	**100.0%**	**1.32 [0.75 , 2.31]**
Total events:	23		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
4.7.15 Mood lability						
King 2009	7	73	9	76	89.4%	0.81 [0.32 , 2.06]
NCT00183339	0	8	3	10	10.6%	0.17 [0.01 , 2.96]
Subtotal (95% CI)		**81**		**86**	**100.0%**	**0.69 [0.27 , 1.74]**
Total events:	7		12			
Heterogeneity: Tau² = 0.02; Chi² = 1.02, df = 1 (P = 0.31); I² = 2%						
Test for overall effect: Z = 0.79 (P = 0.43)						
4.7.16 Numbness						
Hollander 2012	1	22	0	15	100.0%	2.09 [0.09 , 48.04]
Subtotal (95% CI)		**22**		**15**	**100.0%**	**2.09 [0.09 , 48.04]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
4.7.17 Restlessness						
King 2009	13	73	7	76	100.0%	1.93 [0.82 , 4.57]
Subtotal (95% CI)		**73**		**76**	**100.0%**	**1.93 [0.82 , 4.57]**
Total events:	13		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
4.7.18 Sedation						
Gordon 1993	3	6	1	6	21.4%	3.00 [0.42 , 21.30]
Hollander 2005	7	39	4	36	63.0%	1.62 [0.52 , 5.06]
McDougle 1996	2	15	1	15	15.6%	2.00 [0.20 , 19.78]
Subtotal (95% CI)		**60**		**57**	**100.0%**	**1.91 [0.77 , 4.72]**
Total events:	12		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 2 (P = 0.87); I² = 0%						
Test for overall effect: Z = 1.40 (P = 0.16)						
4.7.19 Sleep disturbance						
Hagerman 2018	10	32	3	26	44.6%	2.71 [0.83 , 8.83]
Mouti 2014	10	86	14	79	55.4%	0.66 [0.31 , 1.39]
Subtotal (95% CI)		**118**		**105**	**100.0%**	**1.24 [0.31 , 4.92]**
Total events:	20		17			
Heterogeneity: Tau² = 0.75; Chi² = 3.94, df = 1 (P = 0.05); I² = 75%						
Test for overall effect: Z = 0.30 (P = 0.76)						
4.7.20 Tremor						
Gordon 1993	2	6	1	6	50.9%	2.00 [0.24 , 16.61]
Hollander 2012	1	22	0	15	23.2%	2.09 [0.09 , 48.04]
Remington 2001	2	18	0	18	25.9%	5.00 [0.26 , 97.37]
Subtotal (95% CI)		**46**		**39**	**100.0%**	**2.56 [0.57 , 11.60]**



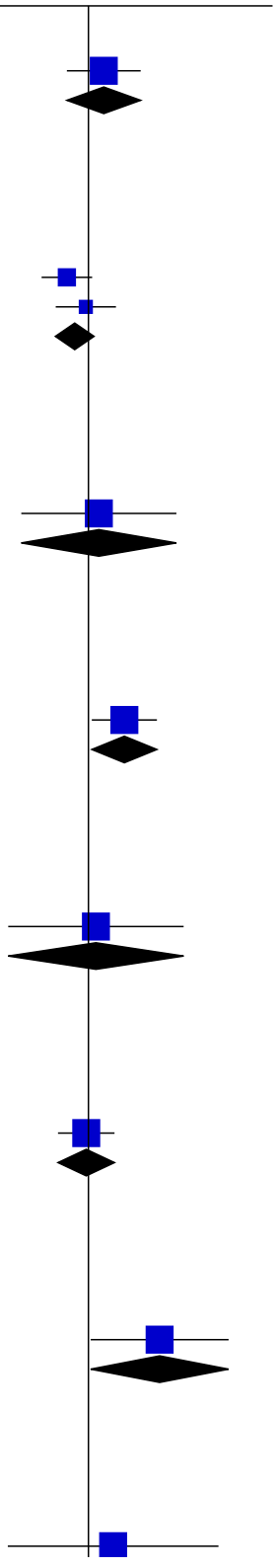
Analysis 4.7. (Continued)

Remington 2001	2	18	0	18	25.9%	5.00 [0.26 , 97.37]
Subtotal (95% CI)		**46**		**39**	**100.0%**	**2.56 [0.57 , 11.60]**
Total events:	5		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 2 (P = 0.88); I² = 0%						
Test for overall effect: Z = 1.22 (P = 0.22)						
4.7.21 Twitching						
Gordon 1993	3	6	0	6	100.0%	7.00 [0.44 , 111.91]
Subtotal (95% CI)		**6**		**6**	**100.0%**	**7.00 [0.44 , 111.91]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.38 (P = 0.17)						
4.7.22 Vertigo						
Hollander 2012	1	22	0	15	100.0%	2.09 [0.09 , 48.04]
Subtotal (95% CI)		**22**		**15**	**100.0%**	**2.09 [0.09 , 48.04]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
Test for subgroup differences: Chi² = 0.00, df = 21 (P < 0.00001), I² = 0%						



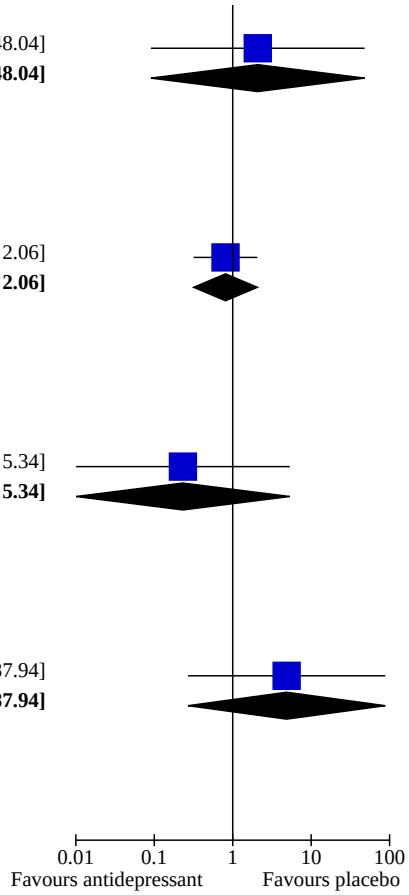
Analysis 4.8. Comparison 4: Antidepressant vs placebo, Outcome 8: Adverse effects: psychological

Study or Subgroup	Antidepressants Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
4.8.1 Anorexia						
Hollander 2005	6	19	4	20	100.0%	1.58 [0.53 , 4.74]
Subtotal (95% CI)		**19**		**20**	**100.0%**	**1.58 [0.53 , 4.74]**
Total events:	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.42)						
4.8.2 Anxiety/nervousness						
Hollander 2005	6	19	12	20	58.7%	0.53 [0.25 , 1.12]
King 2009	8	73	9	76	41.3%	0.93 [0.38 , 2.27]
Subtotal (95% CI)		**92**		**96**	**100.0%**	**0.66 [0.37 , 1.18]**
Total events:	14		21			
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.34); I² = 0%						
Test for overall effect: Z = 1.39 (P = 0.16)						
4.8.3 Depression						
Hollander 2012	2	22	1	15	100.0%	1.36 [0.14 , 13.72]
Subtotal (95% CI)		**22**		**15**	**100.0%**	**1.36 [0.14 , 13.72]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.79)						
4.8.4 Impulsive/intrusive behaviour						
King 2009	14	73	5	76	100.0%	2.92 [1.11 , 7.68]
Subtotal (95% CI)		**73**		**76**	**100.0%**	**2.92 [1.11 , 7.68]**
Total events:	14		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.16 (P = 0.03)						
4.8.5 Self-injury						
NCT00183339	1	8	1	10	100.0%	1.25 [0.09 , 17.02]
Subtotal (95% CI)		**8**		**10**	**100.0%**	**1.25 [0.09 , 17.02]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.17 (P = 0.87)						
4.8.6 Silliness						
King 2009	9	73	10	76	100.0%	0.94 [0.40 , 2.17]
Subtotal (95% CI)		**73**		**76**	**100.0%**	**0.94 [0.40 , 2.17]**
Total events:	9		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
4.8.7 Stereotypy						
King 2009	8	73	1	76	100.0%	8.33 [1.07 , 64.95]
Subtotal (95% CI)		**73**		**76**	**100.0%**	**8.33 [1.07 , 64.95]**
Total events:	8		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.02 (P = 0.04)						
4.8.8 Suicidal ideation						
Hollander 2012	1	22	0	15	100.0%	2.09 [0.09 , 48.04]



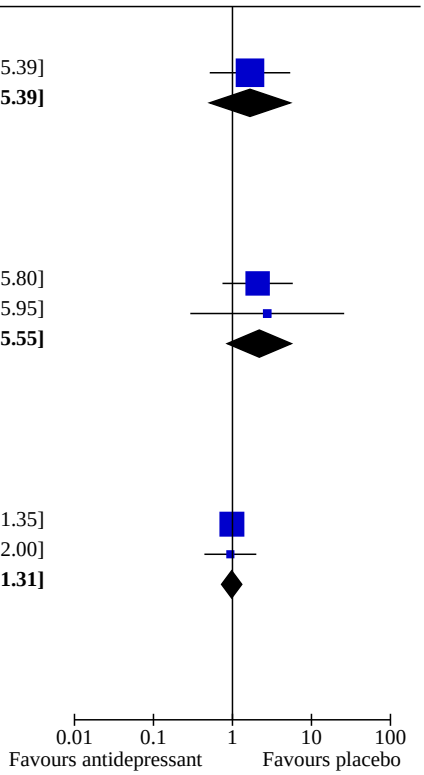
Analysis 4.8. (Continued)

4.8.8 Suicidal ideation						
Hollander 2012	1	22	0	15	100.0%	2.09 [0.09 , 48.04]
Subtotal (95% CI)		**22**		**15**	**100.0%**	**2.09 [0.09 , 48.04]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
4.8.9 Unstable mood						
King 2009	7	73	9	76	100.0%	0.81 [0.32 , 2.06]
Subtotal (95% CI)		**73**		**76**	**100.0%**	**0.81 [0.32 , 2.06]**
Total events:	7		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						
4.8.10 Verbal aggression						
Hollander 2012	0	22	1	15	100.0%	0.23 [0.01 , 5.34]
Subtotal (95% CI)		**22**		**15**	**100.0%**	**0.23 [0.01 , 5.34]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.91 (P = 0.36)						
4.8.11 Vivid or bad dreams						
Hollander 2012	3	22	0	15	100.0%	4.87 [0.27 , 87.94]
Subtotal (95% CI)		**22**		**15**	**100.0%**	**4.87 [0.27 , 87.94]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.28)						
Test for subgroup differences: Chi² = 0.00, df = 10 (P < 0.00001), I² = 0%						



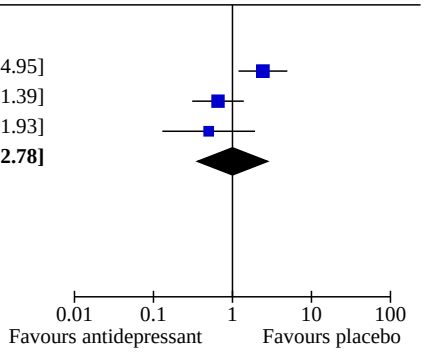
Analysis 4.9. Comparison 4: Antidepressant vs placebo, Outcome 9: Adverse effects: respiratory

Study or Subgroup	Antidepressant Events	Antidepressant Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
4.9.1 Cough						
NCT00183339	4	8	3	10	100.0%	1.67 [0.52 , 5.39]
Subtotal (95% CI)		**8**		**10**	**100.0%**	**1.67 [0.52 , 5.39]**
Total events:	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.39)						
4.9.2 Respiratory						
King 2009	10	73	5	76	82.7%	2.08 [0.75 , 5.80]
Mouti 2014	3	86	1	79	17.3%	2.76 [0.29 , 25.95]
Subtotal (95% CI)		**159**		**155**	**100.0%**	**2.19 [0.86 , 5.55]**
Total events:	13		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 1.64 (P = 0.10)						
4.9.3 Upper respiratory infection (URI)						
Hagerman 2018	23	32	19	26	84.9%	0.98 [0.72 , 1.35]
Herscu 2020	11	78	12	80	15.1%	0.94 [0.44 , 2.00]
Subtotal (95% CI)		**110**		**106**	**100.0%**	**0.98 [0.73 , 1.31]**
Total events:	34		31			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.16 (P = 0.88)						
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%						



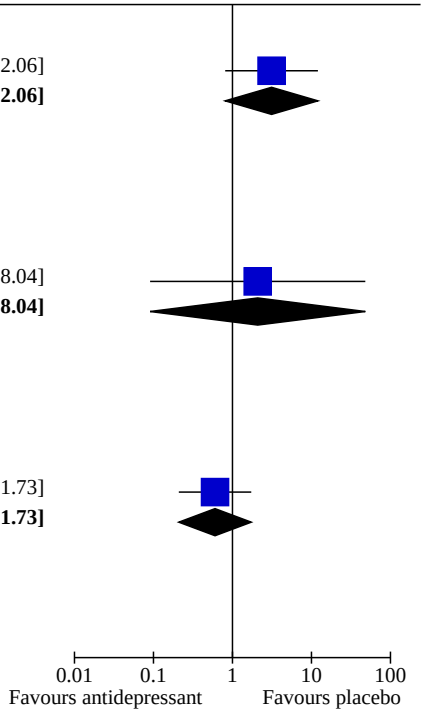
Analysis 4.10. Comparison 4: Antidepressant vs placebo, Outcome 10: Adverse effects: skin

Study or Subgroup	Antidepressant Events	Antidepressant Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
4.10.1 Rash or skin irritation						
King 2009	21	73	9	76	37.6%	2.43 [1.19 , 4.95]
Mouti 2014	10	86	14	79	36.9%	0.66 [0.31 , 1.39]
NCT00183339	2	8	5	10	25.5%	0.50 [0.13 , 1.93]
Subtotal (95% CI)		**167**		**165**	**100.0%**	**1.00 [0.36 , 2.78]**
Total events:	33		28			
Heterogeneity: Tau² = 0.59; Chi² = 7.84, df = 2 (P = 0.02); I² = 74%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Not applicable						



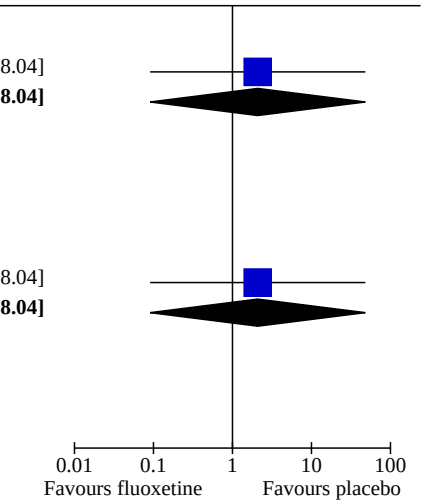
Analysis 4.11. Comparison 4: Antidepressant vs placebo, Outcome 11: Adverse effects: urinary

Study or Subgroup	Antidepressant Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
4.11.1 Enuresis						
NCT00183339	5	8	2	10	100.0%	3.13 [0.81 , 12.06]
Subtotal (95% CI)		**8**		**10**	**100.0%**	**3.13 [0.81 , 12.06]**
Total events:	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.65 (P = 0.10)						
4.11.2 Polyuria						
Hollander 2012	1	22	0	15	100.0%	2.09 [0.09 , 48.04]
Subtotal (95% CI)		**22**		**15**	**100.0%**	**2.09 [0.09 , 48.04]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
4.11.3 Urinary tract infection (UTI)						
Hollander 2005	4	19	7	20	100.0%	0.60 [0.21 , 1.73]
Subtotal (95% CI)		**19**		**20**	**100.0%**	**0.60 [0.21 , 1.73]**
Total events:	4		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.94 (P = 0.35)						
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%						



Analysis 4.12. Comparison 4: Antidepressant vs placebo, Outcome 12: Adverse effects: other

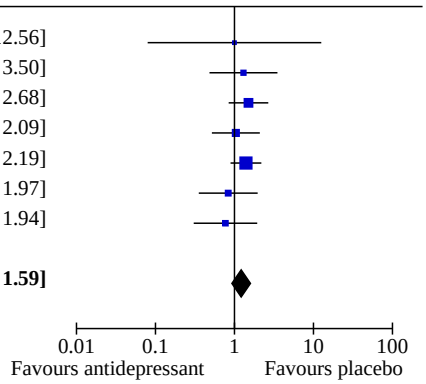
Study or Subgroup	Fluoxetine Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
4.12.1 Salty taste						
Hollander 2012	1	22	0	15	100.0%	2.09 [0.09 , 48.04]
Subtotal (95% CI)		**22**		**15**	**100.0%**	**2.09 [0.09 , 48.04]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
4.12.2 Trembling (mild)						
Hollander 2012	1	22	0	15	100.0%	2.09 [0.09 , 48.04]
Subtotal (95% CI)		**22**		**15**	**100.0%**	**2.09 [0.09 , 48.04]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						



Analysis 4.13. Comparison 4: Antidepressant vs placebo, Outcome 13: Tolerability/acceptability: loss to follow-up

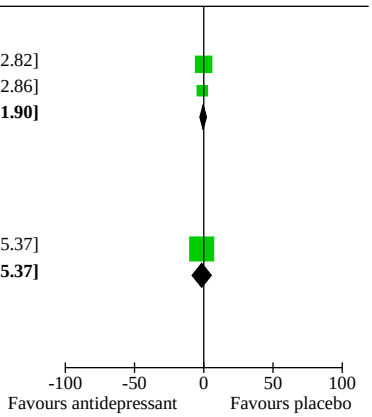
Study or Subgroup	Antidepressant Events	Antidepressant Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Gordon 1993	1	6	1	6	1.1%	1.00 [0.08 , 12.56]
Hagerman 2018	8	32	5	26	7.4%	1.30 [0.48 , 3.50]
Herscu 2020	22	78	15	80	21.9%	1.50 [0.84 , 2.68]
King 2009	13	73	13	76	14.9%	1.04 [0.52 , 2.09]
Mouti 2014	31	75	21	71	36.2%	1.40 [0.89 , 2.19]
NCT00183339	4	8	6	10	9.9%	0.83 [0.35 , 1.97]
Remington 2001	5	13	5	10	8.5%	0.77 [0.30 , 1.94]
Total (95% CI)		**285**		**279**	**100.0%**	**1.22 [0.93 , 1.59]**
Total events:	84		66			

Heterogeneity: Tau² = 0.00; Chi² = 2.81, df = 6 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.16)
Test for subgroup differences: Not applicable



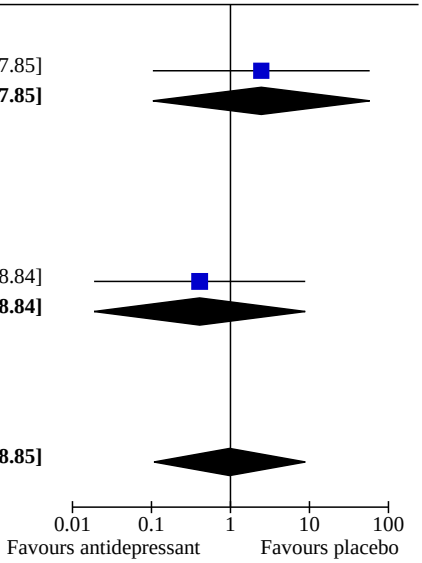
Analysis 4.14. Comparison 4: Antidepressant vs placebo, Outcome 14: Subgroup analyses: gender - irritability

Study or Subgroup	Antidepressant Mean	Antidepressant SD	Antidepressant Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
4.14.1 Male and female participants								
King 2009	10.1	9.3	73	10.2	8.9	76	64.2%	-0.10 [-3.02 , 2.82]
Mouti 2014	12.28	9.19	53	13.34	11.29	53	35.8%	-1.06 [-4.98 , 2.86]
Subtotal (95% CI)			**126**			**129**	**100.0%**	**-0.44 [-2.79 , 1.90]**
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%								
Test for overall effect: Z = 0.37 (P = 0.71)								
4.14.2 Male participants only								
Niederhofer 2003	12.3	6.9	6	13.8	5.1	6	100.0%	-1.50 [-8.37 , 5.37]
Subtotal (95% CI)			**6**			**6**	**100.0%**	**-1.50 [-8.37 , 5.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.43 (P = 0.67)								



Analysis 4.15. Comparison 4: Antidepressant vs placebo, Outcome 15: Serious adverse events

Study or Subgroup	Fluoxetine Events	Fluoxetine Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
4.15.1 Hospitalisation for dehydration						
Hagerman 2018 (1)	1	32	0	26	48.7%	2.45 [0.10 , 57.85]
Subtotal (95% CI)		**32**		**26**	**48.7%**	**2.45 [0.10 , 57.85]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.58)						
4.15.2 Severe diarrhoea						
NCT00183339 (2)	0	8	1	10	51.3%	0.41 [0.02 , 8.84]
Subtotal (95% CI)		**8**		**10**	**51.3%**	**0.41 [0.02 , 8.84]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
Total (95% CI)		**40**		**36**	**100.0%**	**0.98 [0.11 , 8.85]**
Total events:	1		1			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.64$, df = 1 (P = 0.42); $I^2 = 0\%$						
Test for overall effect: Z = 0.02 (P = 0.98)						
Test for subgroup differences: $Chi^2 = 0.64$, df = 1 (P = 0.42), $I^2 = 0\%$						



Footnotes
(1) Sertraline
(2) Fluoxetine

Comparison 5. Atypical vs typical antipsychotics

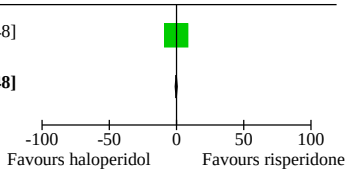
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Irritability	1	30	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.95, 0.48]
5.2 Adverse effects: cardiovascular (tachycardia)	1	12	Risk Ratio (IV, Random, 95% CI)	0.33 [0.02, 6.86]
5.3 Adverse effects: gastrointestinal	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.3.1 Constipation	1	30	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.24, 4.18]
5.3.2 Dry mouth	1	12	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.08, 12.56]
5.3.3 Nausea/vomiting	1	12	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.29, 86.43]
5.4 Adverse effects: metabolic (dichotomous)	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.4.1 Weight gain	1	12	Risk Ratio (IV, Random, 95% CI)	1.18 [0.76, 1.83]
5.4.2 Weight loss	1	12	Risk Ratio (IV, Random, 95% CI)	0.33 [0.02, 6.86]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.5 Adverse effects: metabolic (continuous)	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.5.1 Weight gain (kg)	2	42	Std. Mean Difference (IV, Random, 95% CI)	0.26 [-1.54, 2.06]
5.6 Adverse effects: neurological	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.6.1 Ataxia	1	12	Risk Ratio (IV, Random, 95% CI)	0.33 [0.02, 6.86]
5.6.2 Blunted effect	1	30	Risk Ratio (IV, Random, 95% CI)	0.11 [0.01, 1.90]
5.6.3 Insomnia	1	12	Risk Ratio (IV, Random, 95% CI)	3.00 [0.15, 61.74]
5.6.4 Rigidity	1	12	Risk Ratio (IV, Random, 95% CI)	0.33 [0.02, 6.86]
5.6.5 Sedation	1	12	Risk Ratio (IV, Random, 95% CI)	2.50 [0.76, 8.19]
5.7 Adverse effects: respiratory	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.7.1 Respiratory tract infection	1	30	Risk Ratio (IV, Random, 95% CI)	0.88 [0.43, 1.80]
5.8 Adverse effects: skin	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.8.1 Rash	1	12	Risk Ratio (IV, Random, 95% CI)	0.33 [0.02, 6.86]
5.9 Adverse effects: urinary	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.9.1 Enuresis	2	42	Risk Ratio (IV, Random, 95% CI)	1.00 [0.29, 3.48]
5.10 Tolerability/acceptability: loss to follow-up	2	42	Risk Ratio (IV, Random, 95% CI)	5.00 [0.26, 96.13]

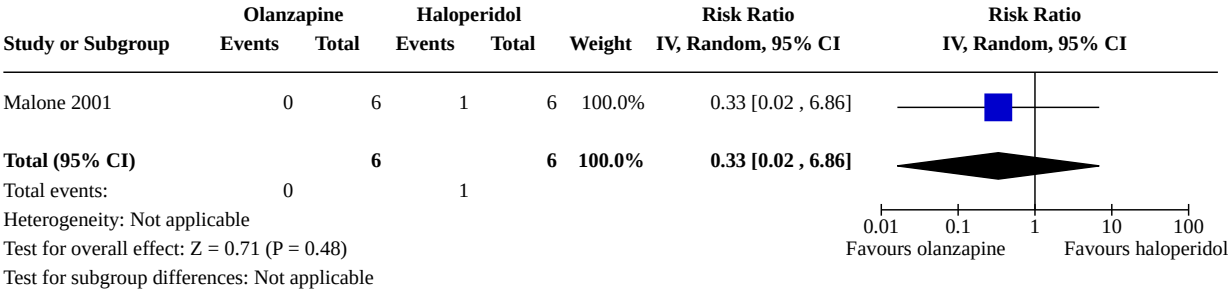
Analysis 5.1. Comparison 5: Atypical vs typical antipsychotics, Outcome 1: Irritability

Study or Subgroup	Risperidone Mean	SD	Total	Haloperidol Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Miral 2008	0.54	0.34	15	0.64	0.48	15	100.0%	-0.23 [-0.95 , 0.48]
Total (95% CI)			**15**			**15**	**100.0%**	**-0.23 [-0.95 , 0.48]**

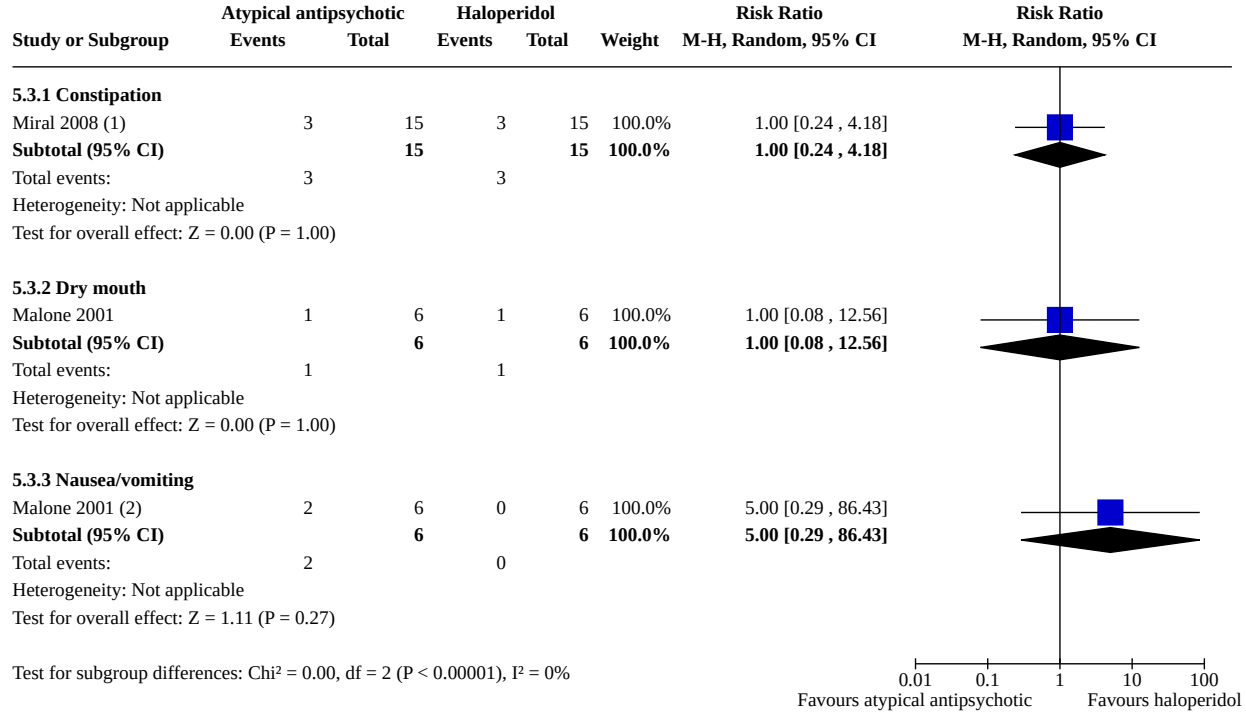
Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.52)
Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5: Atypical vs typical antipsychotics, Outcome 2: Adverse effects: cardiovascular (tachycardia)



Analysis 5.3. Comparison 5: Atypical vs typical antipsychotics, Outcome 3: Adverse effects: gastrointestinal



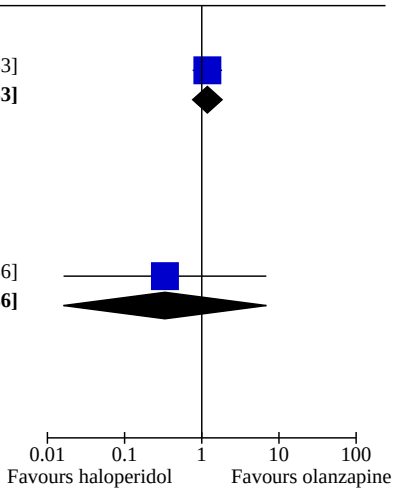
Footnotes

(1) Risperidone vs haloperidol

(2) Olanzapine vs haloperidol

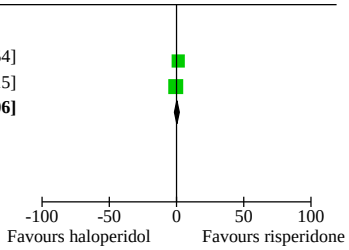
Analysis 5.4. Comparison 5: Atypical vs typical antipsychotics, Outcome 4: Adverse effects: metabolic (dichotomous)

Study or Subgroup	Olanzapine Events	Olanzapine Total	Haloperidol Events	Haloperidol Total	Weight	Risk Ratio IV, Random, 95% CI
5.4.1 Weight gain						
Malone 2001	6	6	5	6	100.0%	1.18 [0.76 , 1.83]
Subtotal (95% CI)		**6**		**6**	**100.0%**	**1.18 [0.76 , 1.83]**
Total events:	6		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.75 (P = 0.45)						
5.4.2 Weight loss						
Malone 2001	0	6	1	6	100.0%	0.33 [0.02 , 6.86]
Subtotal (95% CI)		**6**		**6**	**100.0%**	**0.33 [0.02 , 6.86]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						

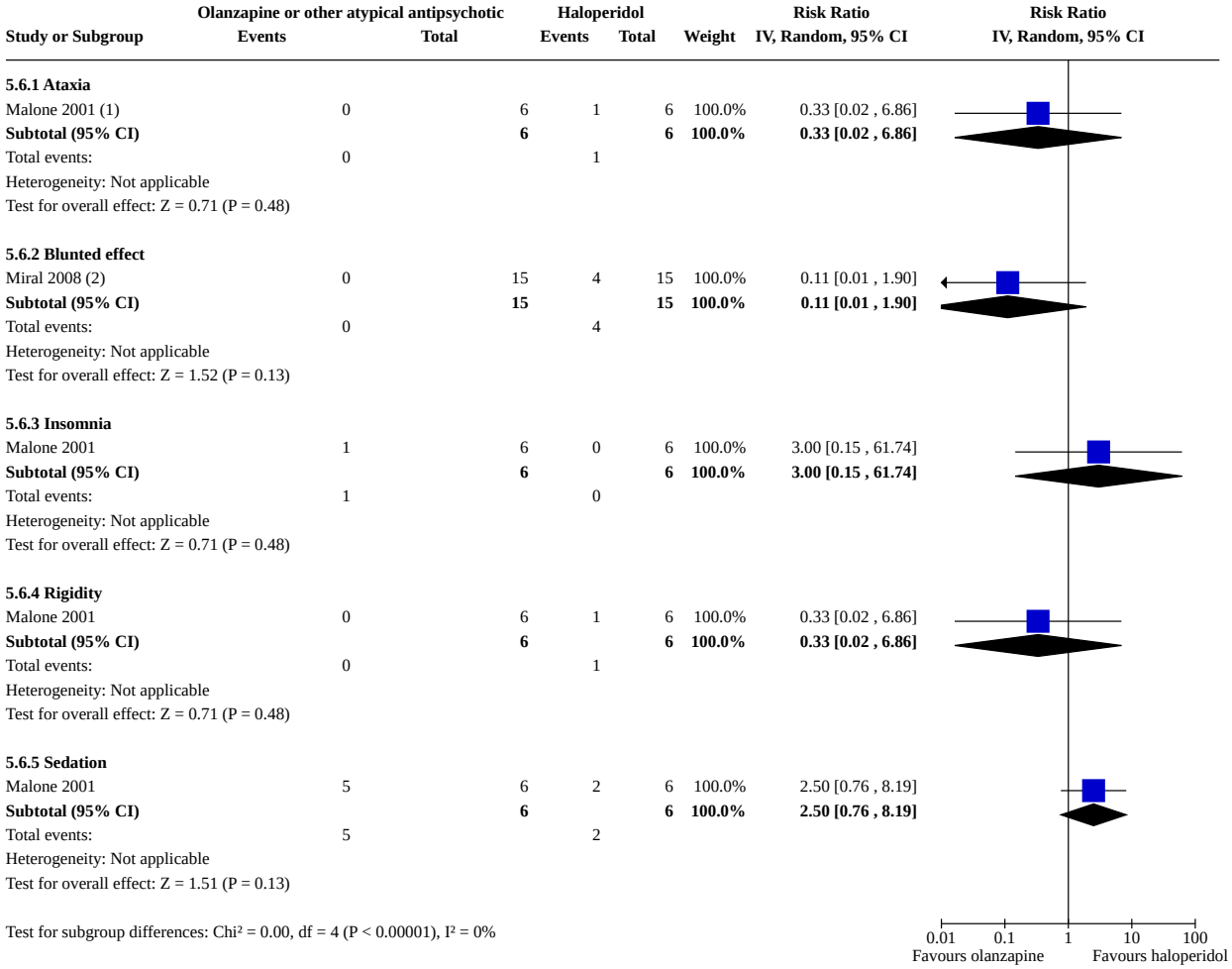


Analysis 5.5. Comparison 5: Atypical vs typical antipsychotics, Outcome 5: Adverse effects: metabolic (continuous)

Study or Subgroup	Atypical antipsychotic Mean	Atypical antipsychotic SD	Atypical antipsychotic Total	Haloperidol Mean	Haloperidol SD	Haloperidol Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.5.1 Weight gain (kg)								
Malone 2001	4.08	1.59	6	1.45	2.22	6	45.7%	1.26 [-0.03 , 2.54]
Miral 2008	4.3	0.7	15	4.6	0.1	15	54.3%	-0.58 [-1.32 , 0.15]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**0.26 [-1.54 , 2.06]**
Heterogeneity: Tau² = 1.41; Chi² = 5.93, df = 1 (P = 0.01); I² = 83%								
Test for overall effect: Z = 0.28 (P = 0.78)								
Test for subgroup differences: Not applicable								



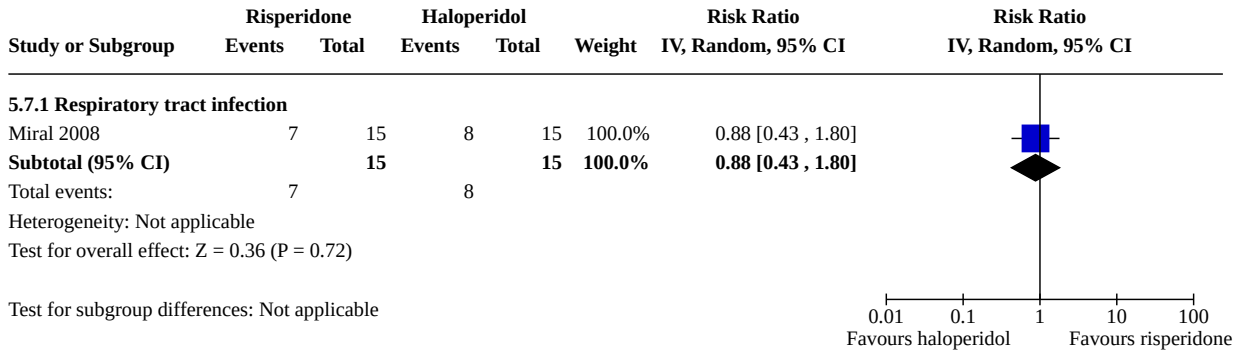
Analysis 5.6. Comparison 5: Atypical vs typical antipsychotics, Outcome 6: Adverse effects: neurological



Footnotes

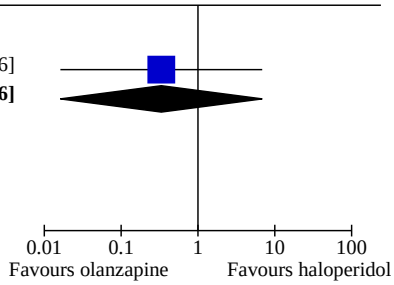
(1) Olanzapine vs haloperidol
(2) risperidone vs haloperidol

Analysis 5.7. Comparison 5: Atypical vs typical antipsychotics, Outcome 7: Adverse effects: respiratory



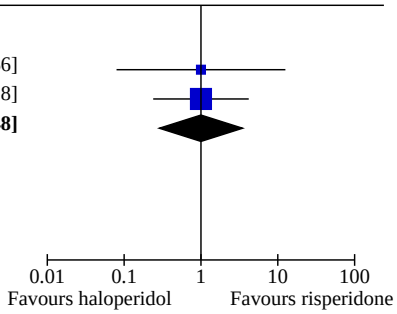
Analysis 5.8. Comparison 5: Atypical vs typical antipsychotics, Outcome 8: Adverse effects: skin

Study or Subgroup	Olanzapine Events	Olanzapine Total	Haloperidol Events	Haloperidol Total	Weight	Risk Ratio IV, Random, 95% CI
5.8.1 Rash						
Malone 2001	0	6	1	6	100.0%	0.33 [0.02 , 6.86]
Subtotal (95% CI)		**6**		**6**	**100.0%**	**0.33 [0.02 , 6.86]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
Test for subgroup differences: Not applicable						



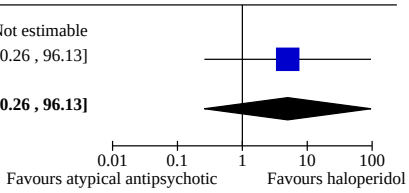
Analysis 5.9. Comparison 5: Atypical vs typical antipsychotics, Outcome 9: Adverse effects: urinary

Study or Subgroup	Haloperidol Events	Haloperidol Total	Risperidone Events	Risperidone Total	Weight	Risk Ratio IV, Random, 95% CI
5.9.1 Enuresis						
Malone 2001	1	6	1	6	24.2%	1.00 [0.08 , 12.56]
Miral 2008	3	15	3	15	75.8%	1.00 [0.24 , 4.18]
Subtotal (95% CI)		**21**		**21**	**100.0%**	**1.00 [0.29 , 3.48]**
Total events:	4		4			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (P = 1.00); $I^2 = 0\%$						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Not applicable						



Analysis 5.10. Comparison 5: Atypical vs typical antipsychotics, Outcome 10: Tolerability/acceptability: loss to follow-up

Study or Subgroup	Atypical antipsychotic Events	Atypical antipsychotic Total	Typical antipsychotic (haloperidol) Events	Typical antipsychotic (haloperidol) Total	Weight	Risk Ratio IV, Random, 95% CI
Malone 2001	0	6	0	6		Not estimable
Miral 2008	2	15	0	15	100.0%	5.00 [0.26 , 96.13]
Total (95% CI)		**21**		**21**	**100.0%**	**5.00 [0.26 , 96.13]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.29)						
Test for subgroup differences: Not applicable						



Comparison 6. Atypical vs atypical antipsychotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Irritability	2	110	Std. Mean Difference (IV, Random, 95% CI)	0.40 [0.02, 0.78]
6.2 Adverse effects: cardiovascular	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only

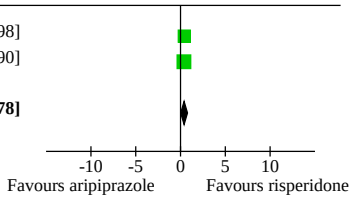
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2.1 Tachycardia	2	120	Risk Ratio (IV, Random, 95% CI)	1.07 [0.16, 7.04]
6.3 Adverse effects: gastrointestinal	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6.3.1 Abdominal pain	1	59	Risk Ratio (IV, Random, 95% CI)	3.10 [0.34, 28.15]
6.3.2 Constipation	2	120	Risk Ratio (IV, Random, 95% CI)	1.30 [0.34, 4.91]
6.3.3 Diarrhoea	1	59	Risk Ratio (IV, Random, 95% CI)	3.10 [0.13, 73.14]
6.3.4 Drooling	2	120	Risk Ratio (IV, Random, 95% CI)	0.72 [0.38, 1.37]
6.3.5 Dry mouth	1	59	Risk Ratio (IV, Random, 95% CI)	5.17 [0.26, 103.21]
6.3.6 Nausea	1	59	Risk Ratio (IV, Random, 95% CI)	0.52 [0.05, 5.40]
6.3.7 Vomiting	2	120	Risk Ratio (IV, Random, 95% CI)	1.61 [0.20, 12.65]
6.4 Adverse effects: metabolic	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6.4.1 Decreased appetite	2	120	Risk Ratio (IV, Random, 95% CI)	1.67 [0.56, 4.96]
6.4.2 Increased appetite	2	120	Risk Ratio (IV, Random, 95% CI)	0.61 [0.15, 2.47]
6.4.3 Weight gain	1	61	Risk Ratio (IV, Random, 95% CI)	0.37 [0.19, 0.70]
6.5 Adverse effects: musculoskeletal	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.5.1 Muscle rigidity	1	61	Risk Ratio (M-H, Random, 95% CI)	2.91 [0.12, 68.66]
6.6 Adverse effects: neurological	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6.6.1 Agitation	1	61	Risk Ratio (IV, Random, 95% CI)	4.84 [0.24, 96.89]
6.6.2 Difficulty sleeping	1	61	Risk Ratio (IV, Random, 95% CI)	6.78 [0.37, 125.95]
6.6.3 Dizziness	2	120	Risk Ratio (IV, Random, 95% CI)	0.73 [0.10, 5.39]
6.6.4 Fatigue	1	59	Risk Ratio (IV, Random, 95% CI)	1.03 [0.29, 3.75]
6.6.5 Headache	1	61	Risk Ratio (IV, Random, 95% CI)	0.97 [0.06, 14.78]
6.6.6 Nausea	1	61	Risk Ratio (IV, Random, 95% CI)	2.91 [0.12, 68.66]
6.6.7 Nervousness	1	59	Risk Ratio (IV, Random, 95% CI)	2.07 [0.20, 21.60]
6.6.8 Restlessness	2	120	Risk Ratio (IV, Random, 95% CI)	0.44 [0.07, 2.88]
6.6.9 Tremor	1	59	Risk Ratio (IV, Random, 95% CI)	1.55 [0.28, 8.62]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.6.10 Sedation	1	61	Risk Ratio (IV, Random, 95% CI)	3.39 [0.76, 15.02]
6.6.11 Somnolence	1	61	Risk Ratio (IV, Random, 95% CI)	8.72 [0.49, 155.27]
6.7 Adverse effects: psychological	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.7.1 Depression	1	59	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.13]
6.8 Adverse effects: skin	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6.8.1 Rash	1	59	Risk Ratio (IV, Random, 95% CI)	1.03 [0.07, 15.77]
6.9 Adverse effects: urinary	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6.9.1 Enuresis	2	120	Risk Ratio (IV, Random, 95% CI)	1.37 [0.04, 53.78]
6.10 Tolerability/acceptability: loss to follow-up	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Analysis 6.1. Comparison 6: Atypical vs atypical antipsychotics, Outcome 1: Irritability

Study or Subgroup	Aripiprazole Mean	SD	Total	Risperidone Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
DeVane 2019	14.1	3.5	27	12.7	3	24	46.2%	0.42 [-0.14 , 0.98]
Ghanizadeh 2014	14.6	5.5	29	12.5	5.4	30	53.8%	0.38 [-0.14 , 0.90]
Total (95% CI)			**56**			**54**	**100.0%**	**0.40 [0.02 , 0.78]**

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 2.07 (P = 0.04)
Test for subgroup differences: Not applicable

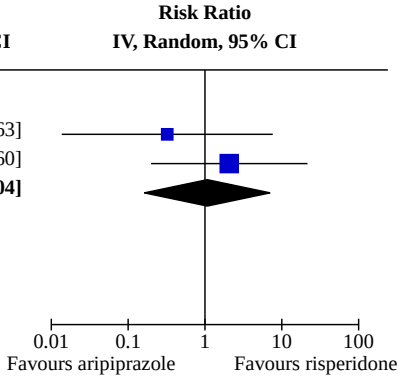


Analysis 6.2. Comparison 6: Atypical vs atypical antipsychotics, Outcome 2: Adverse effects: cardiovascular

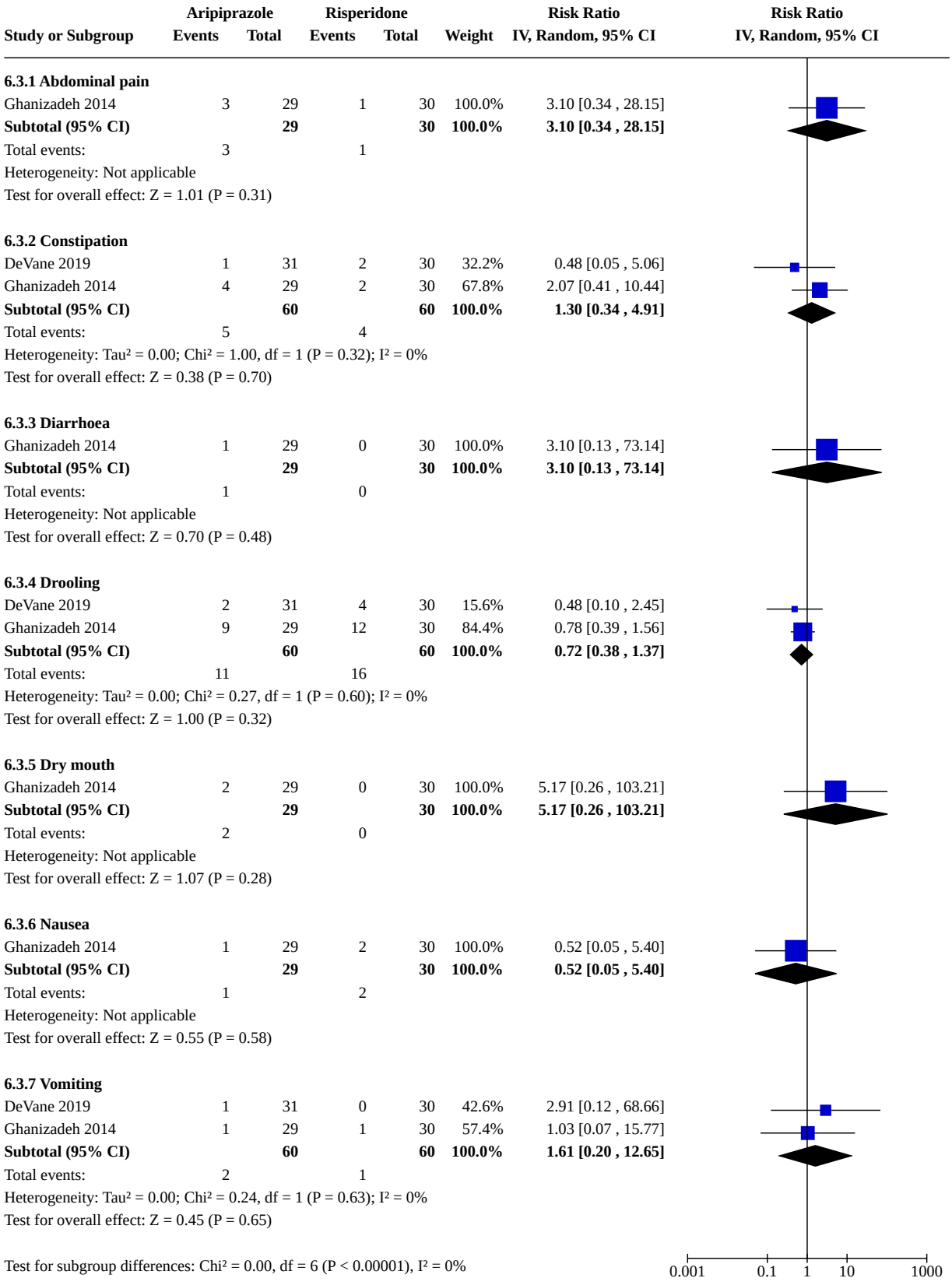
Study or Subgroup	Aripiprazole Events	Total	Risperidone Events	Total	Weight	Risk Ratio IV, Random, 95% CI
6.2.1 Tachycardia						
DeVane 2019	0	31	1	30	35.5%	0.32 [0.01 , 7.63]
Ghanizadeh 2014	2	29	1	30	64.5%	2.07 [0.20 , 21.60]
Subtotal (95% CI)		**60**		**60**	**100.0%**	**1.07 [0.16 , 7.04]**
Total events:	2		2			

Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.94)

Test for subgroup differences: Not applicable

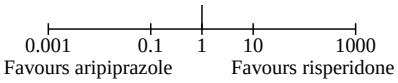


Analysis 6.3. Comparison 6: Atypical vs atypical antipsychotics, Outcome 3: Adverse effects: gastrointestinal



Analysis 6.3. (Continued)

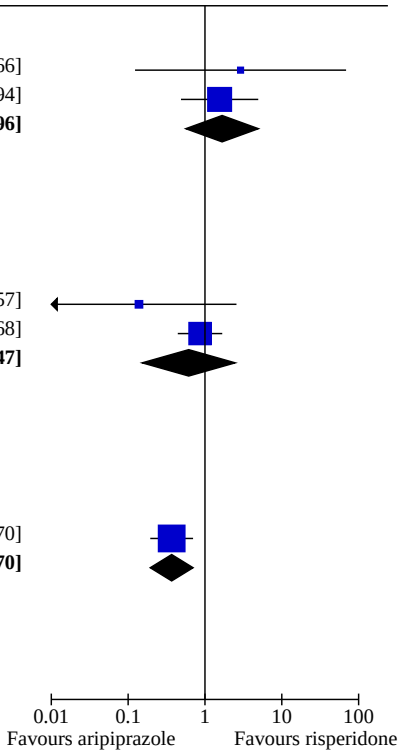
Test for subgroup differences: Chi² = 0.00, df = 6 (P < 0.00001), I² = 0%



Analysis 6.4. Comparison 6: Atypical vs atypical antipsychotics, Outcome 4: Adverse effects: metabolic

Study or Subgroup	Aripiprazole Events	Total	Risperidone Events	Total	Weight	Risk Ratio IV, Random, 95% CI
6.4.1 Decreased appetite						
DeVane 2019	1	31	0	30	11.8%	2.91 [0.12 , 68.66]
Ghanizadeh 2014	6	29	4	30	88.2%	1.55 [0.49 , 4.94]
Subtotal (95% CI)		**60**		**60**	**100.0%**	**1.67 [0.56 , 4.96]**
Total events:	7		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.93 (P = 0.35)						
6.4.2 Increased appetite						
DeVane 2019	0	31	3	30	18.5%	0.14 [0.01 , 2.57]
Ghanizadeh 2014	10	29	12	30	81.5%	0.86 [0.44 , 1.68]
Subtotal (95% CI)		**60**		**60**	**100.0%**	**0.61 [0.15 , 2.47]**
Total events:	10		15			
Heterogeneity: Tau² = 0.50; Chi² = 1.43, df = 1 (P = 0.23); I² = 30%						
Test for overall effect: Z = 0.69 (P = 0.49)						
6.4.3 Weight gain						
DeVane 2019	8	31	21	30	100.0%	0.37 [0.19 , 0.70]
Subtotal (95% CI)		**31**		**30**	**100.0%**	**0.37 [0.19 , 0.70]**
Total events:	8		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.05 (P = 0.002)						

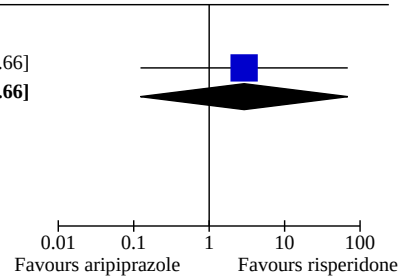
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%



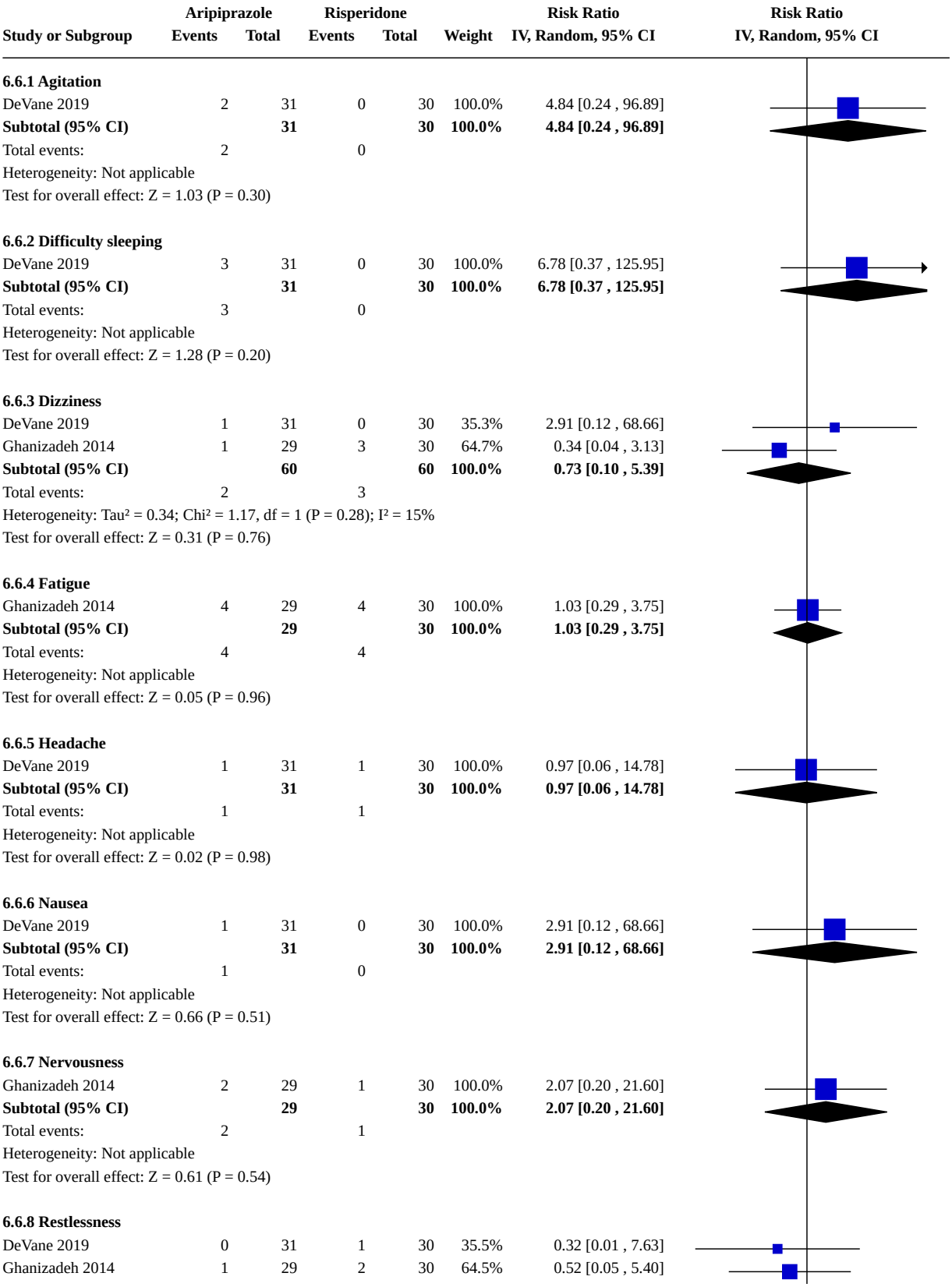
Analysis 6.5. Comparison 6: Atypical vs atypical antipsychotics, Outcome 5: Adverse effects: musculoskeletal

Study or Subgroup	Aripiprazole Events	Total	Risperidone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
6.5.1 Muscle rigidity						
DeVane 2019	1	31	0	30	100.0%	2.91 [0.12 , 68.66]
Subtotal (95% CI)		**31**		**30**	**100.0%**	**2.91 [0.12 , 68.66]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						

Test for subgroup differences: Not applicable

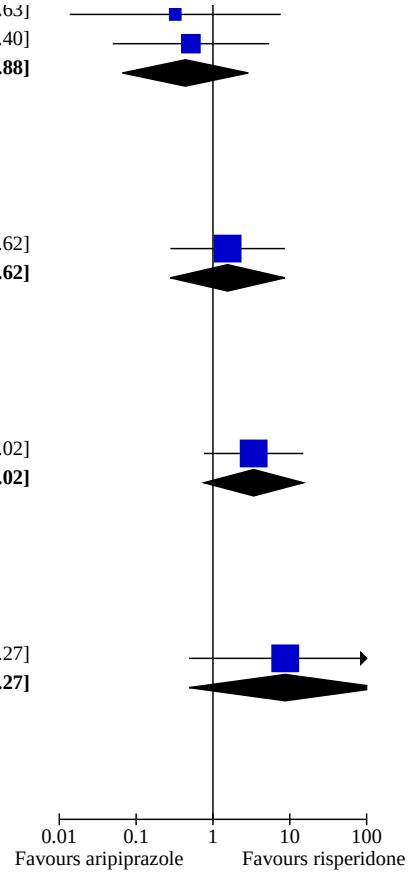


Analysis 6.6. Comparison 6: Atypical vs atypical antipsychotics, Outcome 6: Adverse effects: neurological



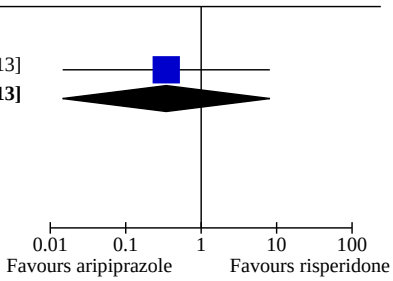
Analysis 6.6. (Continued)

DeVane 2019	0	31	1	30	35.5%	0.32 [0.01 , 7.63]
Ghanizadeh 2014	1	29	2	30	64.5%	0.52 [0.05 , 5.40]
Subtotal (95% CI)		**60**		**60**	**100.0%**	**0.44 [0.07 , 2.88]**
Total events:	1		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%						
Test for overall effect: Z = 0.86 (P = 0.39)						
6.6.9 Tremor						
Ghanizadeh 2014	3	29	2	30	100.0%	1.55 [0.28 , 8.62]
Subtotal (95% CI)		**29**		**30**	**100.0%**	**1.55 [0.28 , 8.62]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.50 (P = 0.62)						
6.6.10 Sedation						
DeVane 2019	7	31	2	30	100.0%	3.39 [0.76 , 15.02]
Subtotal (95% CI)		**31**		**30**	**100.0%**	**3.39 [0.76 , 15.02]**
Total events:	7		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.61 (P = 0.11)						
6.6.11 Somnolence						
DeVane 2019	4	31	0	30	100.0%	8.72 [0.49 , 155.27]
Subtotal (95% CI)		**31**		**30**	**100.0%**	**8.72 [0.49 , 155.27]**
Total events:	4		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.47 (P = 0.14)						
Test for subgroup differences: Chi² = 0.00, df = 10 (P < 0.00001), I² = 0%						



Analysis 6.7. Comparison 6: Atypical vs atypical antipsychotics, Outcome 7: Adverse effects: psychological

Study or Subgroup	Aripiprazole Events	Aripiprazole Total	Risperidone Events	Risperidone Total	Weight	Risk Ratio M-H, Random, 95% CI
6.7.1 Depression						
Ghanizadeh 2014	0	29	1	30	100.0%	0.34 [0.01 , 8.13]
Subtotal (95% CI)		**29**		**30**	**100.0%**	**0.34 [0.01 , 8.13]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
Test for subgroup differences: Not applicable						

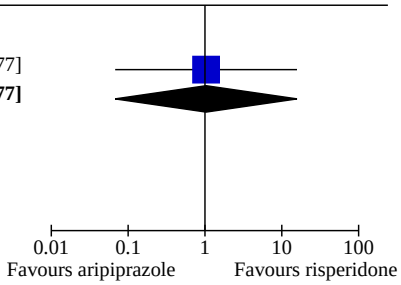


Analysis 6.8. Comparison 6: Atypical vs atypical antipsychotics, Outcome 8: Adverse effects: skin

Study or Subgroup	Aripiprazole Events	Total	Risperidone Events	Total	Weight	Risk Ratio IV, Random, 95% CI
6.8.1 Rash						
Ghanizadeh 2014	1	29	1	30	100.0%	1.03 [0.07 , 15.77]
Subtotal (95% CI)		**29**		**30**	**100.0%**	**1.03 [0.07 , 15.77]**
Total events:	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.98)

Test for subgroup differences: Not applicable

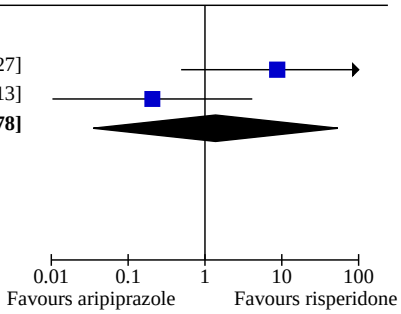


Analysis 6.9. Comparison 6: Atypical vs atypical antipsychotics, Outcome 9: Adverse effects: urinary

Study or Subgroup	Aripiprazole Events	Total	Risperidone Events	Total	Weight	Risk Ratio IV, Random, 95% CI
6.9.1 Enuresis						
DeVane 2019	4	31	0	30	50.6%	8.72 [0.49 , 155.27]
Ghanizadeh 2014	0	29	2	30	49.4%	0.21 [0.01 , 4.13]
Subtotal (95% CI)		**60**		**60**	**100.0%**	**1.37 [0.04 , 53.78]**
Total events:	4		2			

Heterogeneity: $Tau^2 = 4.76$; $Chi^2 = 3.12$, df = 1 (P = 0.08); $I^2 = 68\%$
Test for overall effect: Z = 0.17 (P = 0.87)

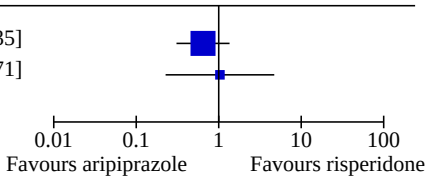
Test for subgroup differences: Not applicable



Analysis 6.10. Comparison 6: Atypical vs atypical antipsychotics, Outcome 10: Tolerability/acceptability: loss to follow-up

Study or Subgroup	Aripiprazole Events	Total	Risperidone Events	Total	Risk Ratio IV, Random, 95% CI
DeVane 2019	8	31	12	30	0.65 [0.31 , 1.35]
Ghanizadeh 2014	3	29	3	30	1.03 [0.23 , 4.71]

Test for subgroup differences: Not applicable

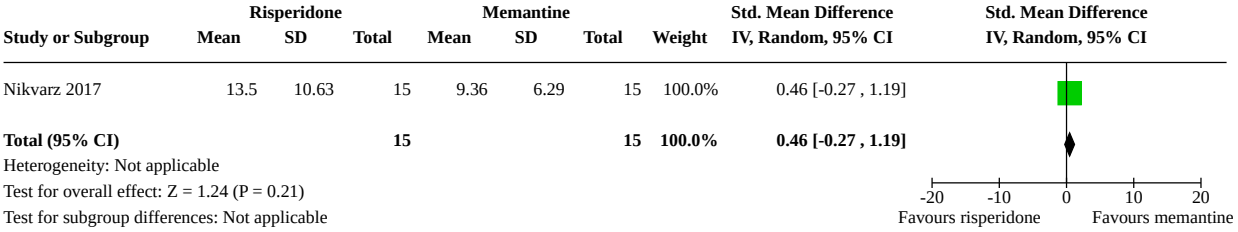


Comparison 7. Atypical antipsychotic vs antidementia

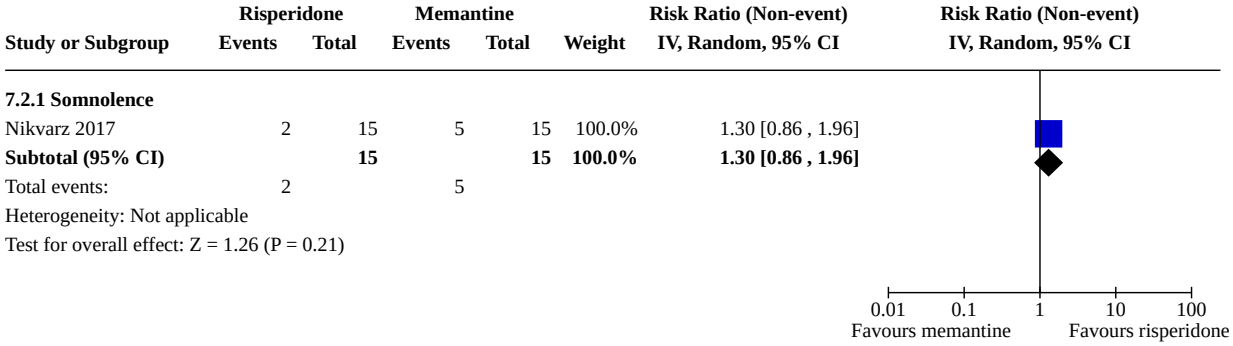
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Irritability	1	30	Std. Mean Difference (IV, Random, 95% CI)	0.46 [-0.27, 1.19]
7.2 Adverse effects: neurological	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2.1 Somnolence	1	30	Risk Ratio (IV, Random, 95% CI)	1.30 [0.86, 1.96]
7.3 Tolerability	1	34	Risk Ratio (IV, Random, 95% CI)	0.38 [0.04, 3.25]

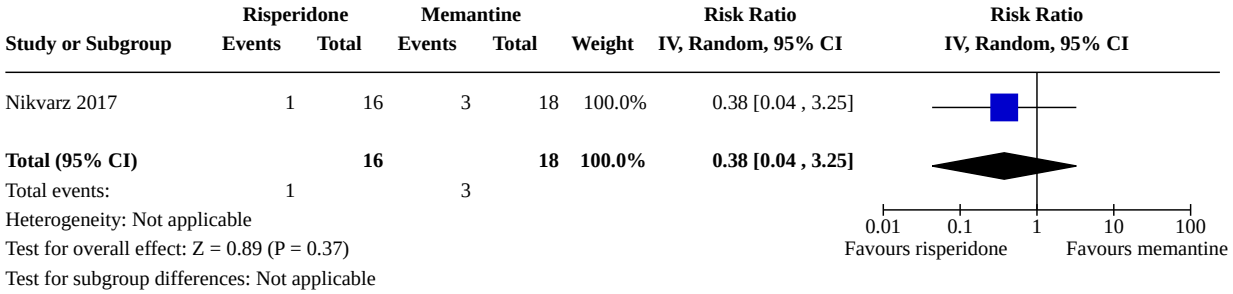
Analysis 7.1. Comparison 7: Atypical antipsychotic vs antidementia, Outcome 1: Irritability



Analysis 7.2. Comparison 7: Atypical antipsychotic vs antidementia, Outcome 2: Adverse effects: neurological



Analysis 7.3. Comparison 7: Atypical antipsychotic vs antidementia, Outcome 3: Tolerability

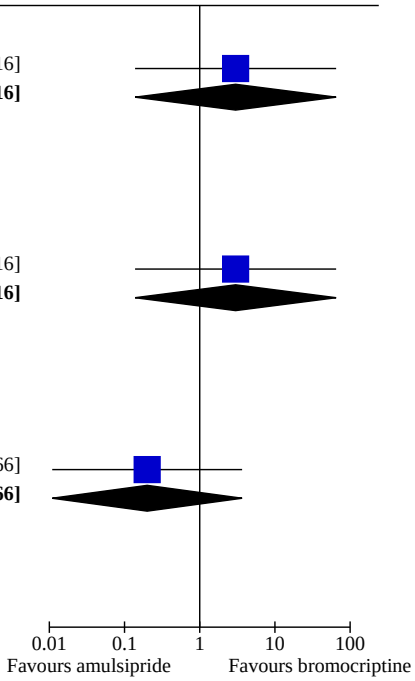


Comparison 8. Atypical antipsychotic vs antiparkinsonian

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Adverse effects: gastrointestinal	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
8.1.1 Diarrhoea	1	18	Risk Ratio (IV, Random, 95% CI)	3.00 [0.14, 65.16]
8.1.2 Increased salivation	1	18	Risk Ratio (IV, Random, 95% CI)	3.00 [0.14, 65.16]
8.1.3 Vomiting	1	18	Risk Ratio (IV, Random, 95% CI)	0.20 [0.01, 3.66]
8.2 Adverse effects: metabolic	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
8.2.1 Decreased appetite	1	18	Risk Ratio (IV, Random, 95% CI)	0.09 [0.01, 1.44]
8.3 Adverse effects: neurological	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
8.3.1 Agitation/excitement	1	18	Risk Ratio (IV, Random, 95% CI)	1.50 [0.32, 6.94]
8.3.2 Increased hyperactivity	1	18	Risk Ratio (IV, Random, 95% CI)	7.00 [0.41, 118.69]
8.3.3 Insomnia	1	18	Risk Ratio (IV, Random, 95% CI)	2.00 [0.48, 8.31]
8.3.4 Sedation	1	18	Risk Ratio (IV, Random, 95% CI)	0.14 [0.01, 2.42]

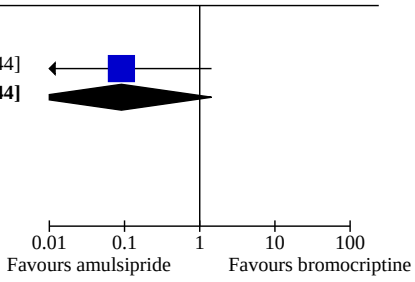
Analysis 8.1. Comparison 8: Atypical antipsychotic vs antiparkinsonian, Outcome 1: Adverse effects: gastrointestinal

Study or Subgroup	Amulspiride Events	Amulspiride Total	Bromocriptine Events	Bromocriptine Total	Weight	Risk Ratio IV, Random, 95% CI
8.1.1 Diarrhoea						
Dollfus 1992	1	9	0	9	100.0%	3.00 [0.14 , 65.16]
Subtotal (95% CI)		**9**		**9**	**100.0%**	**3.00 [0.14 , 65.16]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
8.1.2 Increased salivation						
Dollfus 1992	1	9	0	9	100.0%	3.00 [0.14 , 65.16]
Subtotal (95% CI)		**9**		**9**	**100.0%**	**3.00 [0.14 , 65.16]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
8.1.3 Vomiting						
Dollfus 1992	0	9	2	9	100.0%	0.20 [0.01 , 3.66]
Subtotal (95% CI)		**9**		**9**	**100.0%**	**0.20 [0.01 , 3.66]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.09 (P = 0.28)						
Test for subgroup differences: $Chi^2 = 0.00$, df = 2 (P < 0.00001), $I^2 = 0\%$						

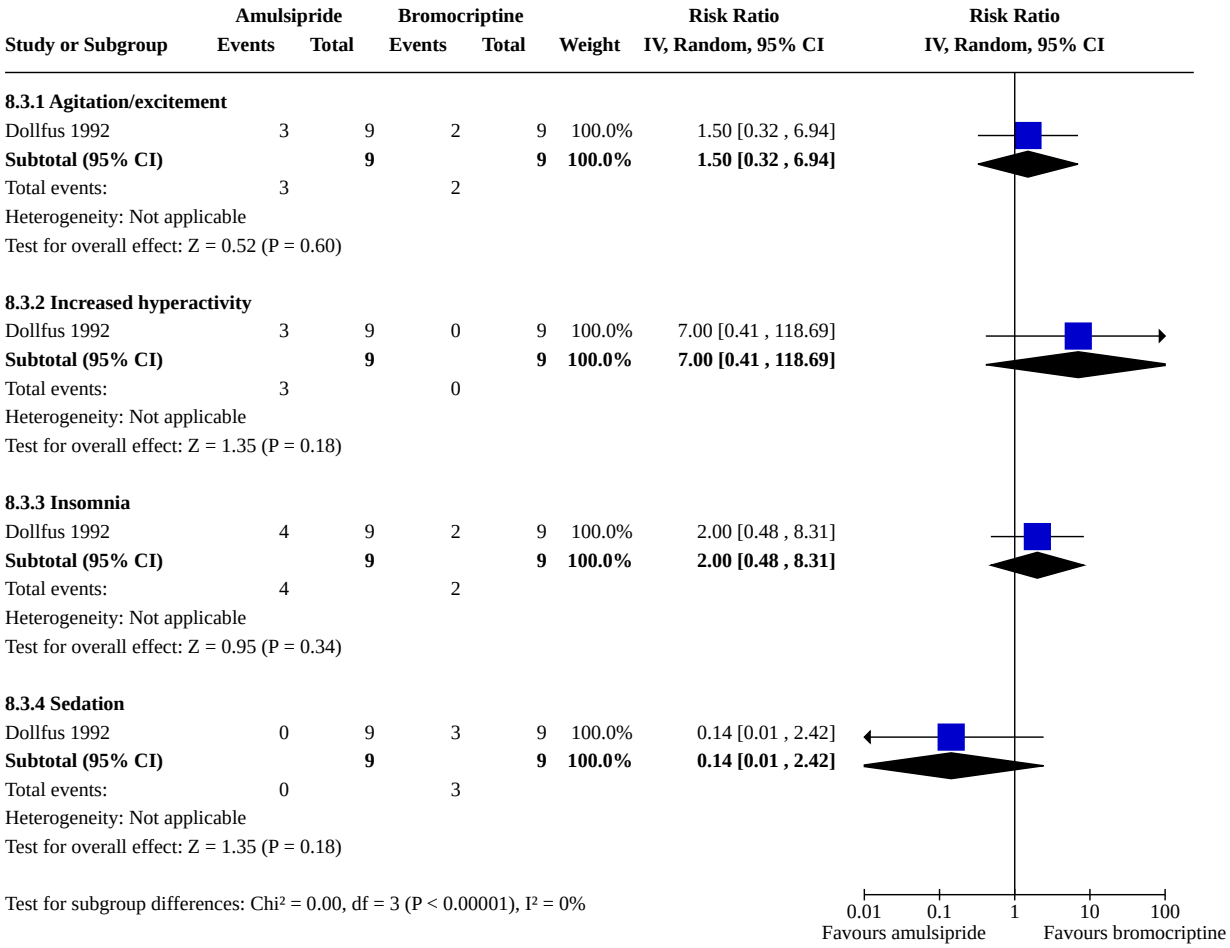


Analysis 8.2. Comparison 8: Atypical antipsychotic vs antiparkinsonian, Outcome 2: Adverse effects: metabolic

Study or Subgroup	Amulspiride Events	Amulspiride Total	Bromocriptine Events	Bromocriptine Total	Weight	Risk Ratio IV, Random, 95% CI
8.2.1 Decreased appetite						
Dollfus 1992	0	9	5	9	100.0%	0.09 [0.01 , 1.44]
Subtotal (95% CI)		**9**		**9**	**100.0%**	**0.09 [0.01 , 1.44]**
Total events:	0		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.70 (P = 0.09)						
Test for subgroup differences: Not applicable						



Analysis 8.3. Comparison 8: Atypical antipsychotic vs antiparkinsonian, Outcome 3: Adverse effects: neurological



Comparison 9. Anticonvulsant vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Irritability	3	97	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.93, 0.59]
9.2 Aggression	2	57	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.71, 0.35]
9.3 Adverse effects: gastrointestinal	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
9.3.1 Abdominal pain	1	30	Risk Ratio (IV, Random, 95% CI)	1.75 [0.38, 8.15]
9.3.2 Constipation	1	30	Risk Ratio (IV, Random, 95% CI)	0.58 [0.11, 3.00]
9.3.3 Diarrhoea	1	30	Risk Ratio (IV, Random, 95% CI)	3.50 [0.44, 27.75]
9.3.4 Nausea	2	70	Risk Ratio (IV, Random, 95% CI)	2.32 [0.80, 6.72]

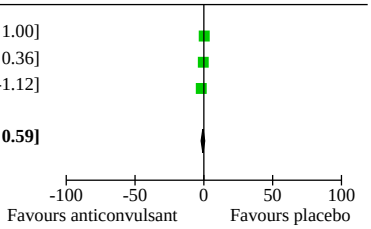
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.3.5 Vomiting	1	30	Risk Ratio (IV, Random, 95% CI)	3.50 [0.44, 27.75]
9.4 Adverse effects: immune system	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
9.4.1 Chills	1	30	Risk Ratio (IV, Random, 95% CI)	2.62 [0.31, 22.46]
9.4.2 Fever	1	30	Risk Ratio (IV, Random, 95% CI)	3.50 [0.44, 27.75]
9.5 Adverse effects: metabolic (dichotomous)	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
9.5.1 Decreased appetite	2	60	Risk Ratio (IV, Random, 95% CI)	5.45 [1.02, 29.23]
9.5.2 Increased appetite	2	70	Risk Ratio (IV, Random, 95% CI)	0.99 [0.05, 18.14]
9.5.3 Weight gain	3	77	Risk Ratio (IV, Random, 95% CI)	1.48 [0.61, 3.62]
9.5.4 Weight loss	1	20	Risk Ratio (IV, Random, 95% CI)	3.00 [0.14, 65.90]
9.6 Adverse effects: metabolic (continuous)	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
9.6.1 Weight gain (kg)	1	11	Std. Mean Difference (IV, Random, 95% CI)	0.48 [-0.77, 1.74]
9.7 Adverse Effects: neurological	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
9.7.1 Aggression	2	48	Risk Ratio (IV, Random, 95% CI)	2.29 [0.37, 14.12]
9.7.2 Agitation	2	47	Risk Ratio (IV, Random, 95% CI)	1.20 [0.21, 6.70]
9.7.3 Dizziness	1	40	Risk Ratio (IV, Random, 95% CI)	4.00 [0.49, 32.72]
9.7.4 Drowsiness	1	30	Risk Ratio (IV, Random, 95% CI)	0.88 [0.21, 3.66]
9.7.5 Echolalia	1	28	Risk Ratio (IV, Random, 95% CI)	1.00 [0.07, 14.45]
9.7.6 Headache	1	27	Risk Ratio (IV, Random, 95% CI)	2.12 [0.09, 47.68]
9.7.7 Hyperactivity	1	20	Risk Ratio (IV, Random, 95% CI)	3.00 [0.14, 65.90]
9.7.8 Hypersomnolence	1	27	Risk Ratio (IV, Random, 95% CI)	0.10 [0.01, 1.78]
9.7.9 Insomnia	4	115	Risk Ratio (IV, Random, 95% CI)	1.69 [0.44, 6.56]
9.7.10 Lethargy	1	30	Risk Ratio (IV, Random, 95% CI)	6.18 [0.35, 110.11]
9.7.11 Paraesthesia	1	40	Risk Ratio (IV, Random, 95% CI)	5.00 [0.64, 39.06]
9.7.12 Sedation	1	40	Risk Ratio (IV, Random, 95% CI)	0.25 [0.03, 2.05]
9.7.13 Self-injury	1	20	Risk Ratio (IV, Random, 95% CI)	3.00 [0.14, 65.90]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.7.14 Somnolence	1	40	Risk Ratio (IV, Random, 95% CI)	7.00 [0.95, 51.80]
9.8 Adverse effects: psychological	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
9.8.5 Impulsivity	1	20	Risk Ratio (IV, Random, 95% CI)	3.00 [0.14, 65.90]
9.9 Adverse effects: skin	2	57	Risk Ratio (IV, Random, 95% CI)	4.63 [0.89, 24.13]
9.9.1 Rash	2	57	Risk Ratio (IV, Random, 95% CI)	4.63 [0.89, 24.13]
9.10 Adverse effects: urinary	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
9.10.1 Enuresis	1	20	Risk Ratio (IV, Random, 95% CI)	0.33 [0.02, 7.32]
9.11 Tolerability/acceptability: loss to follow-up	6	167	Risk Ratio (IV, Random, 95% CI)	1.98 [0.84, 4.66]

Analysis 9.1. Comparison 9: Anticonvulsant vs placebo, Outcome 1: Irritability

Study or Subgroup	Anticonvulsant Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Hellings 2005	18.17	8.79	16	15.45	10.39	14	33.7%	0.28 [-0.44 , 1.00]
Hollander 2010	14.5	6.67	11	17.7	7.94	16	33.1%	-0.42 [-1.19 , 0.36]
Rezaei 2010	8.2	2.44	20	15.3	4.64	20	33.3%	-1.88 [-2.63 , -1.12]
Total (95% CI)			**47**			**50**	**100.0%**	**-0.67 [-1.93 , 0.59]**

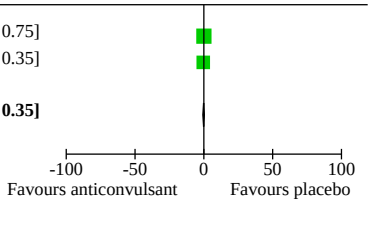
Heterogeneity: Tau² = 1.09; Chi² = 16.81, df = 2 (P = 0.0002); I² = 88%
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 9.2. Comparison 9: Anticonvulsant vs placebo, Outcome 2: Aggression

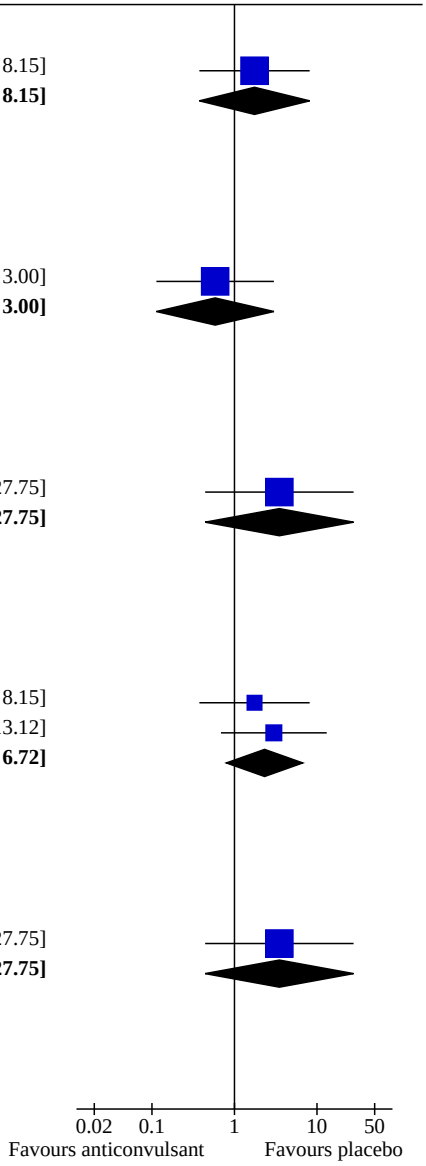
Study or Subgroup	Anticonvulsant Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Hellings 2005	5.86	3.84	16	5.72	4.62	14	54.0%	0.03 [-0.69 , 0.75]
Hollander 2010	5.42	2.17	16	6.25	1.28	11	46.0%	-0.43 [-1.21 , 0.35]
Total (95% CI)			**32**			**25**	**100.0%**	**-0.18 [-0.71 , 0.35]**

Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable



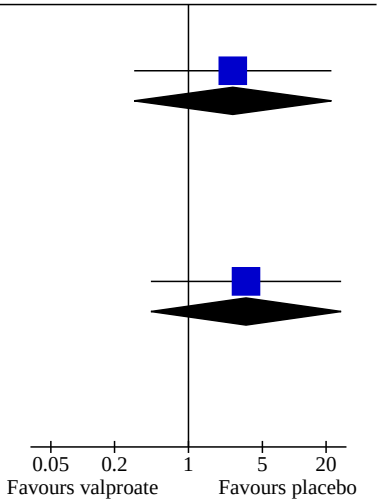
Analysis 9.3. Comparison 9: Anticonvulsant vs placebo, Outcome 3: Adverse effects: gastrointestinal

Study or Subgroup	Anticonvulsant Events	Anticonvulsant Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
9.3.1 Abdominal pain						
Hellings 2005	4	16	2	14	100.0%	1.75 [0.38 , 8.15]
Subtotal (95% CI)		**16**		**14**	**100.0%**	**1.75 [0.38 , 8.15]**
Total events:	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
9.3.2 Constipation						
Hellings 2005	2	16	3	14	100.0%	0.58 [0.11 , 3.00]
Subtotal (95% CI)		**16**		**14**	**100.0%**	**0.58 [0.11 , 3.00]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
9.3.3 Diarrhoea						
Hellings 2005	4	16	1	14	100.0%	3.50 [0.44 , 27.75]
Subtotal (95% CI)		**16**		**14**	**100.0%**	**3.50 [0.44 , 27.75]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.19 (P = 0.24)						
9.3.4 Nausea						
Hellings 2005	4	16	2	14	47.9%	1.75 [0.38 , 8.15]
Rezaei 2010	6	20	2	20	52.1%	3.00 [0.69 , 13.12]
Subtotal (95% CI)		**36**		**34**	**100.0%**	**2.32 [0.80 , 6.72]**
Total events:	10		4			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.25$, df = 1 (P = 0.62); $I^2 = 0\%$						
Test for overall effect: Z = 1.55 (P = 0.12)						
9.3.5 Vomiting						
Hellings 2005	4	16	1	14	100.0%	3.50 [0.44 , 27.75]
Subtotal (95% CI)		**16**		**14**	**100.0%**	**3.50 [0.44 , 27.75]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.19 (P = 0.24)						



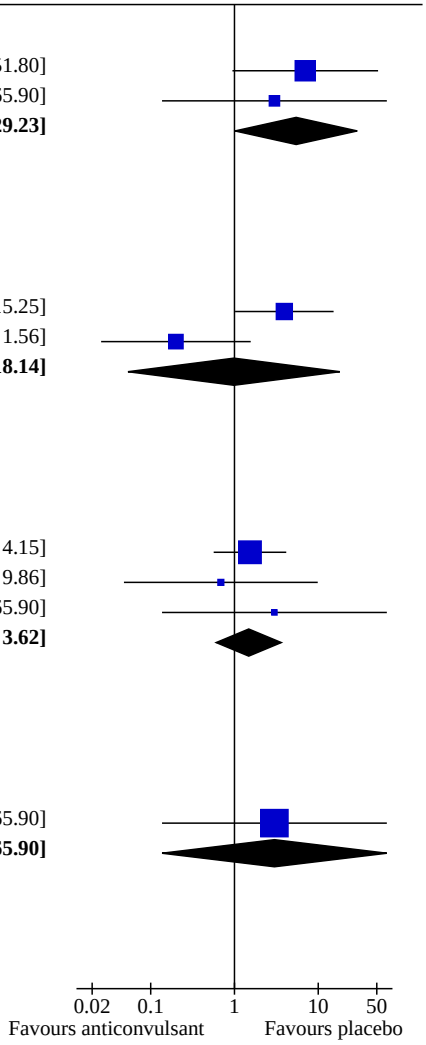
Analysis 9.4. Comparison 9: Anticonvulsant vs placebo, Outcome 4: Adverse effects: immune system

Study or Subgroup	Valproate Events	Valproate Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
9.4.1 Chills						
Hellings 2005	3	16	1	14	100.0%	2.63 [0.31 , 22.46]
Subtotal (95% CI)		**16**		**14**	**100.0%**	**2.63 [0.31 , 22.46]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.88 (P = 0.38)						
9.4.2 Fever						
Hellings 2005	4	16	1	14	100.0%	3.50 [0.44 , 27.75]
Subtotal (95% CI)		**16**		**14**	**100.0%**	**3.50 [0.44 , 27.75]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.19 (P = 0.24)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						



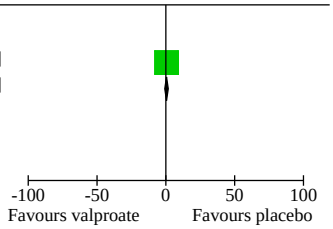
Analysis 9.5. Comparison 9: Anticonvulsant vs placebo, Outcome 5: Adverse effects: metabolic (dichotomous)

Study or Subgroup	Anticonvulsant Events	Anticonvulsant Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
9.5.1 Decreased appetite						
Rezaei 2010	7	20	1	20	70.4%	7.00 [0.95 , 51.80]
Wasserman 2006	1	10	0	10	29.6%	3.00 [0.14 , 65.90]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**5.45 [1.02 , 29.23]**
Total events:	8		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.98 (P = 0.05)						
9.5.2 Increased appetite						
Hellings 2005	9	16	2	14	53.5%	3.94 [1.02 , 15.25]
Rezaei 2010	1	20	5	20	46.5%	0.20 [0.03 , 1.56]
Subtotal (95% CI)		**36**		**34**	**100.0%**	**0.99 [0.05 , 18.14]**
Total events:	10		7			
Heterogeneity: Tau² = 3.65; Chi² = 5.63, df = 1 (P = 0.02); I² = 82%						
Test for overall effect: Z = 0.01 (P = 0.99)						
9.5.3 Weight gain						
Hellings 2005	7	16	4	14	80.4%	1.53 [0.56 , 4.15]
Hollander 2010	1	16	1	11	11.3%	0.69 [0.05 , 9.86]
Wasserman 2006	1	10	0	10	8.4%	3.00 [0.14 , 65.90]
Subtotal (95% CI)		**42**		**35**	**100.0%**	**1.48 [0.61 , 3.62]**
Total events:	9		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 2 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.86 (P = 0.39)						
9.5.4 Weight loss						
Wasserman 2006	1	10	0	10	100.0%	3.00 [0.14 , 65.90]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**3.00 [0.14 , 65.90]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						



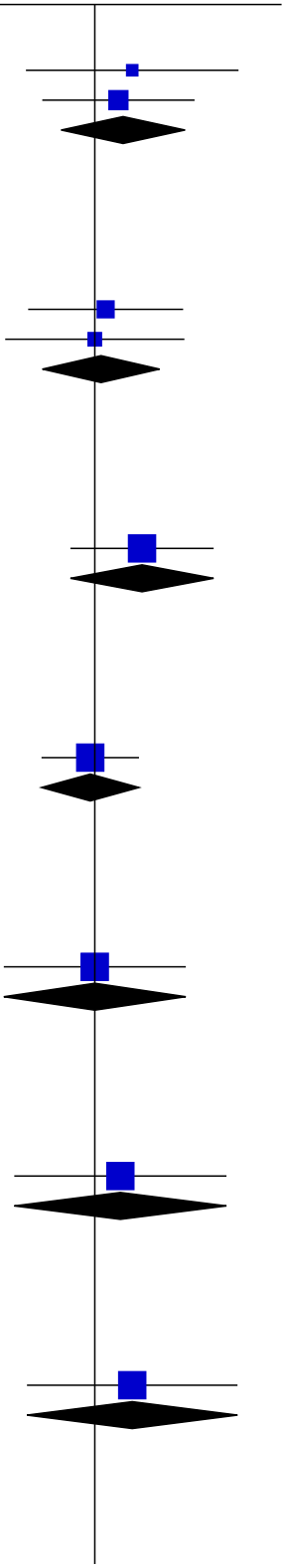
Analysis 9.6. Comparison 9: Anticonvulsant vs placebo, Outcome 6: Adverse effects: metabolic (continuous)

Study or Subgroup	Valproate Mean	Valproate SD	Valproate Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
9.6.1 Weight gain (kg)								
Hellings 2005	1.98	1.88	7	1.1	1.1	4	100.0%	0.48 [-0.77 , 1.74]
Subtotal (95% CI)			**7**			**4**	**100.0%**	**0.48 [-0.77 , 1.74]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.76 (P = 0.45)								
Test for subgroup differences: Not applicable								

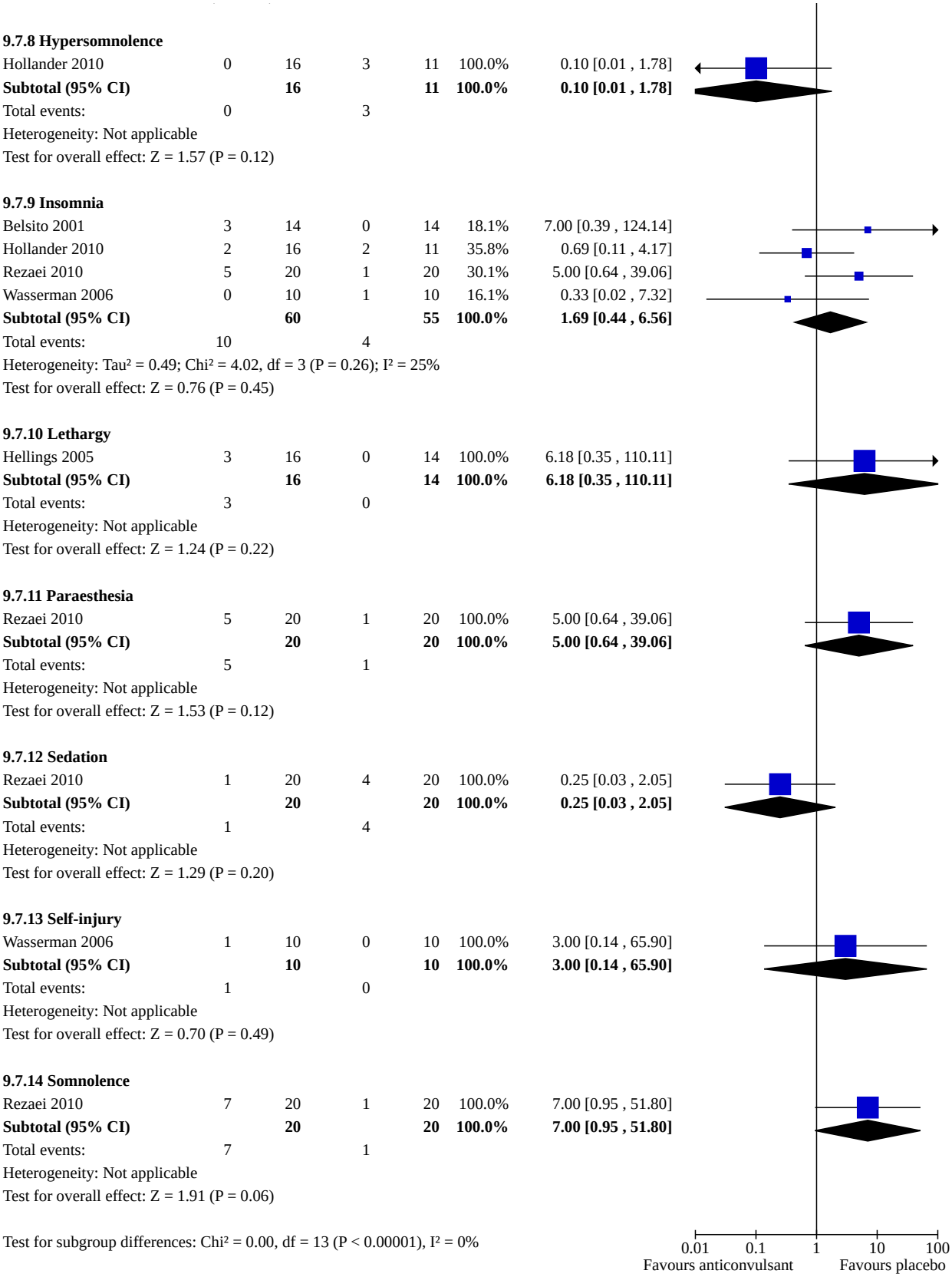


Analysis 9.7. Comparison 9: Anticonvulsant vs placebo, Outcome 7: Adverse Effects: neurological

Study or Subgroup	Anticonvulsant Events	Anticonvulsant Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
9.7.1 Aggression						
Belsito 2001	1	14	0	14	33.9%	3.00 [0.13 , 67.91]
Wasserman 2006	2	10	1	10	66.1%	2.00 [0.21 , 18.69]
Subtotal (95% CI)		**24**		**24**	**100.0%**	**2.29 [0.37 , 14.12]**
Total events:	3		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%						
Test for overall effect: Z = 0.90 (P = 0.37)						
9.7.2 Agitation						
Hollander 2010	2	16	1	11	57.2%	1.38 [0.14 , 13.37]
Wasserman 2006	1	10	1	10	42.8%	1.00 [0.07 , 13.87]
Subtotal (95% CI)		**26**		**21**	**100.0%**	**1.20 [0.21 , 6.70]**
Total events:	3		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.21 (P = 0.84)						
9.7.3 Dizziness						
Rezaei 2010	4	20	1	20	100.0%	4.00 [0.49 , 32.72]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**4.00 [0.49 , 32.72]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						
9.7.4 Drowsiness						
Hellings 2005	3	16	3	14	100.0%	0.88 [0.21 , 3.66]
Subtotal (95% CI)		**16**		**14**	**100.0%**	**0.88 [0.21 , 3.66]**
Total events:	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.18 (P = 0.85)						
9.7.5 Echolalia						
Belsito 2001	1	14	1	14	100.0%	1.00 [0.07 , 14.45]
Subtotal (95% CI)		**14**		**14**	**100.0%**	**1.00 [0.07 , 14.45]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
9.7.6 Headache						
Hollander 2010	1	16	0	11	100.0%	2.12 [0.09 , 47.68]
Subtotal (95% CI)		**16**		**11**	**100.0%**	**2.12 [0.09 , 47.68]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
9.7.7 Hyperactivity						
Wasserman 2006	1	10	0	10	100.0%	3.00 [0.14 , 65.90]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**3.00 [0.14 , 65.90]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
9.7.8 Hypersomnolence						

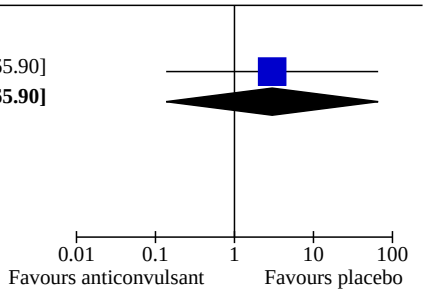


Analysis 9.7. (Continued)



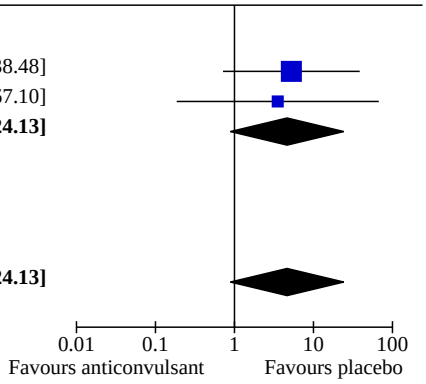
Analysis 9.8. Comparison 9: Anticonvulsant vs placebo, Outcome 8: Adverse effects: psychological

Study or Subgroup	Anticonvulsant Events	Anticonvulsant Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
9.8.5 Impulsivity						
Wasserman 2006	1	10	0	10	100.0%	3.00 [0.14 , 65.90]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**3.00 [0.14 , 65.90]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
Test for subgroup differences: Not applicable						



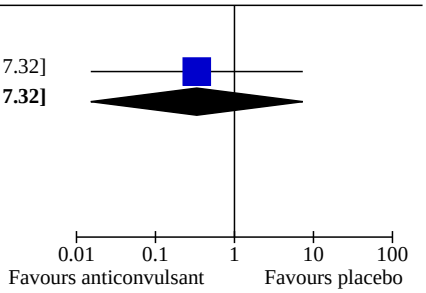
Analysis 9.9. Comparison 9: Anticonvulsant vs placebo, Outcome 9: Adverse effects: skin

Study or Subgroup	Anticonvulsant Events	Anticonvulsant Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
9.9.1 Rash						
Hellings 2005	6	16	1	14	68.6%	5.25 [0.72 , 38.48]
Hollander 2010	2	16	0	11	31.4%	3.53 [0.19 , 67.10]
Subtotal (95% CI)		**32**		**25**	**100.0%**	**4.63 [0.89 , 24.13]**
Total events:	8		1			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.05$, df = 1 (P = 0.83); $I^2 = 0\%$						
Test for overall effect: Z = 1.82 (P = 0.07)						
Total (95% CI)		**32**		**25**	**100.0%**	**4.63 [0.89 , 24.13]**
Total events:	8		1			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.05$, df = 1 (P = 0.83); $I^2 = 0\%$						
Test for overall effect: Z = 1.82 (P = 0.07)						
Test for subgroup differences: Not applicable						



Analysis 9.10. Comparison 9: Anticonvulsant vs placebo, Outcome 10: Adverse effects: urinary

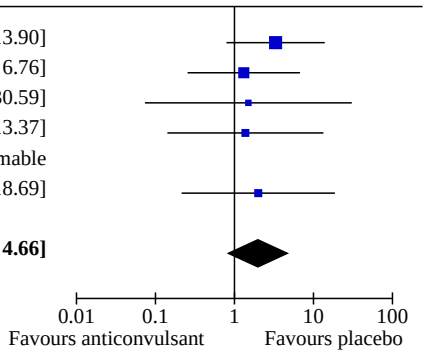
Study or Subgroup	Anticonvulsant Events	Anticonvulsant Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
9.10.1 Enuresis						
Wasserman 2006	0	10	1	10	100.0%	0.33 [0.02 , 7.32]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**0.33 [0.02 , 7.32]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
Test for subgroup differences: Not applicable						



Analysis 9.11. Comparison 9: Anticonvulsant vs placebo, Outcome 11: Tolerability/acceptability: loss to follow-up

Study or Subgroup	Anticonvulsant Events	Anticonvulsant Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Belsito 2001	7	19	2	18	35.7%	3.32 [0.79 , 13.90]
Hellings 2005	3	16	2	14	27.3%	1.31 [0.25 , 6.76]
Hollander 2006a	1	9	0	4	8.1%	1.50 [0.07 , 30.59]
Hollander 2010	2	16	1	11	14.2%	1.38 [0.14 , 13.37]
Rezaei 2010	0	20	0	20		Not estimable
Wasserman 2006	2	10	1	10	14.7%	2.00 [0.21 , 18.69]
Total (95% CI)		**90**		**77**	**100.0%**	**1.98 [0.84 , 4.66]**
Total events:	15		6			

Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 4 (P = 0.93); I² = 0%
Test for overall effect: Z = 1.56 (P = 0.12)
Test for subgroup differences: Not applicable



Comparison 10. Antidepressant vs antidepressant

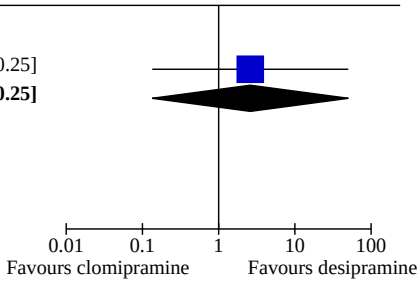
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Adverse effects: cardiovascular	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
10.1.1 Tachycardia	1	36	Risk Ratio (IV, Random, 95% CI)	2.60 [0.13, 50.25]
10.2 Adverse effects: gastrointestinal	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
10.2.1 Constipation	1	36	Risk Ratio (IV, Random, 95% CI)	1.50 [0.35, 6.35]
10.2.2 Dry mouth	1	36	Risk Ratio (IV, Random, 95% CI)	0.50 [0.12, 2.12]
10.2.3 Nausea/abdominal pain	1	36	Risk Ratio (IV, Random, 95% CI)	1.00 [0.10, 9.96]
10.2.4 Vomiting	1	36	Risk Ratio (IV, Random, 95% CI)	1.56 [0.07, 35.67]

Analysis 10.1. Comparison 10: Antidepressant vs antidepressant, Outcome 1: Adverse effects: cardiovascular

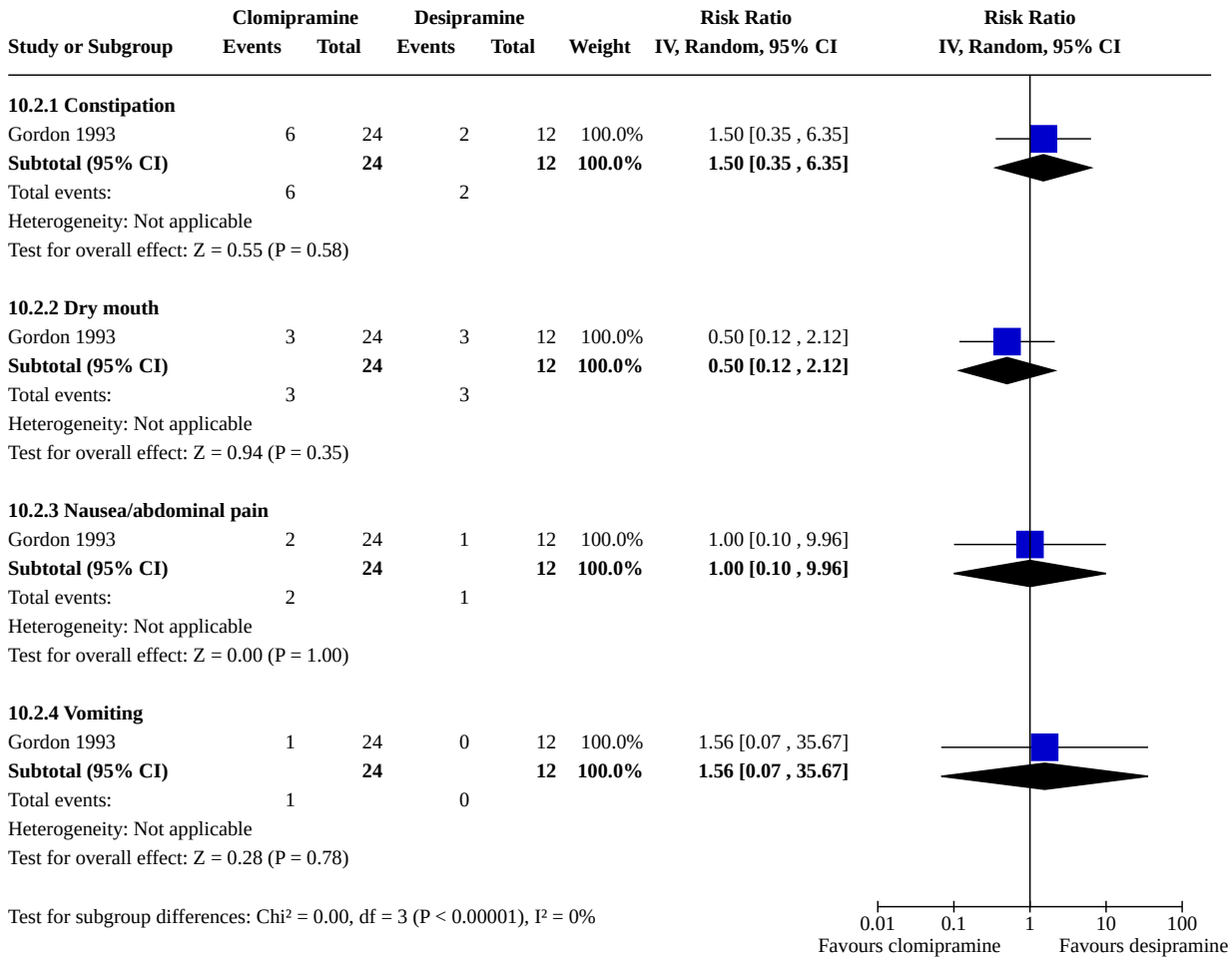
Study or Subgroup	Clomipramine Events	Clomipramine Total	Desipramine Events	Desipramine Total	Weight	Risk Ratio IV, Random, 95% CI
10.1.1 Tachycardia						
Gordon 1993	2	24	0	12	100.0%	2.60 [0.13 , 50.25]
Subtotal (95% CI)		**24**		**12**	**100.0%**	**2.60 [0.13 , 50.25]**
Total events:	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)

Test for subgroup differences: Not applicable



Analysis 10.2. Comparison 10: Antidepressant vs antidepressant, Outcome 2: Adverse effects: gastrointestinal



Comparison 11. Antidementia versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Irritability (continuous)	3	130	Std. Mean Difference (IV, Random, 95% CI)	-0.40 [-1.31, 0.52]
11.2 Irritability (dichotomous)	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
11.2.1 Partial response (≥ 25% reduction in irritability score)	1	40	Risk Ratio (IV, Random, 95% CI)	1.38 [0.97, 1.97]
11.2.2 Complete response (≥ 50% reduction in irritability score)	1	40	Risk Ratio (IV, Random, 95% CI)	1.60 [0.98, 2.61]
11.2.3 Irritability	1	317	Risk Ratio (IV, Random, 95% CI)	0.51 [0.16, 1.66]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.3 Aggression	1	50	Std. Mean Difference (IV, Random, 95% CI)	0.54 [-0.05, 1.13]
11.4 Adverse effects: gastrointestinal	6		Risk Ratio (IV, Random, 95% CI)	Subtotals only
11.4.1 Abdominal pain	2	83	Risk Ratio (IV, Random, 95% CI)	0.97 [0.21, 4.50]
11.4.2 Constipation	2	83	Risk Ratio (IV, Random, 95% CI)	0.33 [0.04, 3.01]
11.4.3 Diarrhoea	1	43	Risk Ratio (IV, Random, 95% CI)	2.87 [0.12, 66.75]
11.4.4 Dry mouth	1	40	Risk Ratio (IV, Random, 95% CI)	0.14 [0.01, 2.60]
11.4.5 Gastroenteritis	1	317	Risk Ratio (IV, Random, 95% CI)	7.13 [0.37, 136.97]
11.4.6 Nausea	1	40	Risk Ratio (IV, Random, 95% CI)	2.00 [0.41, 9.71]
11.4.7 Vomiting	2	438	Risk Ratio (IV, Random, 95% CI)	0.54 [0.18, 1.67]
11.5 Adverse events: metabolic	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.5.1 Decreased appetite	4	163	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.24, 4.07]
11.5.2 Increased appetite	4	163	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.54, 2.43]
11.6 Adverse effects: musculoskeletal pain	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
11.7 Adverse effects: neurological	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.7.1 Daytime drowsiness	2	80	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.41, 1.77]
11.7.2 Dizziness	2	83	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.27, 3.61]
11.7.3 Fatigue	2	83	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.48, 4.02]
11.7.4 Headache	2	438	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.26, 2.75]
11.7.5 Hyperactivity	2	438	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.07, 1.73]
11.7.6 Insomnia	4	227	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.37, 2.59]
11.7.7 Morning drowsiness	1	40	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.71, 2.68]
11.7.8 Sedation	2	83	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.30, 5.98]
11.7.9 Tremor	1	40	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 69.52]
11.7.10 Decreased energy	1	23	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.09, 1.52]
11.8 Adverse events: other	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only

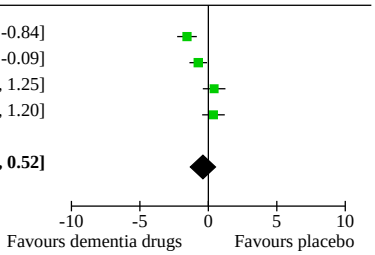
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.8.1 Pyrexia	2	438	Risk Ratio (IV, Random, 95% CI)	0.68 [0.19, 2.41]
11.8.2 Increased infections	1	23	Risk Ratio (IV, Random, 95% CI)	0.69 [0.35, 1.35]
11.9 Adverse events: psychological	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
11.9.1 Agitation	2	438	Risk Ratio (IV, Random, 95% CI)	1.89 [0.45, 8.05]
11.9.2 Aggression	1	121	Risk Ratio (IV, Random, 95% CI)	1.69 [0.42, 6.78]
11.9.3 Anxiety	3	478	Risk Ratio (IV, Random, 95% CI)	0.41 [0.03, 5.61]
11.9.4 Irritability	3	461	Risk Ratio (IV, Random, 95% CI)	0.87 [0.43, 1.76]
11.9.5 Mood changes	1	23	Risk Ratio (IV, Random, 95% CI)	1.68 [0.95, 2.96]
11.9.6 Emotional lability	1	23	Risk Ratio (IV, Random, 95% CI)	1.83 [0.19, 17.51]
11.9.7 Anger	1	23	Risk Ratio (IV, Random, 95% CI)	0.31 [0.01, 6.85]
11.9.8 Self-injury	1	23	Risk Ratio (IV, Random, 95% CI)	2.77 [0.12, 61.65]
11.10 Adverse events: respiratory	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
11.10.1 Cough	2	438	Risk Ratio (IV, Random, 95% CI)	1.83 [0.63, 5.34]
11.10.2 Nasopharyngitis	2	438	Risk Ratio (IV, Random, 95% CI)	0.61 [0.08, 4.35]
11.10.3 Upper respiratory tract infection	1	317	Risk Ratio (IV, Random, 95% CI)	7.13 [0.37, 136.97]
11.11 Adverse effects: skin	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
11.11.1 Rash	1	40	Risk Ratio (IV, Random, 95% CI)	2.00 [0.20, 20.33]
11.11.2 Skin irritation	1	23	Risk Ratio (IV, Random, 95% CI)	0.46 [0.15, 1.40]
11.12 Serious adverse events	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
11.12.1 Affective disorder	1	121	Risk Ratio (IV, Random, 95% CI)	3.05 [0.13, 73.40]
11.13 Tolerability/acceptability: loss to follow-up	5	553	Risk Ratio (IV, Random, 95% CI)	0.95 [0.83, 1.09]
11.14 Subgroup analysis: age - irritability (continuous)	4	140	Std. Mean Difference (IV, Random, 95% CI)	-0.45 [-1.24, 0.33]
11.14.1 Children only	3	130	Std. Mean Difference (IV, Random, 95% CI)	-0.40 [-1.31, 0.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.14.2 Adults only	1	10	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-2.06, 0.56]

Analysis 11.1. Comparison 11: Antidementia versus placebo, Outcome 1: Irritability (continuous)

Study or Subgroup	Dementia-related drugs Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ghaleiha 2013a	8.9	1.55	20	12.75	3.05	20	25.4%	-1.56 [-2.28 , -0.84]
Ghaleiha 2014	5.3	4.25	20	8.8	5.03	20	26.2%	-0.74 [-1.38 , -0.09]
Handen 2011 (1)	0.94	0.67	9	0.67	0.59	16	24.2%	0.42 [-0.40 , 1.25]
Handen 2011 (2)	0.86	0.67	9	0.65	0.46	16	24.2%	0.37 [-0.45 , 1.20]
Total (95% CI)			**58**			**72**	**100.0%**	**-0.40 [-1.31 , 0.52]**

Heterogeneity: Tau² = 0.73; Chi² = 18.02, df = 3 (P = 0.0004); I² = 83%
Test for overall effect: Z = 0.85 (P = 0.40)
Test for subgroup differences: Not applicable

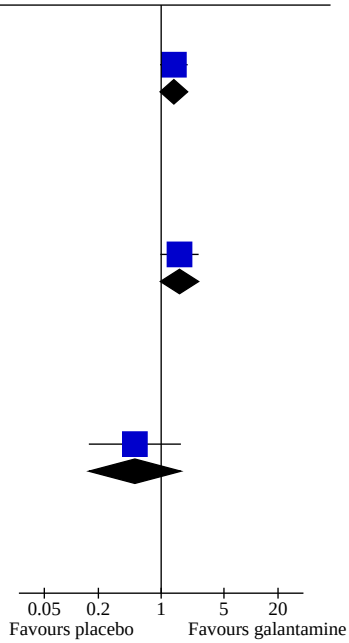


Footnotes
(1) Donepezil 10mg/day
(2) Donepezil 5mg/day

Analysis 11.2. Comparison 11: Antidementia versus placebo, Outcome 2: Irritability (dichotomous)

Study or Subgroup	Galantamine/memantine Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
11.2.1 Partial response (≥ 25% reduction in irritability score)						
Ghaleiha 2014	18	20	13	20	100.0%	1.38 [0.97 , 1.97]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**1.38 [0.97 , 1.97]**
Total events:	18		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.81 (P = 0.07)						
11.2.2 Complete response (≥ 50% reduction in irritability score)						
Ghaleiha 2014	16	20	10	20	100.0%	1.60 [0.98 , 2.61]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**1.60 [0.98 , 2.61]**
Total events:	16		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.88 (P = 0.06)						
11.2.3 Irritability						
Hardan 2019	4	157	8	160	100.0%	0.51 [0.16 , 1.66]
Subtotal (95% CI)		**157**		**160**	**100.0%**	**0.51 [0.16 , 1.66]**
Total events:	4		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						

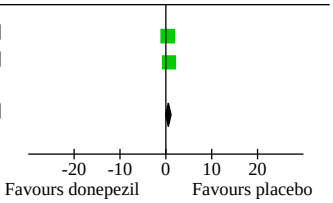
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%



Analysis 11.3. Comparison 11: Antidementia versus placebo, Outcome 3: Aggression

Study or Subgroup	Donepezil Mean	Donepezil SD	Donepezil Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Handen 2011 (1)	7.83	6.24	9	5.67	4.44	16	51.0%	0.41 [-0.42 , 1.23]
Handen 2011 (2)	8.39	6.28	9	5.2	3.14	16	49.0%	0.69 [-0.16 , 1.53]
Total (95% CI)			**18**			**32**	**100.0%**	**0.54 [-0.05 , 1.13]**

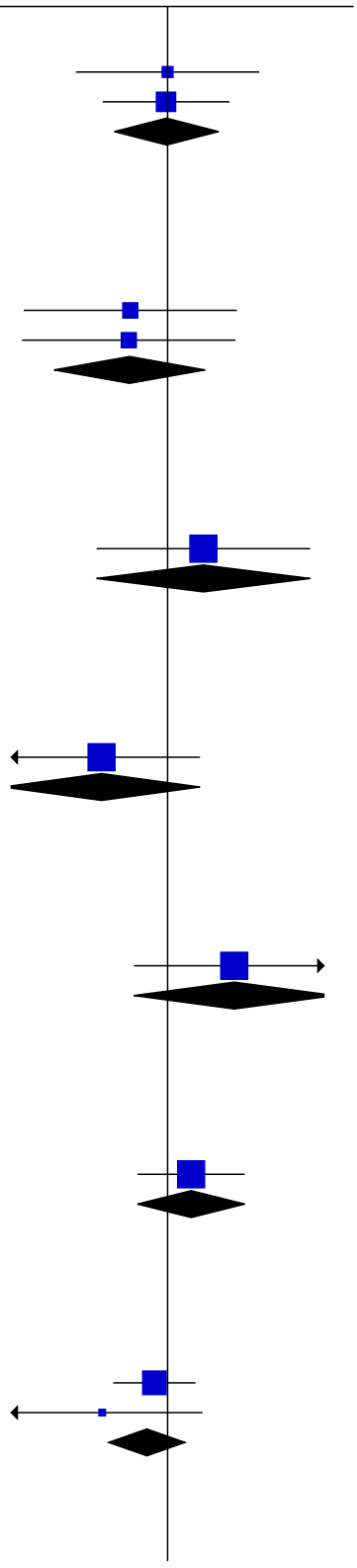
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.81 (P = 0.07)
Test for subgroup differences: Not applicable



Footnotes
(1) 5mg donepezil
(2) 10mg donepezil

Analysis 11.4. Comparison 11: Antidementia versus placebo, Outcome 4: Adverse effects: gastrointestinal

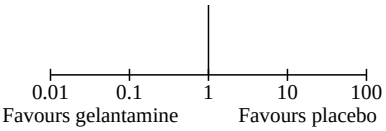
Study or Subgroup	Gelantamine Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
11.4.1 Abdominal pain						
Ghaleiha 2013a	1	20	1	20	32.3%	1.00 [0.07 , 14.90]
NCT01972074	2	22	2	21	67.7%	0.95 [0.15 , 6.17]
Subtotal (95% CI)		**42**		**41**	**100.0%**	**0.97 [0.21 , 4.50]**
Total events:	3		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.04 (P = 0.97)						
11.4.2 Constipation						
Ghaleiha 2014	0	20	1	20	50.1%	0.33 [0.01 , 7.72]
NCT01972074	0	22	1	21	49.9%	0.32 [0.01 , 7.42]
Subtotal (95% CI)		**42**		**41**	**100.0%**	**0.33 [0.04 , 3.01]**
Total events:	0		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.99 (P = 0.32)						
11.4.3 Diarrhoea						
NCT01972074	1	22	0	21	100.0%	2.87 [0.12 , 66.75]
Subtotal (95% CI)		**22**		**21**	**100.0%**	**2.87 [0.12 , 66.75]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
11.4.4 Dry mouth						
Akhondzadeh 2008	0	20	3	20	100.0%	0.14 [0.01 , 2.60]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.14 [0.01 , 2.60]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
11.4.5 Gastroenteritis						
Hardan 2019	3	157	0	160	100.0%	7.13 [0.37 , 136.97]
Subtotal (95% CI)		**157**		**160**	**100.0%**	**7.13 [0.37 , 136.97]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
11.4.6 Nausea						
Ghaleiha 2013a	4	20	2	20	100.0%	2.00 [0.41 , 9.71]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**2.00 [0.41 , 9.71]**
Total events:	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
11.4.7 Vomiting						
Aman 2017	4	60	6	61	85.6%	0.68 [0.20 , 2.28]
Hardan 2019	0	157	3	160	14.4%	0.15 [0.01 , 2.80]
Subtotal (95% CI)		**217**		**221**	**100.0%**	**0.54 [0.18 , 1.67]**
Total events:	4		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 1.07 (P = 0.29)						



Analysis 11.4. (Continued)

Test for overall effect: Z = 1.07 (P = 0.29)

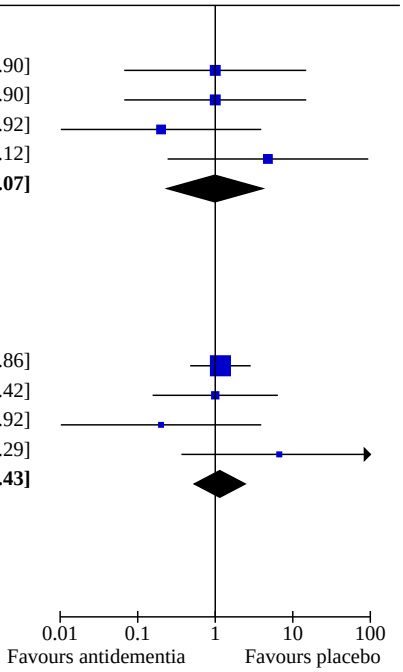
Test for subgroup differences: Chi² = 0.00, df = 6 (P < 0.00001), I² = 0%



Analysis 11.5. Comparison 11: Antidementia versus placebo, Outcome 5: Adverse events: metabolic

Study or Subgroup	Piracetam Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
11.5.1 Decreased appetite						
Akhondzadeh 2008	1	20	1	20	27.4%	1.00 [0.07 , 14.90]
Ghaleiha 2013a	1	20	1	20	27.4%	1.00 [0.07 , 14.90]
Ghaleiha 2014	0	20	2	20	22.6%	0.20 [0.01 , 3.92]
NCT01972074	2	22	0	21	22.5%	4.78 [0.24 , 94.12]
Subtotal (95% CI)		**82**		**81**	**100.0%**	**0.99 [0.24 , 4.07]**
Total events:	4		4			
Heterogeneity: Tau² = 0.00; Chi² = 2.18, df = 3 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.02 (P = 0.99)						
11.5.2 Increased appetite						
Akhondzadeh 2008	7	20	6	20	70.5%	1.17 [0.48 , 2.86]
Ghaleiha 2013a	2	20	2	20	16.4%	1.00 [0.16 , 6.42]
Ghaleiha 2014	0	20	2	20	6.4%	0.20 [0.01 , 3.92]
NCT01972074	3	22	0	21	6.7%	6.70 [0.37 , 122.29]
Subtotal (95% CI)		**82**		**81**	**100.0%**	**1.14 [0.54 , 2.43]**
Total events:	12		10			
Heterogeneity: Tau² = 0.00; Chi² = 2.77, df = 3 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.35 (P = 0.73)						

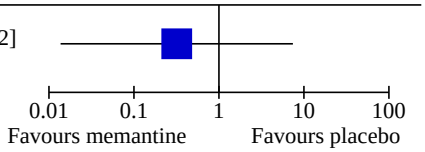
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%



Analysis 11.6. Comparison 11: Antidementia versus placebo, Outcome 6: Adverse effects: musculoskeletal pain

Study or Subgroup	Memantine Events	Total	Placebo Events	Total	Risk Ratio IV, Random, 95% CI
NCT01972074	0	22	1	21	0.32 [0.01 , 7.42]

Test for subgroup differences: Not applicable

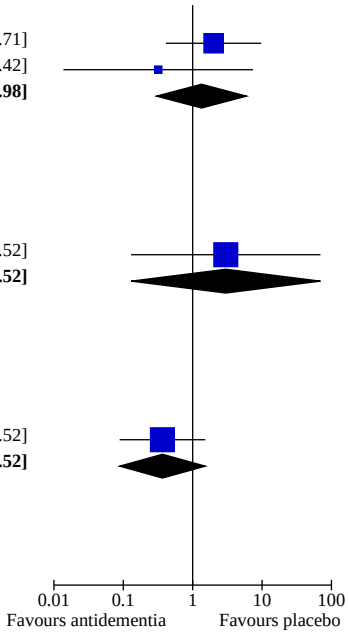


Analysis 11.7. Comparison 11: Antidementia versus placebo, Outcome 7: Adverse effects: neurological

Study or Subgroup	Piracetam or memantine (NCT) Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
11.7.1 Daytime drowsiness						
Akhondzadeh 2008	7	20	9	20	90.1%	0.78 [0.36 , 1.68]
Ghaleiha 2014	2	20	1	20	9.9%	2.00 [0.20 , 20.33]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**0.85 [0.41 , 1.77]**
Total events:	9		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.59, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.67)						
11.7.2 Dizziness						
Ghaleiha 2013a	3	20	3	20	77.1%	1.00 [0.23 , 4.37]
NCT01972074	1	22	1	21	22.9%	0.95 [0.06 , 14.30]
Subtotal (95% CI)		**42**		**41**	**100.0%**	**0.99 [0.27 , 3.61]**
Total events:	4		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.02 (P = 0.99)						
11.7.3 Fatigue						
Akhondzadeh 2008	5	20	3	20	67.7%	1.67 [0.46 , 6.06]
NCT01972074	2	22	2	21	32.3%	0.95 [0.15 , 6.17]
Subtotal (95% CI)		**42**		**41**	**100.0%**	**1.39 [0.48 , 4.02]**
Total events:	7		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						
11.7.4 Headache						
Aman 2017	3	60	3	61	56.4%	1.02 [0.21 , 4.84]
Hardan 2019	2	157	3	160	43.6%	0.68 [0.12 , 4.01]
Subtotal (95% CI)		**217**		**221**	**100.0%**	**0.85 [0.26 , 2.75]**
Total events:	5		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.27 (P = 0.79)						
11.7.5 Hyperactivity						
Aman 2017	1	60	4	61	55.0%	0.25 [0.03 , 2.21]
Hardan 2019	1	157	2	160	45.0%	0.51 [0.05 , 5.56]
Subtotal (95% CI)		**217**		**221**	**100.0%**	**0.35 [0.07 , 1.73]**
Total events:	2		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%						
Test for overall effect: Z = 1.29 (P = 0.20)						
11.7.6 Insomnia						
Aman 2017	4	60	3	61	43.1%	1.36 [0.32 , 5.80]
Ghaleiha 2013a	1	20	1	20	12.8%	1.00 [0.07 , 14.90]
NCT01972074	3	22	2	21	32.3%	1.43 [0.27 , 7.73]
Soorya 2021	0	12	4	11	11.8%	0.10 [0.01 , 1.71]
Subtotal (95% CI)		**114**		**113**	**100.0%**	**0.98 [0.37 , 2.59]**
Total events:	8		10			
Heterogeneity: Tau² = 0.02; Chi² = 3.06, df = 3 (P = 0.38); I² = 2%						
Test for overall effect: Z = 0.04 (P = 0.96)						
11.7.7 Morning drowsiness						
Akhondzadeh 2008	11	20	8	20	100.0%	1.38 [0.71 , 2.68]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**1.38 [0.71 , 2.68]**
Total events:	11		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.94 (P = 0.35)						
11.7.8 Sedation						
Ghaleiha 2013a	4	20	2	20	78.2%	2.00 [0.41 , 9.71]

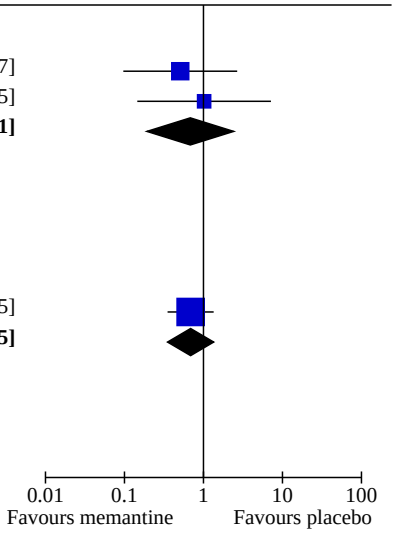
Analysis 11.7. (Continued)

11.7.8 Sedation						
Ghaleiha 2013a	4	20	2	20	78.2%	2.00 [0.41 , 9.71]
NCT01972074	0	22	1	21	21.8%	0.32 [0.01 , 7.42]
Subtotal (95% CI)		**42**		**41**	**100.0%**	**1.34 [0.30 , 5.98]**
Total events:	4		3			
Heterogeneity: Tau² = 0.09; Chi² = 1.06, df = 1 (P = 0.30); I² = 5%						
Test for overall effect: Z = 0.38 (P = 0.70)						
11.7.9 Tremor						
Ghaleiha 2014	1	20	0	20	100.0%	3.00 [0.13 , 69.52]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**3.00 [0.13 , 69.52]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
11.7.10 Decreased energy						
Soorya 2021	2	12	5	11	100.0%	0.37 [0.09 , 1.52]
Subtotal (95% CI)		**12**		**11**	**100.0%**	**0.37 [0.09 , 1.52]**
Total events:	2		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.38 (P = 0.17)						
Test for subgroup differences: Chi² = 0.00, df = 9 (P < 0.00001), I² = 0%						



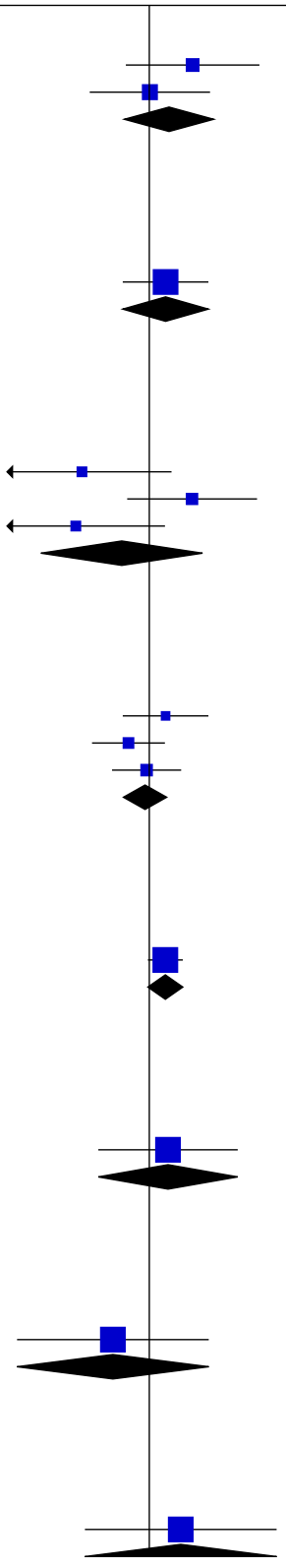
Analysis 11.8. Comparison 11: Antidementia versus placebo, Outcome 8: Adverse events: other

Study or Subgroup	Memantine Events	Memantine Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
11.8.1 Pyrexia						
Aman 2017	2	60	4	61	57.9%	0.51 [0.10 , 2.67]
Hardan 2019	2	157	2	160	42.1%	1.02 [0.15 , 7.15]
Subtotal (95% CI)		**217**		**221**	**100.0%**	**0.68 [0.19 , 2.41]**
Total events:	4		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.60 (P = 0.55)						
11.8.2 Increased infections						
Soorya 2021	6	12	8	11	100.0%	0.69 [0.35 , 1.35]
Subtotal (95% CI)		**12**		**11**	**100.0%**	**0.69 [0.35 , 1.35]**
Total events:	6		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.09 (P = 0.27)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						



Analysis 11.9. Comparison 11: Antidementia versus placebo, Outcome 9: Adverse events: psychological

Study or Subgroup	Memantine or gelantamine Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
11.9.1 Agitation						
Aman 2017	4	60	1	61	44.8%	4.07 [0.47 , 35.34]
Hardan 2019	2	157	2	160	55.2%	1.02 [0.15 , 7.15]
Subtotal (95% CI)		**217**		**221**	**100.0%**	**1.89 [0.45 , 8.05]**
Total events:	6		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 0.87 (P = 0.39)						
11.9.2 Aggression						
Aman 2017	5	60	3	61	100.0%	1.69 [0.42 , 6.78]
Subtotal (95% CI)		**60**		**61**	**100.0%**	**1.69 [0.42 , 6.78]**
Total events:	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.75 (P = 0.46)						
11.9.3 Anxiety						
Aman 2017 (1)	0	60	4	61	31.0%	0.11 [0.01 , 2.05]
Ghaleiha 2014 (2)	4	20	1	20	37.9%	4.00 [0.49 , 32.72]
Hardan 2019 (1)	0	157	5	160	31.1%	0.09 [0.01 , 1.66]
Subtotal (95% CI)		**237**		**241**	**100.0%**	**0.41 [0.03 , 5.61]**
Total events:	4		10			
Heterogeneity: Tau² = 3.56; Chi² = 6.01, df = 2 (P = 0.05); I² = 67%						
Test for overall effect: Z = 0.67 (P = 0.50)						
11.9.4 Irritability						
Aman 2017	5	60	3	61	25.5%	1.69 [0.42 , 6.78]
Hardan 2019	4	157	8	160	35.3%	0.51 [0.16 , 1.66]
Soorya 2021	4	12	4	11	39.2%	0.92 [0.30 , 2.81]
Subtotal (95% CI)		**229**		**232**	**100.0%**	**0.87 [0.43 , 1.76]**
Total events:	13		15			
Heterogeneity: Tau² = 0.00; Chi² = 1.69, df = 2 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.38 (P = 0.70)						
11.9.5 Mood changes						
Soorya 2021	11	12	6	11	100.0%	1.68 [0.95 , 2.96]
Subtotal (95% CI)		**12**		**11**	**100.0%**	**1.68 [0.95 , 2.96]**
Total events:	11		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.80 (P = 0.07)						
11.9.6 Emotional lability						
Soorya 2021	2	12	1	11	100.0%	1.83 [0.19 , 17.51]
Subtotal (95% CI)		**12**		**11**	**100.0%**	**1.83 [0.19 , 17.51]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.60)						
11.9.7 Anger						
Soorya 2021	0	12	1	11	100.0%	0.31 [0.01 , 6.85]
Subtotal (95% CI)		**12**		**11**	**100.0%**	**0.31 [0.01 , 6.85]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						
11.9.8 Self-injury						
Soorya 2021	1	12	0	11	100.0%	2.77 [0.12 , 61.65]
Subtotal (95% CI)		**12**		**11**	**100.0%**	**2.77 [0.12 , 61.65]**



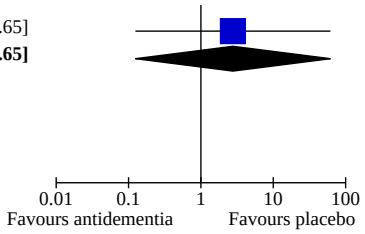
Analysis 11.9. (Continued)

Soorya 2021	1	12	0	11	100.0%	2.77 [0.12 , 61.65]
Subtotal (95% CI)		**12**		**11**	**100.0%**	**2.77 [0.12 , 61.65]**
Total events:	1		0			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.64 (P = 0.52)

Test for subgroup differences: Chi² = 0.00, df = 7 (P < 0.00001), I² = 0%



Footnotes

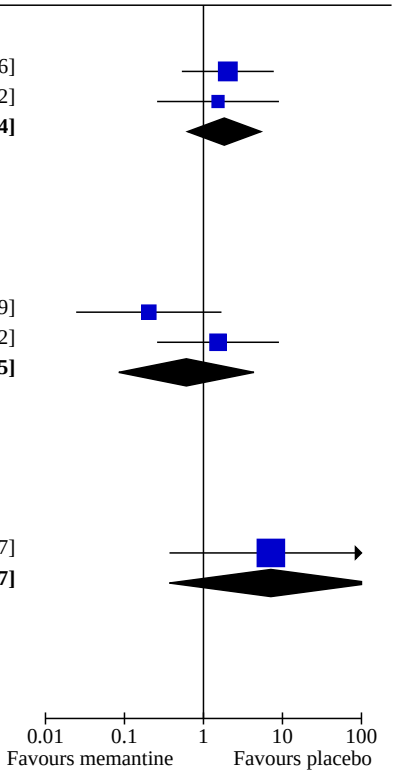
(1) Memantine vs placebo

(2) Gelantamine vs placebo

Analysis 11.10. Comparison 11: Antidementia versus placebo, Outcome 10: Adverse events: respiratory

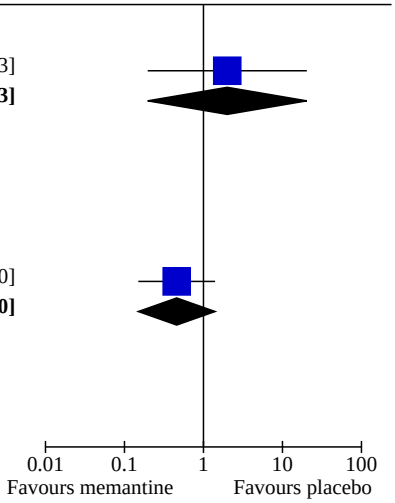
Study or Subgroup	Memantine Events	Memantine Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
11.10.1 Cough						
Aman 2017	6	60	3	61	63.7%	2.03 [0.53 , 7.76]
Hardan 2019	3	157	2	160	36.3%	1.53 [0.26 , 9.02]
Subtotal (95% CI)		**217**		**221**	**100.0%**	**1.83 [0.63 , 5.34]**
Total events:	9		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.11 (P = 0.27)						
11.10.2 Nasopharyngitis						
Aman 2017	1	60	5	61	45.7%	0.20 [0.02 , 1.69]
Hardan 2019	3	157	2	160	54.3%	1.53 [0.26 , 9.02]
Subtotal (95% CI)		**217**		**221**	**100.0%**	**0.61 [0.08 , 4.35]**
Total events:	4		7			
Heterogeneity: Tau² = 1.04; Chi² = 2.05, df = 1 (P = 0.15); I² = 51%						
Test for overall effect: Z = 0.50 (P = 0.62)						
11.10.3 Upper respiratory tract infection						
Hardan 2019	3	157	0	160	100.0%	7.13 [0.37 , 136.97]
Subtotal (95% CI)		**157**		**160**	**100.0%**	**7.13 [0.37 , 136.97]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						

Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%



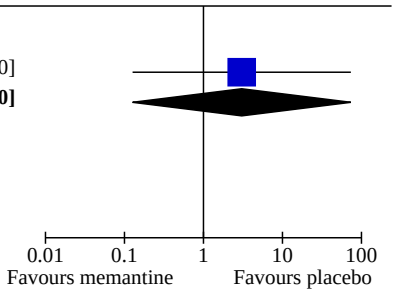
Analysis 11.11. Comparison 11: Antidementia versus placebo, Outcome 11: Adverse effects: skin

Study or Subgroup	Memantine Events	Memantine Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
11.11.1 Rash						
Ghaleiha 2013a	2	20	1	20	100.0%	2.00 [0.20 , 20.33]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**2.00 [0.20 , 20.33]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
11.11.2 Skin irritation						
Soorya 2021	3	12	6	11	100.0%	0.46 [0.15 , 1.40]
Subtotal (95% CI)		**12**		**11**	**100.0%**	**0.46 [0.15 , 1.40]**
Total events:	3		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.37 (P = 0.17)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						



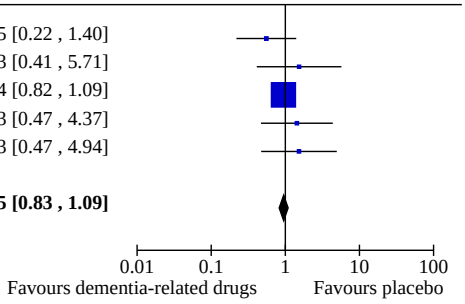
Analysis 11.12. Comparison 11: Antidementia versus placebo, Outcome 12: Serious adverse events

Study or Subgroup	Memantine Events	Memantine Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
11.12.1 Affective disorder						
Aman 2017	1	60	0	61	100.0%	3.05 [0.13 , 73.40]
Subtotal (95% CI)		**60**		**61**	**100.0%**	**3.05 [0.13 , 73.40]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Not applicable						

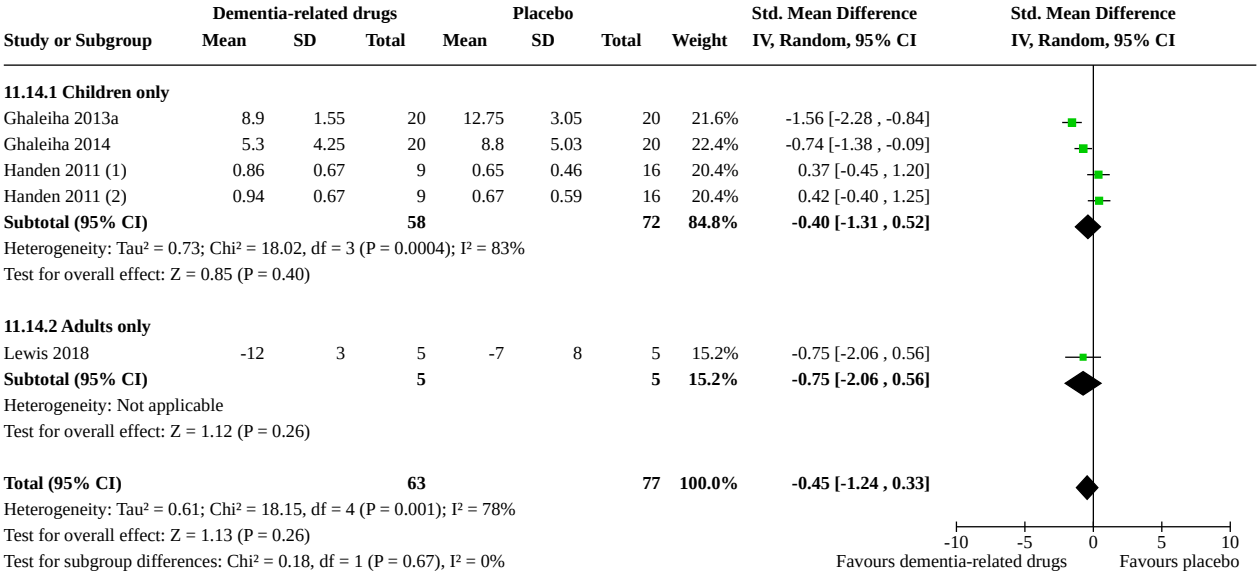


Analysis 11.13. Comparison 11: Antidementia versus placebo, Outcome 13: Tolerability/acceptability: loss to follow-up

Study or Subgroup	Dementia-related drugs Events	Dementia-related drugs Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Aman 2017	6	60	11	61	2.2%	0.55 [0.22 , 1.40]
Ghaleiha 2014	5	25	3	23	1.1%	1.53 [0.41 , 5.71]
Hardan 2019	108	158	116	160	93.8%	0.94 [0.82 , 1.09]
NCT01972074	6	22	4	21	1.5%	1.43 [0.47 , 4.37]
Soorya 2021	5	12	3	11	1.4%	1.53 [0.47 , 4.94]
Total (95% CI)		**277**		**276**	**100.0%**	**0.95 [0.83 , 1.09]**
Total events:	130		137			
Heterogeneity: Tau² = 0.00; Chi² = 2.96, df = 4 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
Test for subgroup differences: Not applicable						



Analysis 11.14. Comparison 11: Antidementia versus placebo, Outcome 14: Subgroup analysis: age - irritability (continuous)



Footnotes
(1) 5mg donepezil
(2) 10mg donepezil

Comparison 12. Antiparkinsonian vs placebo

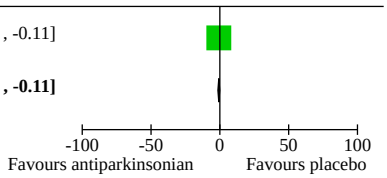
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Irritability	1	40	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-1.39, -0.11]
12.2 Adverse effects: gastrointestinal	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
12.2.1 Abdominal pain	1	40	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 7.72]
12.2.2 Constipation	1	40	Risk Ratio (IV, Random, 95% CI)	0.20 [0.01, 3.92]
12.2.3 Drooling	1	40	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 7.72]
12.3 Adverse effects: metabolic	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
12.3.1 Decreased appetite	1	40	Risk Ratio (IV, Random, 95% CI)	0.11 [0.01, 1.94]
12.3.2 Increased appetite	1	40	Risk Ratio (IV, Random, 95% CI)	3.00 [0.69, 13.12]
12.4 Adverse effects: neurological	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
12.4.1 Daytime drowsiness	1	40	Risk Ratio (IV, Random, 95% CI)	3.00 [0.13, 69.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.4.2 Insomnia	2	79	Risk Ratio (IV, Random, 95% CI)	2.26 [0.55, 9.26]
12.4.3 Nervousness	1	40	Risk Ratio (IV, Random, 95% CI)	0.33 [0.04, 2.94]
12.4.4 Somnolence	1	39	Risk Ratio (IV, Random, 95% CI)	5.25 [0.27, 102.74]
12.4.5 Tremor	1	40	Risk Ratio (IV, Random, 95% CI)	3.00 [0.13, 69.52]
12.5 Adverse effects: psychological	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
12.5.2 Adverse behaviour	1	39	Risk Ratio (IV, Random, 95% CI)	0.53 [0.11, 2.55]
12.6 Tolerability/acceptability: loss to follow-up	1	40	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 7.72]

Analysis 12.1. Comparison 12: Antiparkinsonian vs placebo, Outcome 1: Irritability

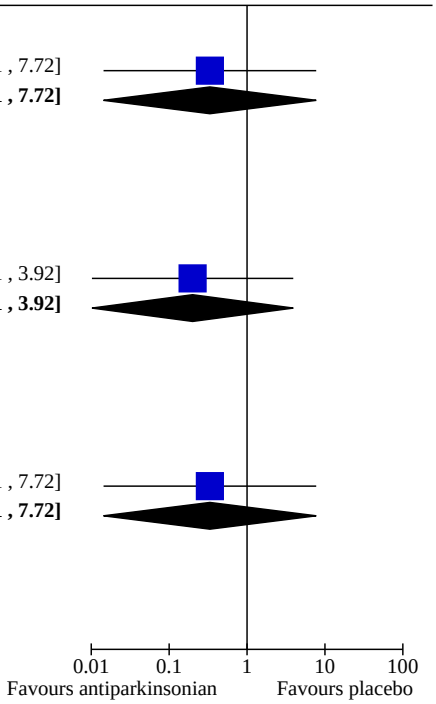
Study or Subgroup	Antiparkinsonian Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Mohammadi 2013	-8.65	4.65	20	-5.35	3.95	20	100.0%	-0.75 [-1.39 , -0.11]
Total (95% CI)			**20**			**20**	**100.0%**	**-0.75 [-1.39 , -0.11]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.28 (P = 0.02)
Test for subgroup differences: Not applicable



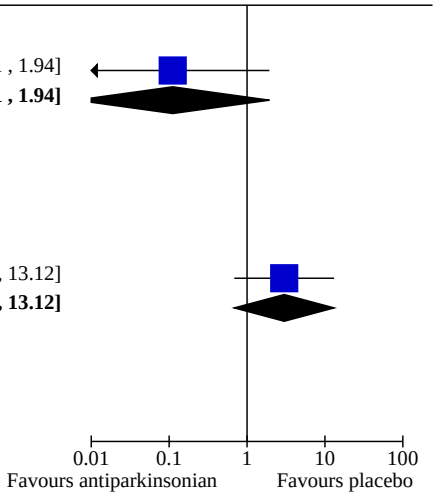
Analysis 12.2. Comparison 12: Antiparkinsonian vs placebo, Outcome 2: Adverse effects: gastrointestinal

Study or Subgroup	Antiparkinsonian Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
12.2.1 Abdominal pain						
Mohammadi 2013	0	20	1	20	100.0%	0.33 [0.01 , 7.72]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.33 [0.01 , 7.72]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
12.2.2 Constipation						
Mohammadi 2013	0	20	2	20	100.0%	0.20 [0.01 , 3.92]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.20 [0.01 , 3.92]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
12.2.3 Drooling						
Mohammadi 2013	0	20	1	20	100.0%	0.33 [0.01 , 7.72]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.33 [0.01 , 7.72]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%						



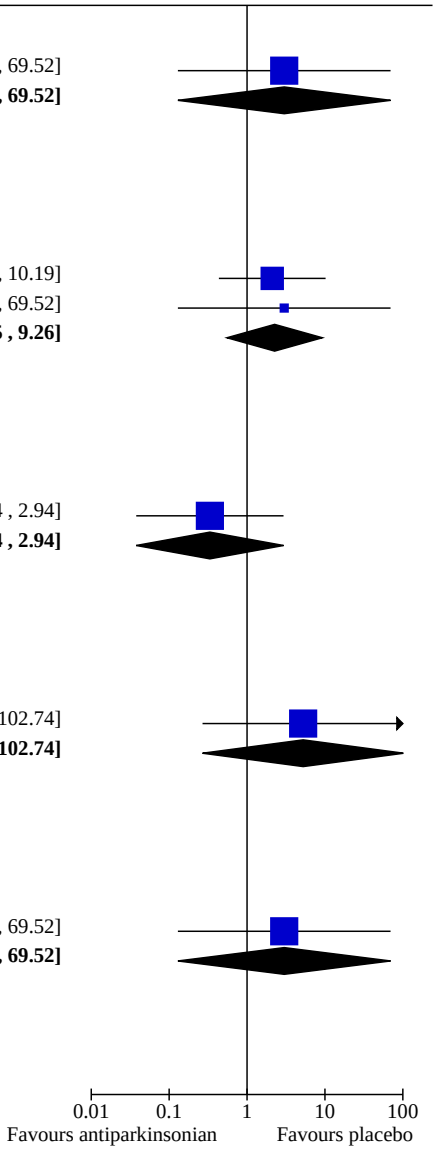
Analysis 12.3. Comparison 12: Antiparkinsonian vs placebo, Outcome 3: Adverse effects: metabolic

Study or Subgroup	Antiparkinsonian Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
12.3.1 Decreased appetite						
Mohammadi 2013	0	20	4	20	100.0%	0.11 [0.01 , 1.94]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.11 [0.01 , 1.94]**
Total events:	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.51 (P = 0.13)						
12.3.2 Increased appetite						
Mohammadi 2013	6	20	2	20	100.0%	3.00 [0.69 , 13.12]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**3.00 [0.69 , 13.12]**
Total events:	6		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.46 (P = 0.14)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						



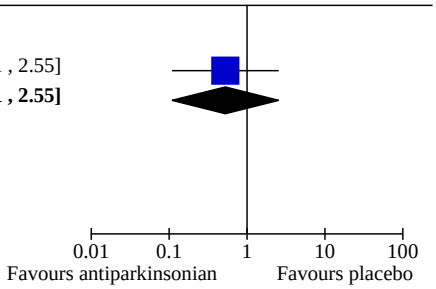
Analysis 12.4. Comparison 12: Antiparkinsonian vs placebo, Outcome 4: Adverse effects: neurological

Study or Subgroup	Antiparkinsonian Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
12.4.1 Daytime drowsiness						
Mohammadi 2013	1	20	0	20	100.0%	3.00 [0.13 , 69.52]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**3.00 [0.13 , 69.52]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
12.4.2 Insomnia						
King 2001	4	19	2	20	79.9%	2.11 [0.43 , 10.19]
Mohammadi 2013	1	20	0	20	20.1%	3.00 [0.13 , 69.52]
Subtotal (95% CI)		**39**		**40**	**100.0%**	**2.26 [0.55 , 9.26]**
Total events:	5		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%						
Test for overall effect: Z = 1.13 (P = 0.26)						
12.4.3 Nervousness						
Mohammadi 2013	1	20	3	20	100.0%	0.33 [0.04 , 2.94]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.33 [0.04 , 2.94]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
12.4.4 Somnolence						
King 2001	2	19	0	20	100.0%	5.25 [0.27 , 102.74]
Subtotal (95% CI)		**19**		**20**	**100.0%**	**5.25 [0.27 , 102.74]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.09 (P = 0.27)						
12.4.5 Tremor						
Mohammadi 2013	1	20	0	20	100.0%	3.00 [0.13 , 69.52]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**3.00 [0.13 , 69.52]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Chi² = 0.00, df = 4 (P < 0.00001), I² = 0%						



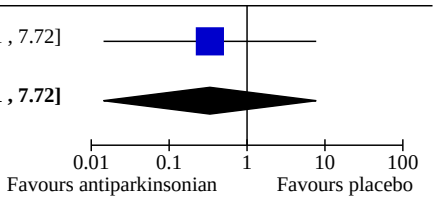
Analysis 12.5. Comparison 12: Antiparkinsonian vs placebo, Outcome 5: Adverse effects: psychological

Study or Subgroup	Antiparkinsonian Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
12.5.2 Adverse behaviour						
King 2001	2	19	4	20	100.0%	0.53 [0.11 , 2.55]
Subtotal (95% CI)		**19**		**20**	**100.0%**	**0.53 [0.11 , 2.55]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.80 (P = 0.43)						
Test for subgroup differences: Not applicable						



Analysis 12.6. Comparison 12: Antiparkinsonian vs placebo, Outcome 6: Tolerability/acceptability: loss to follow-up

Study or Subgroup	Antiparkinsonian Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Mohammadi 2013	0	20	1	20	100.0%	0.33 [0.01 , 7.72]
Total (95% CI)		**20**		**20**	**100.0%**	**0.33 [0.01 , 7.72]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Not applicable						



Comparison 13. Anxiolytic versus placebo

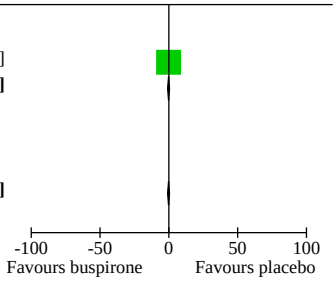
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Irritabilty (continuous)	1	34	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.88, 0.47]
13.1.1 Anxiolytics vs placebo	1	34	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.88, 0.47]
13.2 Irritability (dichotomous)	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
13.2.1 Response rate (> 25% decrease in irritability score)	1	34	Risk Ratio (IV, Random, 95% CI)	1.83 [1.04, 3.22]
13.3 Adverse effects: gastrointestinal	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
13.3.1 Constipation	1	166	Risk Ratio (IV, Random, 95% CI)	0.97 [0.35, 2.67]
13.3.2 Diarrhoea	1	166	Risk Ratio (IV, Random, 95% CI)	1.04 [0.68, 1.61]
13.3.3 Vomiting	1	166	Risk Ratio (IV, Random, 95% CI)	1.02 [0.68, 1.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.4 Adverse effects: immune System	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
13.4.1 Nasopharyngitis	1	166	Risk Ratio (IV, Random, 95% CI)	0.87 [0.33, 2.28]
13.4.2 Pyrexia	1	166	Risk Ratio (IV, Random, 95% CI)	1.00 [0.73, 1.37]
13.4.3 Upper respiratory tract infection	1	166	Risk Ratio (IV, Random, 95% CI)	0.40 [0.18, 0.91]
13.5 Adverse effects: metabolic	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
13.5.1 Decreased appetite	1	166	Risk Ratio (IV, Random, 95% CI)	1.11 [0.62, 1.99]
13.5.2 Increased appetite	2	200	Risk Ratio (IV, Random, 95% CI)	1.50 [0.93, 2.42]
13.6 Adverse effects: neurological	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.6.1 Hyperactivity	1	166	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.47, 1.30]
13.6.2 Increased aggression	1	166	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.60, 1.38]
13.6.3 Insomnia	1	166	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.90, 1.78]
13.6.4 Irritability	1	166	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.48, 1.47]
13.6.5 Somnolence	1	166	Risk Ratio (M-H, Random, 95% CI)	1.70 [0.58, 4.97]
13.7 Adverse effects: psychological	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.7.1 Anxiety	1	166	Risk Ratio (M-H, Random, 95% CI)	2.76 [0.48, 15.83]
13.8 Adverse effects: respiratory system	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
13.8.1 Cough	1	166	Risk Ratio (IV, Random, 95% CI)	0.90 [0.64, 1.26]
13.8.2 Epistaxis	1	166	Risk Ratio (IV, Random, 95% CI)	0.52 [0.19, 1.43]
13.8.3 Nasal congestion	1	166	Risk Ratio (IV, Random, 95% CI)	0.80 [0.36, 1.77]
13.8.4 Rhinorrhoea	1	166	Risk Ratio (IV, Random, 95% CI)	1.12 [0.66, 1.88]
13.8.5 Sinus congestion	1	166	Risk Ratio (IV, Random, 95% CI)	0.90 [0.55, 1.47]
13.9 Adverse effects: skin	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
13.9.1 Rash	1	166	Risk Ratio (IV, Random, 95% CI)	1.19 [0.52, 2.73]
13.10 Other adverse effects	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.10.1 Ear infection	1	166	Risk Ratio (IV, Random, 95% CI)	1.10 [0.50, 2.41]
13.10.2 Ear and labyrinth disorders	1	166	Risk Ratio (IV, Random, 95% CI)	2.92 [0.51, 16.72]
13.10.3 Eye disorders	1	166	Risk Ratio (IV, Random, 95% CI)	3.11 [0.72, 13.44]
13.10.4 Renal and urinary disorders	1	166	Risk Ratio (IV, Random, 95% CI)	0.97 [0.41, 2.30]
13.11 Tolerability/acceptability: loss to follow-up	2	206	Risk Ratio (IV, Random, 95% CI)	0.88 [0.45, 1.73]

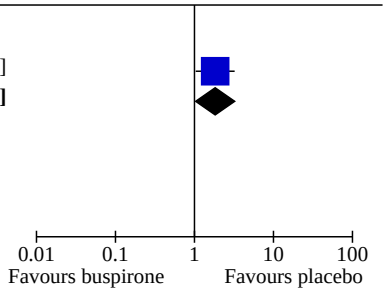
Analysis 13.1. Comparison 13: Anxiolytic versus placebo, Outcome 1: Irritabilty (continuous)

Study or Subgroup	Buspirone Mean	Buspirone SD	Buspirone Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
13.1.1 Anxiolytics vs placebo								
Ghanizadeh 2015	16.6	7.6	16	18.2	7.7	18	100.0%	-0.20 [-0.88 , 0.47]
Subtotal (95% CI)			**16**			**18**	**100.0%**	**-0.20 [-0.88 , 0.47]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.59 (P = 0.55)								
Total (95% CI)			**16**			**18**	**100.0%**	**-0.20 [-0.88 , 0.47]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.59 (P = 0.55)								
Test for subgroup differences: Not applicable								



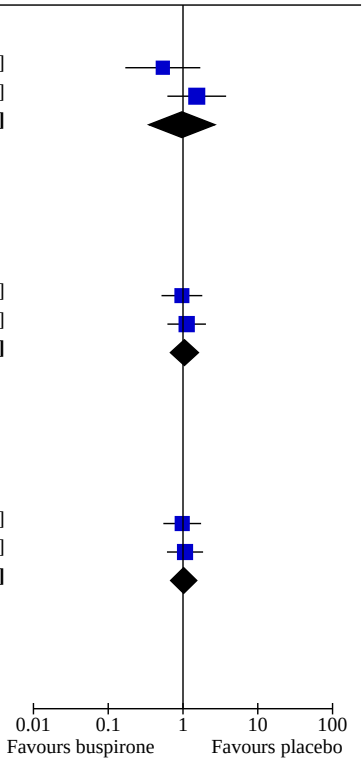
Analysis 13.2. Comparison 13: Anxiolytic versus placebo, Outcome 2: Irritability (dichotomous)

Study or Subgroup	Buspirone Events	Buspirone Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
13.2.1 Response rate (> 25% decrease in irritability score)						
Ghanizadeh 2015	13	16	8	18	100.0%	1.83 [1.04 , 3.22]
Subtotal (95% CI)		**16**		**18**	**100.0%**	**1.83 [1.04 , 3.22]**
Total events:	13		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.08 (P = 0.04)						
Test for subgroup differences: Not applicable						



Analysis 13.3. Comparison 13: Anxiolytic versus placebo, Outcome 3: Adverse effects: gastrointestinal

Study or Subgroup	Anxiolytics (buspirone) Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
13.3.1 Constipation						
Chugani 2016 (1)	5	54	5	29	43.9%	0.54 [0.17 , 1.70]
Chugani 2016 (2)	15	55	5	28	56.1%	1.53 [0.62 , 3.77]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**0.97 [0.35 , 2.67]**
Total events:	20		10			
Heterogeneity: Tau² = 0.27; Chi² = 1.95, df = 1 (P = 0.16); I² = 49%						
Test for overall effect: Z = 0.07 (P = 0.95)						
13.3.2 Diarrhoea						
Chugani 2016 (1)	18	54	10	29	47.2%	0.97 [0.52 , 1.81]
Chugani 2016 (2)	22	55	10	28	52.8%	1.12 [0.62 , 2.03]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**1.04 [0.68 , 1.61]**
Total events:	40		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.84)						
13.3.3 Vomiting						
Chugani 2016 (1)	20	54	11	29	47.8%	0.98 [0.55 , 1.75]
Chugani 2016 (2)	23	55	11	28	52.2%	1.06 [0.61 , 1.86]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**1.02 [0.68 , 1.53]**
Total events:	43		22			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.10 (P = 0.92)						
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%						



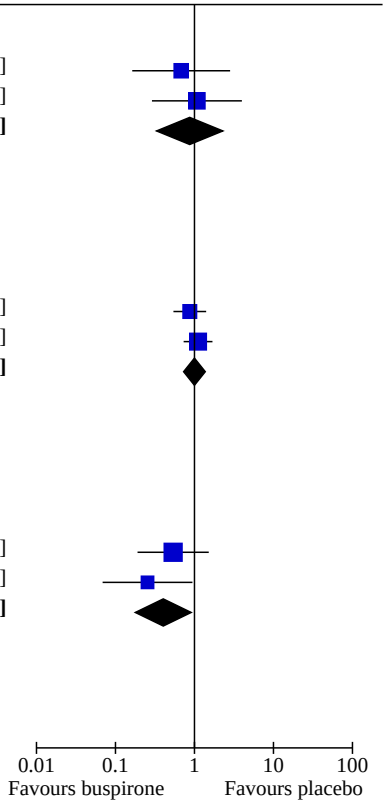
Footnotes

(1) 2.5mg buspirone vs placebo

(2) 5.0mg buspirone vs placebo

Analysis 13.4. Comparison 13: Anxiolytic versus placebo, Outcome 4: Adverse effects: immune System

Study or Subgroup	Buspirone Events	Buspirone Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
13.4.1 Nasopharyngitis						
Chugani 2016 (1)	4	55	3	28	45.8%	0.68 [0.16 , 2.83]
Chugani 2016 (2)	6	54	3	29	54.2%	1.07 [0.29 , 3.98]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**0.87 [0.33 , 2.28]**
Total events:	10		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.28 (P = 0.78)						
13.4.2 Pyrexia						
Chugani 2016 (1)	24	55	14	28	43.7%	0.87 [0.54 , 1.41]
Chugani 2016 (2)	31	54	15	29	56.3%	1.11 [0.73 , 1.69]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**1.00 [0.73 , 1.37]**
Total events:	55		29			
Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
13.4.3 Upper respiratory tract infection						
Chugani 2016 (2)	6	54	6	29	61.4%	0.54 [0.19 , 1.52]
Chugani 2016 (1)	3	55	6	28	38.6%	0.25 [0.07 , 0.94]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**0.40 [0.18 , 0.91]**
Total events:	9		12			
Heterogeneity: Tau² = 0.00; Chi² = 0.77, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 2.19 (P = 0.03)						
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%						



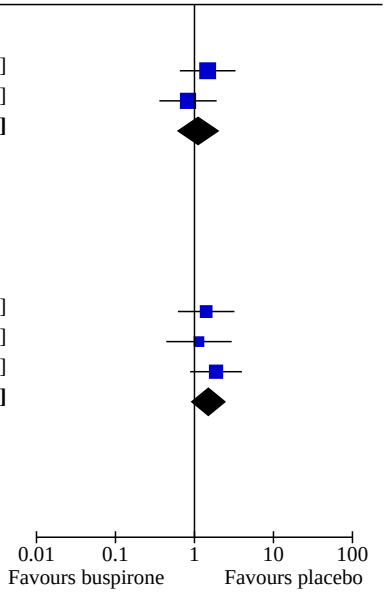
Footnotes

(1) Buspirone 5.0mg vs placebo

(2) Buspirone 2.5mg vs placebo

Analysis 13.5. Comparison 13: Anxiolytic versus placebo, Outcome 5: Adverse effects: metabolic

Study or Subgroup	Buspirone Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
13.5.1 Decreased appetite						
Chugani 2016 (1)	17	54	6	28	51.4%	1.47 [0.65 , 3.31]
Chugani 2016 (2)	11	55	7	29	48.6%	0.83 [0.36 , 1.91]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**1.11 [0.62 , 1.99]**
Total events:	28		13			
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.33); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
13.5.2 Increased appetite						
Chugani 2016 (2)	16	55	6	29	34.1%	1.41 [0.62 , 3.20]
Chugani 2016 (1)	11	54	5	28	25.4%	1.14 [0.44 , 2.96]
Ghanizadeh 2015	10	16	6	18	40.5%	1.88 [0.88 , 3.99]
Subtotal (95% CI)		**125**		**75**	**100.0%**	**1.50 [0.93 , 2.42]**
Total events:	37		17			
Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 2 (P = 0.71); I² = 0%						
Test for overall effect: Z = 1.65 (P = 0.10)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						



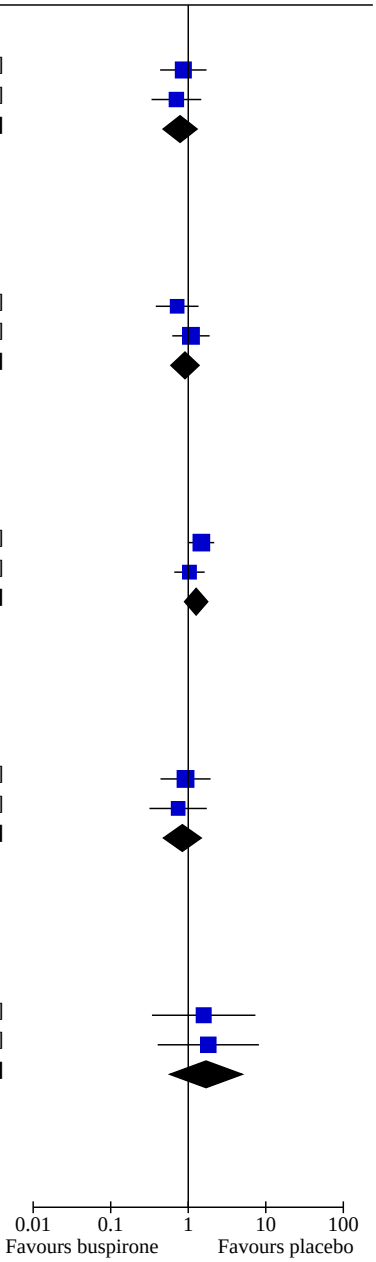
Footnotes

(1) 2.5mg buspirone versus placebo

(2) 5.0mg buspirone versus placebo

Analysis 13.6. Comparison 13: Anxiolytic versus placebo, Outcome 6: Adverse effects: neurological

Study or Subgroup	Buspirone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
13.6.1 Hyperactivity						
Chugani 2016 (1)	15	54	9	28	53.4%	0.86 [0.43 , 1.72]
Chugani 2016 (2)	12	55	9	29	46.6%	0.70 [0.34 , 1.47]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**0.79 [0.47 , 1.30]**
Total events:	27		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%						
Test for overall effect: Z = 0.94 (P = 0.35)						
13.6.2 Increased aggression						
Chugani 2016 (2)	15	55	11	29	43.3%	0.72 [0.38 , 1.36]
Chugani 2016 (1)	23	54	11	28	56.7%	1.08 [0.62 , 1.89]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**0.91 [0.60 , 1.38]**
Total events:	38		22			
Heterogeneity: Tau² = 0.00; Chi² = 0.91, df = 1 (P = 0.34); I² = 0%						
Test for overall effect: Z = 0.46 (P = 0.65)						
13.6.3 Insomnia						
Chugani 2016 (2)	42	55	15	29	56.0%	1.48 [1.01 , 2.16]
Chugani 2016 (1)	28	54	14	28	44.0%	1.04 [0.66 , 1.63]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**1.26 [0.90 , 1.78]**
Total events:	70		29			
Heterogeneity: Tau² = 0.02; Chi² = 1.38, df = 1 (P = 0.24); I² = 27%						
Test for overall effect: Z = 1.33 (P = 0.18)						
13.6.4 Irritability						
Chugani 2016 (2)	14	55	8	29	56.7%	0.92 [0.44 , 1.94]
Chugani 2016 (1)	10	54	7	28	43.3%	0.74 [0.32 , 1.74]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**0.84 [0.48 , 1.47]**
Total events:	24		15			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						
13.6.5 Somnolence						
Chugani 2016 (2)	6	55	2	29	48.9%	1.58 [0.34 , 7.35]
Chugani 2016 (1)	7	54	2	28	51.1%	1.81 [0.40 , 8.16]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**1.70 [0.58 , 4.97]**
Total events:	13		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.96 (P = 0.33)						
Test for subgroup differences: Chi² = 0.00, df = 4 (P < 0.00001), I² = 0%						



Footnotes

(1) 2.5mg buspirone versus placebo

(2) 5.0mg buspirone versus placebo

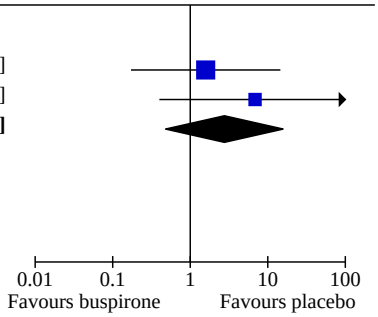
Analysis 13.7. Comparison 13: Anxiolytic versus placebo, Outcome 7: Adverse effects: psychological

Study or Subgroup	Buspirone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
13.7.1 Anxiety						
Chugani 2016 (1)	3	55	1	29	62.1%	1.58 [0.17 , 14.54]
Chugani 2016 (2)	6	54	0	28	37.9%	6.85 [0.40 , 117.44]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**2.76 [0.48 , 15.83]**
Total events:	9		1			

Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 1 (P = 0.41); I² = 0%

Test for overall effect: Z = 1.14 (P = 0.26)

Test for subgroup differences: Not applicable



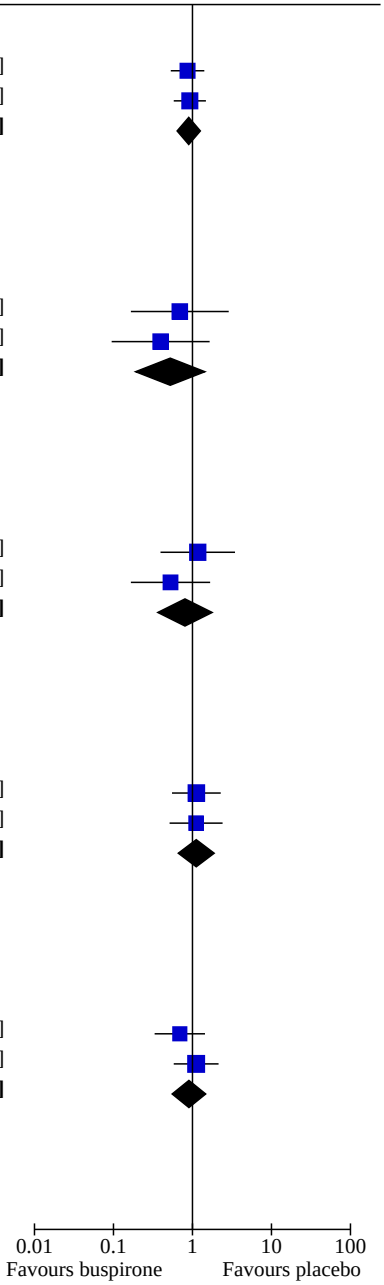
Footnotes

(1) 5.0mg buspirone versus placebo

(2) 2.5mg buspirone versus placebo

Analysis 13.8. Comparison 13: Anxiolytic versus placebo, Outcome 8: Adverse effects: respiratory system

Study or Subgroup	Buspirone Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
13.8.1 Cough						
Chugani 2016 (1)	23	55	14	29	47.9%	0.87 [0.53 , 1.41]
Chugani 2016 (2)	25	54	14	28	52.1%	0.93 [0.58 , 1.48]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**0.90 [0.64 , 1.26]**
Total events:	48		28			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.63 (P = 0.53)						
13.8.2 Epistaxis						
Chugani 2016 (2)	4	54	3	28	50.1%	0.69 [0.17 , 2.88]
Chugani 2016 (1)	3	55	4	29	49.9%	0.40 [0.09 , 1.65]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**0.52 [0.19 , 1.43]**
Total events:	7		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						
13.8.3 Nasal congestion						
Chugani 2016 (2)	9	54	4	28	53.1%	1.17 [0.39 , 3.46]
Chugani 2016 (1)	5	55	5	29	46.9%	0.53 [0.17 , 1.67]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**0.80 [0.36 , 1.77]**
Total events:	14		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 1 (P = 0.33); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						
13.8.4 Rhinorrhoea						
Chugani 2016 (1)	17	55	8	29	54.2%	1.12 [0.55 , 2.28]
Chugani 2016 (2)	15	54	7	28	45.8%	1.11 [0.51 , 2.41]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**1.12 [0.66 , 1.88]**
Total events:	32		15			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.41 (P = 0.68)						
13.8.5 Sinus congestion						
Chugani 2016 (2)	12	54	9	28	44.2%	0.69 [0.33 , 1.44]
Chugani 2016 (1)	19	55	9	29	55.8%	1.11 [0.58 , 2.14]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**0.90 [0.55 , 1.47]**
Total events:	31		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 1 (P = 0.34); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.68)						
Test for subgroup differences: Chi² = 0.00, df = 4 (P < 0.00001), I² = 0%						



Footnotes

(1) 5.0 mg

(2) 2.5 mg

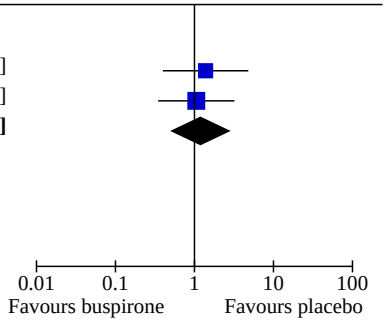
Analysis 13.9. Comparison 13: Anxiolytic versus placebo, Outcome 9: Adverse effects: skin

Study or Subgroup	Buspirone Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
13.9.1 Rash						
Chugani 2016 (1)	8	54	3	28	44.4%	1.38 [0.40 , 4.81]
Chugani 2016 (2)	8	55	4	29	55.6%	1.05 [0.35 , 3.21]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**1.19 [0.52 , 2.73]**
Total events:	16		7			

Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%

Test for overall effect: Z = 0.41 (P = 0.68)

Test for subgroup differences: Not applicable



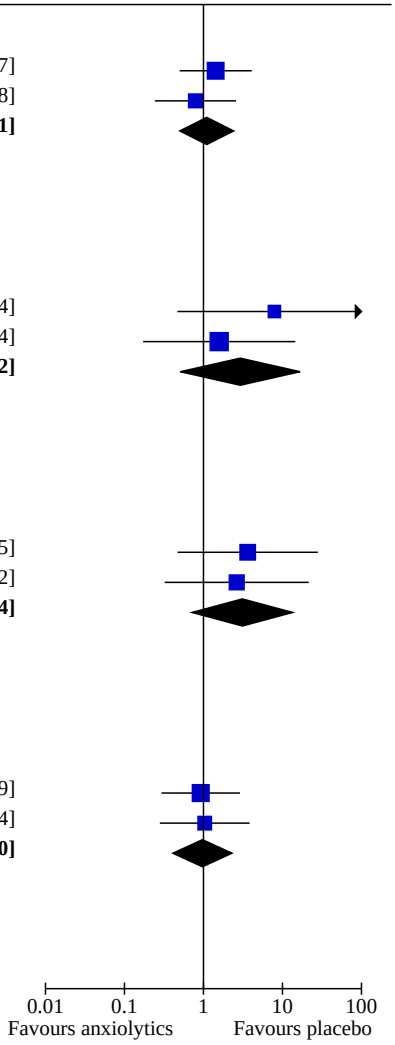
Footnotes

(1) 2.5 mg

(2) 5.0 mg

Analysis 13.10. Comparison 13: Anxiolytic versus placebo, Outcome 10: Other adverse effects

Study or Subgroup	Anxiolytics Events	Anxiolytics Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
13.10.1 Ear infection						
Chugani 2016 (1)	11	54	4	28	55.9%	1.43 [0.50 , 4.07]
Chugani 2016 (2)	6	55	4	29	44.1%	0.79 [0.24 , 2.58]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**1.10 [0.50 , 2.41]**
Total events:	17		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						
13.10.2 Ear and labyrinth disorders						
Chugani 2016 (1)	7	54	0	28	38.1%	7.91 [0.47 , 133.64]
Chugani 2016 (2)	3	55	1	29	61.9%	1.58 [0.17 , 14.54]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**2.92 [0.51 , 16.72]**
Total events:	10		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.77, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 1.20 (P = 0.23)						
13.10.3 Eye disorders						
Chugani 2016 (1)	7	54	1	28	51.3%	3.63 [0.47 , 28.05]
Chugani 2016 (2)	5	55	1	29	48.7%	2.64 [0.32 , 21.52]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**3.11 [0.72 , 13.44]**
Total events:	12		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 1.52 (P = 0.13)						
13.10.4 Renal and urinary disorders						
Chugani 2016 (2)	7	55	4	29	56.7%	0.92 [0.29 , 2.89]
Chugani 2016 (1)	6	54	3	28	43.3%	1.04 [0.28 , 3.84]
Subtotal (95% CI)		**109**		**57**	**100.0%**	**0.97 [0.41 , 2.30]**
Total events:	13		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.07 (P = 0.95)						
Test for subgroup differences: Chi² = 0.00, df = 3 (P < 0.00001), I² = 0%						



Footnotes

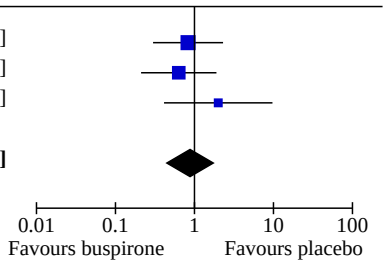
(1) 2.5 mg

(2) 5.0 mg

Analysis 13.11. Comparison 13: Anxiolytic versus placebo, Outcome 11: Tolerability/acceptability: loss to follow-up

Study or Subgroup	Buspirone Events	Buspirone Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Chugani 2016 (1)	8	54	5	28	43.9%	0.83 [0.30 , 2.30]
Chugani 2016 (2)	6	55	5	29	37.8%	0.63 [0.21 , 1.90]
Ghanizadeh 2015	4	20	2	20	18.3%	2.00 [0.41 , 9.71]
Total (95% CI)		**129**		**77**	**100.0%**	**0.88 [0.45 , 1.73]**
Total events:	18		12			

Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 2 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)
Test for subgroup differences: Not applicable



Footnotes
(1) Buspirone 2.5mg
(2) Buspirone 5.0mg

Comparison 14. Experimental versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Irritability	28	1205	Std. Mean Difference (IV, Random, 95% CI)	-0.30 [-0.53, -0.07]
14.1.1 Arbaclofen	1	130	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.68, 0.02]
14.1.2 Baclofen	1	58	Std. Mean Difference (IV, Random, 95% CI)	0.88 [0.34, 1.42]
14.1.3 Bumetanide	2	104	Std. Mean Difference (IV, Random, 95% CI)	-0.74 [-1.84, 0.37]
14.1.4 Celecoxib	1	40	Std. Mean Difference (IV, Random, 95% CI)	-1.27 [-1.95, -0.58]
14.1.5 Dextromethorphan	1	8	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-1.52, 1.26]
14.1.6 Dextromethorphan/quinidine	1	14	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-1.43, 0.69]
14.1.7 Folinic acid	1	55	Std. Mean Difference (IV, Random, 95% CI)	0.63 [0.08, 1.17]
14.1.8 Lofexedine	1	12	Std. Mean Difference (IV, Random, 95% CI)	-0.50 [-1.66, 0.66]
14.1.9 L-carnosine	1	42	Std. Mean Difference (IV, Random, 95% CI)	0.20 [-0.41, 0.80]
14.1.10 Minocycline	1	46	Std. Mean Difference (IV, Random, 95% CI)	0.89 [0.28, 1.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1.11 N-acetylcysteine	4	125	Std. Mean Difference (IV, Random, 95% CI)	-0.61 [-1.16, -0.06]
14.1.12 Naltrexone	1	40	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.80, 0.44]
14.1.13 Nicotine	1	8	Std. Mean Difference (IV, Random, 95% CI)	-0.72 [-2.19, 0.75]
14.1.14 Pioglitazone	1	40	Std. Mean Difference (IV, Random, 95% CI)	-0.77 [-1.42, -0.13]
14.1.15 Palmitoylethanolamide	1	62	Std. Mean Difference (IV, Random, 95% CI)	-0.49 [-1.00, 0.01]
14.1.16 Prednisolone (steroid)	1	26	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.96, 0.58]
14.1.17 Pregnenolone	1	59	Std. Mean Difference (IV, Random, 95% CI)	-0.55 [-1.07, -0.03]
14.1.18 Propentofylline	1	48	Std. Mean Difference (IV, Random, 95% CI)	0.56 [-0.01, 1.14]
14.1.19 Resveratol	1	62	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.79, 0.21]
14.1.20 Riluzole	2	54	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-1.10, 0.42]
14.1.21 Simvastatin	1	66	Std. Mean Difference (IV, Random, 95% CI)	-0.88 [-1.38, -0.37]
14.1.22 Sulforaphane	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.86 [-1.39, -0.33]
14.1.23 Tetrahydrobiopterin	1	46	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.68, 0.48]
14.2 Self-injury	5	285	Std. Mean Difference (IV, Random, 95% CI)	0.14 [-0.09, 0.38]
14.2.1 Bumetanide	2	148	Std. Mean Difference (IV, Random, 95% CI)	0.20 [-0.21, 0.60]
14.2.2 N-acetylcysteine	2	127	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.29, 0.44]
14.2.3 Trichuris suris ova	1	10	Std. Mean Difference (IV, Random, 95% CI)	-0.30 [-1.55, 0.95]
14.3 Adverse effects: gastrointestinal	32		Risk Ratio (IV, Random, 95% CI)	Subtotals only
14.3.1 Abdominal pain	14	734	Risk Ratio (IV, Random, 95% CI)	1.38 [0.95, 2.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.3.2 Change in bowel habits	2	54	Risk Ratio (IV, Random, 95% CI)	0.39 [0.05, 3.26]
14.3.3 Constipation	13	665	Risk Ratio (IV, Random, 95% CI)	1.29 [0.77, 2.16]
14.3.4 Diarrhoea	18	982	Risk Ratio (IV, Random, 95% CI)	0.83 [0.55, 1.25]
14.3.5 Drooling	1	11	Risk Ratio (IV, Random, 95% CI)	0.29 [0.01, 5.79]
14.3.6 Dry mouth	5	173	Risk Ratio (IV, Random, 95% CI)	0.87 [0.37, 2.09]
14.3.7 Dyspepsia	1	31	Risk Ratio (IV, Random, 95% CI)	0.31 [0.01, 7.15]
14.3.8 Encopresis	1	31	Risk Ratio (IV, Random, 95% CI)	0.31 [0.01, 7.15]
14.3.9 Flatulance	1	10	Risk Ratio (IV, Random, 95% CI)	3.00 [0.15, 59.89]
14.3.10 Increased salivation	1	40	Risk Ratio (IV, Random, 95% CI)	1.00 [0.39, 2.58]
14.3.11 Nausea	15	768	Risk Ratio (IV, Random, 95% CI)	1.36 [0.90, 2.06]
14.3.12 Thirst	4	224	Risk Ratio (IV, Random, 95% CI)	3.32 [1.10, 10.01]
14.3.13 Vomiting	13	793	Risk Ratio (IV, Random, 95% CI)	1.34 [0.91, 1.98]
14.4 Adverse effects: immune system	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
14.4.1 Fever	2	102	Risk Ratio (IV, Random, 95% CI)	2.94 [0.46, 18.53]
14.4.2 Influenza	1	31	Risk Ratio (IV, Random, 95% CI)	0.31 [0.01, 7.15]
14.5 Adverse effects: metabolic (dichotomous)	27		Risk Ratio (IV, Random, 95% CI)	Subtotals only
14.5.1 Decreased appetite	15	806	Risk Ratio (IV, Random, 95% CI)	1.62 [0.95, 2.75]
14.5.2 Hypoglycemia	2	120	Risk Ratio (IV, Random, 95% CI)	0.71 [0.09, 5.68]
14.5.3 Hypokalemia	4	331	Risk Ratio (IV, Random, 95% CI)	12.48 [4.04, 38.62]
14.5.4 Hyponatremia	1	38	Risk Ratio (IV, Random, 95% CI)	3.00 [0.13, 69.31]
14.5.5 Increased appetite	14	676	Risk Ratio (IV, Random, 95% CI)	1.42 [1.02, 1.98]
14.5.6 Weight gain	2	39	Risk Ratio (IV, Random, 95% CI)	0.32 [0.04, 2.77]
14.5.7 Weight loss	4	306	Risk Ratio (IV, Random, 95% CI)	1.49 [0.50, 4.39]
14.5.8 Weight loss (0.12-0.67 kg)	1	11	Risk Ratio (IV, Random, 95% CI)	9.43 [0.65, 137.77]
14.5.9 Weight loss (0.45-2.19 kg)	1	11	Risk Ratio (IV, Random, 95% CI)	0.17 [0.01, 2.92]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.6 Adverse effects: metabolic (continuous)	1	23	Mean Difference (IV, Random, 95% CI)	0.13 [-0.24, 0.50]
14.6.1 Change in weight (kg)	1	23	Mean Difference (IV, Random, 95% CI)	0.13 [-0.24, 0.50]
14.7 Adverse effects: musculoskeletal	8		Risk Ratio (IV, Random, 95% CI)	Subtotals only
14.7.1 Arthralgia	1	10	Risk Ratio (IV, Random, 95% CI)	0.33 [0.02, 6.65]
14.7.2 Difficulty walking	1	40	Risk Ratio (IV, Random, 95% CI)	0.20 [0.01, 3.92]
14.7.3 Impaired balance	1	12	Risk Ratio (IV, Random, 95% CI)	1.67 [0.08, 33.75]
14.7.4 Myalgia	2	155	Risk Ratio (IV, Random, 95% CI)	1.54 [0.79, 3.04]
14.7.5 Slow movement	1	31	Risk Ratio (IV, Random, 95% CI)	4.17 [0.22, 80.25]
14.7.6 Stiffness	2	43	Risk Ratio (IV, Random, 95% CI)	2.03 [0.41, 10.15]
14.7.7 Weakness	3	90	Risk Ratio (IV, Random, 95% CI)	0.63 [0.21, 1.89]
14.8 Adverse effects: neurological	33		Risk Ratio (IV, Random, 95% CI)	Subtotals only
14.8.1 Agitation/excitement	5	220	Risk Ratio (IV, Random, 95% CI)	0.76 [0.39, 1.48]
14.8.2 Anxiety	3	250	Risk Ratio (IV, Random, 95% CI)	1.06 [0.44, 2.57]
14.8.3 Daytime drowsiness	6	172	Risk Ratio (IV, Random, 95% CI)	1.57 [0.75, 3.28]
14.8.4 Dazed	1	11	Risk Ratio (IV, Random, 95% CI)	2.57 [0.13, 52.12]
14.8.5 Difficulty concentrating	1	12	Risk Ratio (IV, Random, 95% CI)	2.50 [0.42, 14.83]
14.8.6 Difficulty sleeping	6	326	Risk Ratio (IV, Random, 95% CI)	0.81 [0.44, 1.50]
14.8.7 Dizziness	9	441	Risk Ratio (IV, Random, 95% CI)	1.21 [0.67, 2.18]
14.8.8 Drowsiness	5	298	Risk Ratio (IV, Random, 95% CI)	3.45 [1.21, 9.81]
14.8.9 Fatigue	7	338	Risk Ratio (IV, Random, 95% CI)	1.23 [0.70, 2.17]
14.8.10 Headache	18	943	Risk Ratio (IV, Random, 95% CI)	0.91 [0.66, 1.26]
14.8.11 Hypoactivity	3	28	Risk Ratio (IV, Random, 95% CI)	0.44 [0.07, 2.95]
14.8.12 Increased aggression	4	149	Risk Ratio (IV, Random, 95% CI)	0.78 [0.36, 1.70]
14.8.13 Increased hyperactivity	6	321	Risk Ratio (IV, Random, 95% CI)	0.75 [0.35, 1.58]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.8.14 Increased irritability	5	177	Risk Ratio (IV, Random, 95% CI)	1.11 [0.71, 1.72]
14.8.15 Increased stereotypies	1	41	Risk Ratio (IV, Random, 95% CI)	0.52 [0.10, 2.80]
14.8.16 Insomnia	8	488	Risk Ratio (IV, Random, 95% CI)	1.04 [0.66, 1.65]
14.8.17 Migraine	1	10	Risk Ratio (IV, Random, 95% CI)	3.00 [0.15, 59.89]
14.8.18 Nervousness	4	159	Risk Ratio (IV, Random, 95% CI)	1.86 [0.47, 7.37]
14.8.19 New onset seizures	1	46	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 7.78]
14.8.20 Restlessness	5	158	Risk Ratio (IV, Random, 95% CI)	1.22 [0.53, 2.82]
14.8.21 Rocking	1	11	Risk Ratio (IV, Random, 95% CI)	0.29 [0.01, 5.79]
14.8.22 Sedation	13	624	Risk Ratio (IV, Random, 95% CI)	0.93 [0.61, 1.42]
14.8.23 Syncope	1	89	Risk Ratio (IV, Random, 95% CI)	2.80 [0.30, 25.94]
14.8.24 Tremor	4	140	Risk Ratio (IV, Random, 95% CI)	1.80 [0.44, 7.37]
14.8.25 Twitching	2	71	Risk Ratio (IV, Random, 95% CI)	3.60 [0.42, 31.04]
14.9 Adverse effects: psychological	10		Risk Ratio (IV, Random, 95% CI)	Subtotals only
14.9.1 Anorexia	1	20	Risk Ratio (IV, Random, 95% CI)	0.53 [0.20, 1.40]
14.9.2 Aggression	1	150	Risk Ratio (IV, Random, 95% CI)	1.17 [0.37, 3.66]
14.9.3 Depression	3	108	Risk Ratio (IV, Random, 95% CI)	1.93 [0.62, 6.00]
14.9.4 Increased self-injurious behaviour	3	105	Risk Ratio (IV, Random, 95% CI)	0.46 [0.11, 1.84]
14.9.5 Irritability	2	162	Risk Ratio (IV, Random, 95% CI)	0.91 [0.36, 2.27]
14.9.6 Mental symptoms	1	20	Risk Ratio (IV, Random, 95% CI)	1.00 [0.41, 2.45]
14.9.7 Repetitive behaviour	1	46	Risk Ratio (IV, Random, 95% CI)	0.50 [0.05, 5.14]
14.9.8 Worsening of temper tantrums	2	52	Risk Ratio (IV, Random, 95% CI)	1.88 [0.30, 11.83]
14.10 Adverse effects: respiratory	6		Risk Ratio (IV, Random, 95% CI)	Subtotals only
14.10.1 Aggravation of asthma	1	71	Risk Ratio (IV, Random, 95% CI)	3.26 [0.14, 77.35]
14.10.2 Congestion/cold	4	256	Risk Ratio (IV, Random, 95% CI)	1.02 [0.62, 1.68]

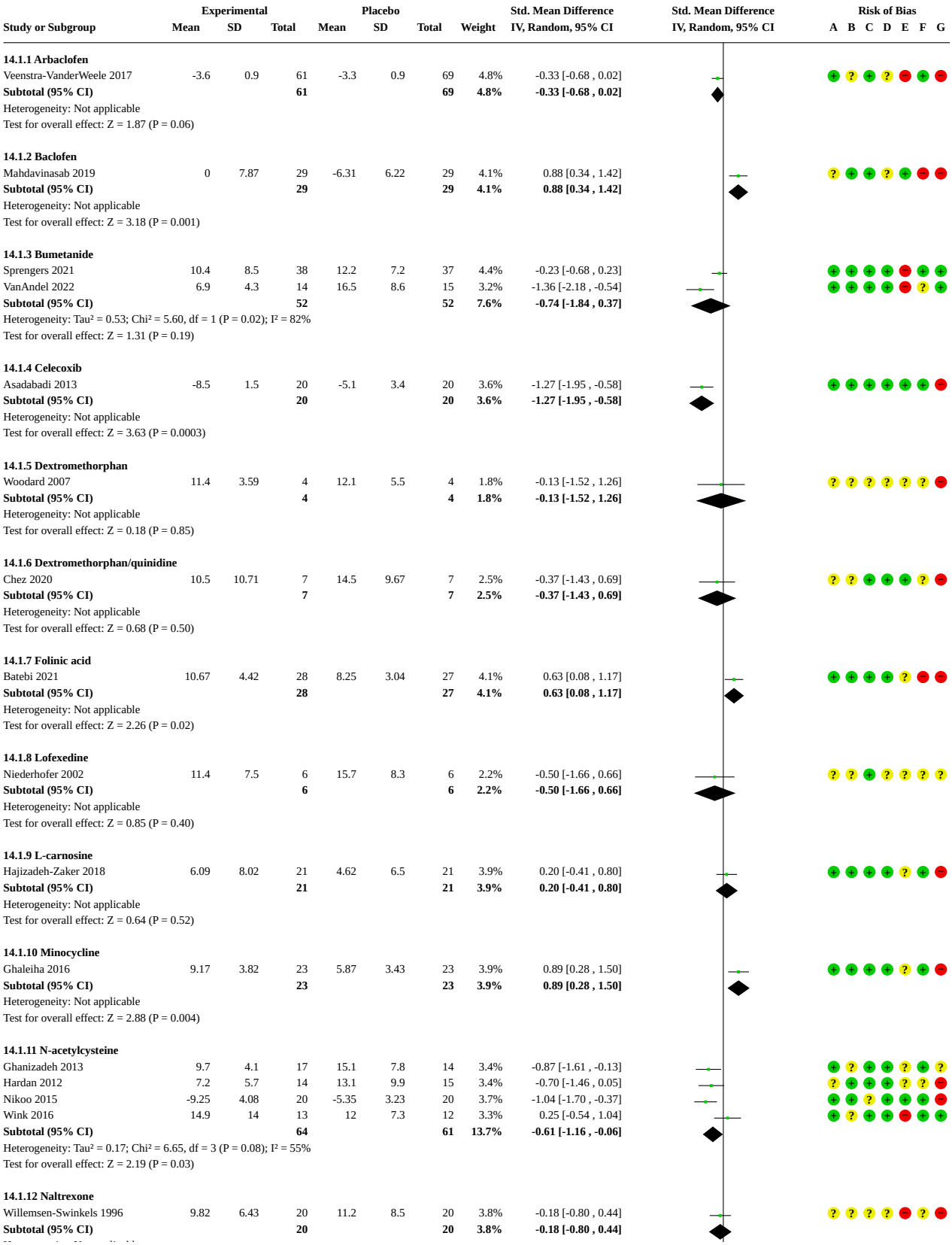
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.10.3 Cough	3	248	Risk Ratio (IV, Random, 95% CI)	1.16 [0.55, 2.49]
14.10.4 Ear infection	1	31	Risk Ratio (IV, Random, 95% CI)	1.88 [0.19, 18.60]
14.10.5 Lung congestion	1	20	Risk Ratio (IV, Random, 95% CI)	1.00 [0.60, 1.68]
14.10.6 Nasopharyngitis	1	150	Risk Ratio (IV, Random, 95% CI)	0.78 [0.22, 2.79]
14.10.7 Respiratory adverse effects	1	71	Risk Ratio (IV, Random, 95% CI)	5.43 [0.27, 109.19]
14.11 Adverse effects: skin	12		Risk Ratio (IV, Random, 95% CI)	Subtotals only
14.11.1 Hives	1	31	Risk Ratio (IV, Random, 95% CI)	0.31 [0.01, 7.15]
14.11.2 Itches	2	62	Risk Ratio (IV, Random, 95% CI)	0.55 [0.07, 4.19]
14.11.3 Rash	7	440	Risk Ratio (IV, Random, 95% CI)	0.76 [0.30, 1.92]
14.11.4 Skin adverse effects	1	71	Risk Ratio (IV, Random, 95% CI)	1.09 [0.16, 7.30]
14.11.5 Skin lesion	2	98	Risk Ratio (IV, Random, 95% CI)	1.66 [0.74, 3.70]
14.12 Adverse effects: urinary	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
14.12.1 Diuresis	1	89	Risk Ratio (IV, Random, 95% CI)	0.93 [0.25, 3.51]
14.12.2 Enuresis	3	205	Risk Ratio (IV, Random, 95% CI)	2.70 [0.82, 8.87]
14.12.3 Urinary retention	2	88	Risk Ratio (IV, Random, 95% CI)	0.74 [0.05, 10.49]
14.12.4 Urinary tract infection	1	31	Risk Ratio (IV, Random, 95% CI)	0.31 [0.01, 7.15]
14.13 Adverse effects: other	7		Risk Ratio (IV, Random, 95% CI)	Subtotals only
14.13.1 Blurred vision	1	31	Risk Ratio (IV, Random, 95% CI)	2.50 [0.11, 56.98]
14.13.2 Dilated pupils	1	20	Risk Ratio (IV, Random, 95% CI)	0.67 [0.05, 9.19]
14.13.3 Fever	1	150	Risk Ratio (IV, Random, 95% CI)	0.49 [0.13, 1.88]
14.13.4 Sweating	3	129	Risk Ratio (IV, Random, 95% CI)	0.75 [0.15, 3.86]
14.13.5 Vision: conjunctivitis	1	10	Risk Ratio (IV, Random, 95% CI)	0.33 [0.02, 6.65]
14.14 Tolerability/acceptability: loss to follow-up	30	1913	Risk Ratio (IV, Random, 95% CI)	1.07 [0.89, 1.28]
14.15 Subgroup analyses: age - irritability (option 1)	28	1242	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.42, -0.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.15.1 Children only	23	1014	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.46, 0.04]
14.15.2 Adults only	3	84	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.69, 0.17]
14.15.3 Children and adults	2	144	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.61, 0.05]
14.16 Subgroup analyses: age - irritability (option 2)	28	1179	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.42, 0.01]
14.16.1 Celecoxib: children only	1	40	Std. Mean Difference (IV, Random, 95% CI)	-1.27 [-1.95, -0.58]
14.16.2 D-cycloserine: children only	1	67	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.53, 0.43]
14.16.3 Dextromethorphan: children only	1	8	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-1.52, 1.26]
14.16.4 Mecamylamine: children only	1	20	Std. Mean Difference (IV, Random, 95% CI)	0.18 [-0.71, 1.08]
14.16.5 Riluzole: children only	1	40	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-1.27, 0.00]
14.16.6 Riluzole: children and adults	1	14	Std. Mean Difference (IV, Random, 95% CI)	0.18 [-0.87, 1.23]
14.16.7 Pioglitazone: children only	1	40	Std. Mean Difference (IV, Random, 95% CI)	-0.77 [-1.42, -0.13]
14.16.8 N-acetylcysteine: children only	4	125	Std. Mean Difference (IV, Random, 95% CI)	-0.61 [-1.16, -0.06]
14.16.9 *Trichuris suis* ova: adults only	1	10	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-1.50, 1.00]
14.16.10 Tetrahydrobiopterin: children only	1	46	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.68, 0.48]
14.16.11 Lofexedine: children only	1	12	Std. Mean Difference (IV, Random, 95% CI)	-0.50 [-1.66, 0.66]
14.16.12 Naltrexone: adults only	1	20	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-1.05, 0.70]
14.16.13 Minocycline: children only	1	46	Std. Mean Difference (IV, Random, 95% CI)	0.89 [0.28, 1.50]
14.16.14 Propentofylline: children only	1	48	Std. Mean Difference (IV, Random, 95% CI)	0.56 [-0.01, 1.14]

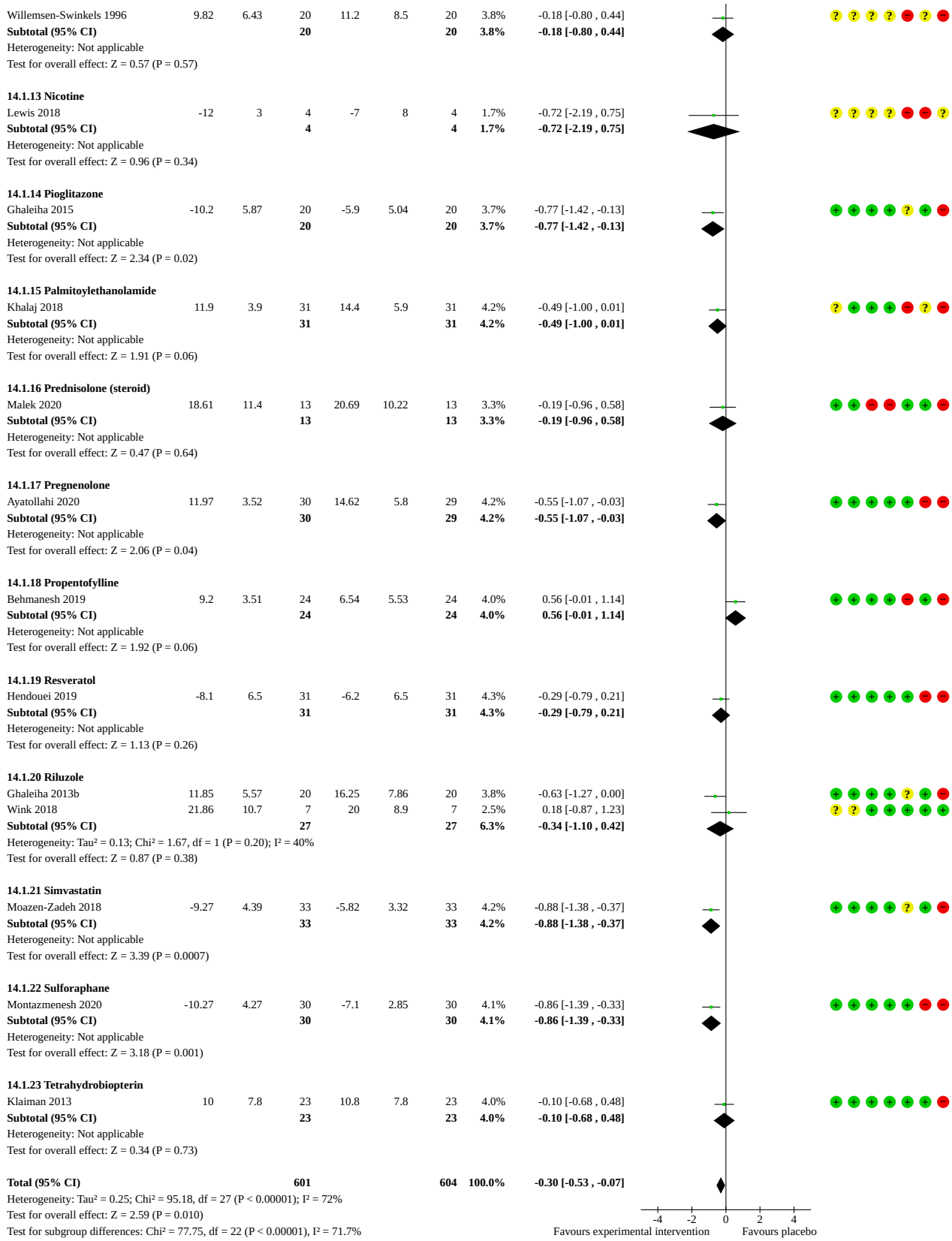
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.16.15 Sulforaphane: children only	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.86 [-1.39, -0.33]
14.16.16 Folinic acid: children only	1	55	Std. Mean Difference (IV, Random, 95% CI)	0.63 [0.08, 1.17]
14.16.17 L-carnosine: children only	1	42	Std. Mean Difference (IV, Random, 95% CI)	0.20 [-0.41, 0.80]
14.16.18 Prednisolone (steroid): children only	1	26	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.96, 0.58]
14.16.19 Dextromethorphan/quinidine: adults only	1	14	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-1.43, 0.69]
14.16.20 Pregnenolone: children only	1	59	Std. Mean Difference (IV, Random, 95% CI)	-0.55 [-1.07, -0.03]
14.16.21 Baclofen: children only	1	58	Std. Mean Difference (IV, Random, 95% CI)	0.88 [0.34, 1.42]
14.16.22 Palmitoylethanolamide: children only	1	62	Std. Mean Difference (IV, Random, 95% CI)	-0.49 [-1.00, 0.01]
14.16.23 Bumetanide: children only	1	75	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.55, 0.35]
14.16.24 Resveratol: children only	1	62	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.79, 0.21]
14.16.25 Arbaclofen: children and adults	1	130	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.68, 0.02]
14.17 Subgroup analyses: age - self-injury (option 1)	3	147	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.30, 0.35]
14.17.1 Children only	2	127	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.29, 0.44]
14.17.2 Adults only	1	20	Std. Mean Difference (IV, Random, 95% CI)	-0.31 [-1.20, 0.57]
14.18 Subgroup analyses: age - self-injury (option 2)	5	285	Std. Mean Difference (IV, Random, 95% CI)	0.14 [-0.09, 0.38]
14.18.1 N-acetylcysteine: children only	1	98	Std. Mean Difference (IV, Random, 95% CI)	0.18 [-0.22, 0.58]
14.18.2 N-acetylcysteine: children only	1	29	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.99, 0.48]
14.18.3 *Trichuris suis* ova: adults only	1	10	Std. Mean Difference (IV, Random, 95% CI)	-0.30 [-1.55, 0.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.18.4 Bumetanide: children only	2	148	Std. Mean Difference (IV, Random, 95% CI)	0.20 [-0.21, 0.60]

Analysis 14.1. Comparison 14: Experimental versus placebo, Outcome 1: Irritability

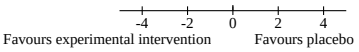


Analysis 14.1. (Continued)



Analysis 14.1. (Continued)

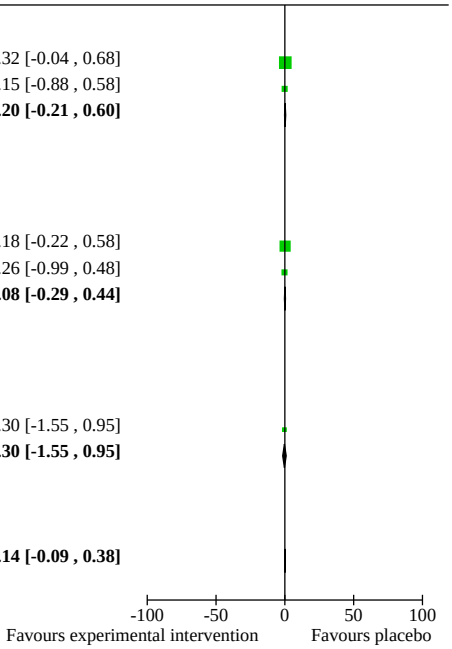
Test for overall effect: Z = 2.59 (P = 0.010)
Test for subgroup differences: Chi² = 77.75, df = 22 (P < 0.00001), I² = 71.7%



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

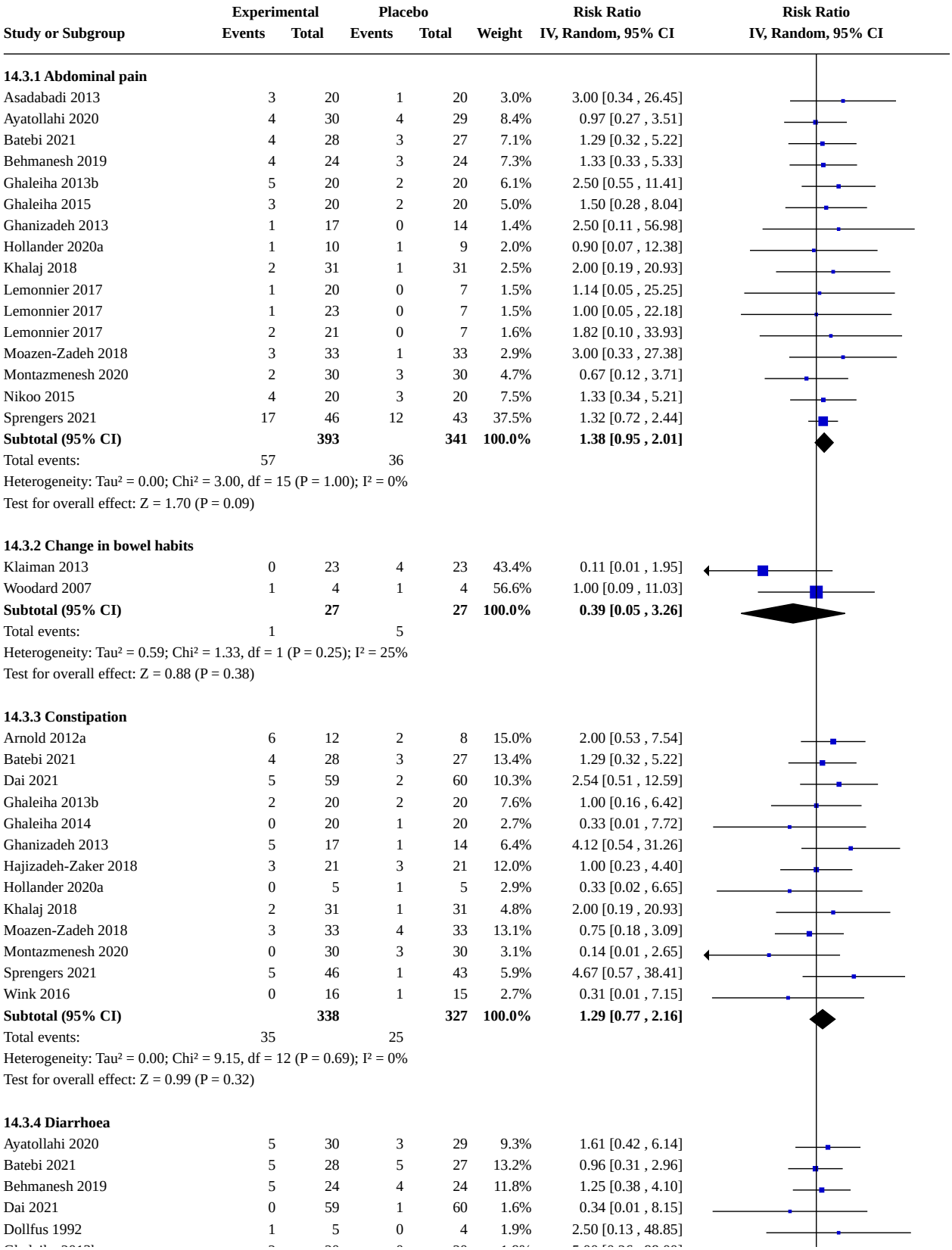
Analysis 14.2. Comparison 14: Experimental versus placebo, Outcome 2: Self-injury

Study or Subgroup	Experimental Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
14.2.1 Bumetanide								
Dai 2021 (1)	-0.14	0.57	59	-0.42	1.08	60	41.6%	0.32 [-0.04 , 0.68]
VanAndel 2022 (2)	1	1.8	14	1.3	2.1	15	10.2%	-0.15 [-0.88 , 0.58]
Subtotal (95% CI)			**73**			**75**	**51.8%**	**0.20 [-0.21 , 0.60]**
Heterogeneity: Tau² = 0.02; Chi² = 1.28, df = 1 (P = 0.26); I² = 22%								
Test for overall effect: Z = 0.95 (P = 0.34)								
14.2.2 N-acetylcysteine								
Dean 2019 (3)	2.2	2.9	48	1.7	2.6	50	34.5%	0.18 [-0.22 , 0.58]
Hardan 2012 (3)	2.2	2.3	14	3	3.6	15	10.2%	-0.26 [-0.99 , 0.48]
Subtotal (95% CI)			**62**			**65**	**44.7%**	**0.08 [-0.29 , 0.44]**
Heterogeneity: Tau² = 0.00; Chi² = 1.05, df = 1 (P = 0.30); I² = 5%								
Test for overall effect: Z = 0.40 (P = 0.69)								
14.2.3 Trichuris suris ova								
Hollander 2020a (4)	-0.37	2.5	5	0.42	2.31	5	3.5%	-0.30 [-1.55 , 0.95]
Subtotal (95% CI)			**5**			**5**	**3.5%**	**-0.30 [-1.55 , 0.95]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.46 (P = 0.64)								
Total (95% CI)			**140**			**145**	**100.0%**	**0.14 [-0.09 , 0.38]**
Heterogeneity: Tau² = 0.00; Chi² = 3.20, df = 4 (P = 0.53); I² = 0%								
Test for overall effect: Z = 1.21 (P = 0.22)								
Test for subgroup differences: Chi² = 0.62, df = 2 (P = 0.73), I² = 0%								



Footnotes
(1) Bumetanide
(2) Bumetanide
(3) N-acetyl cysteine
(4) Trichuris suris ova

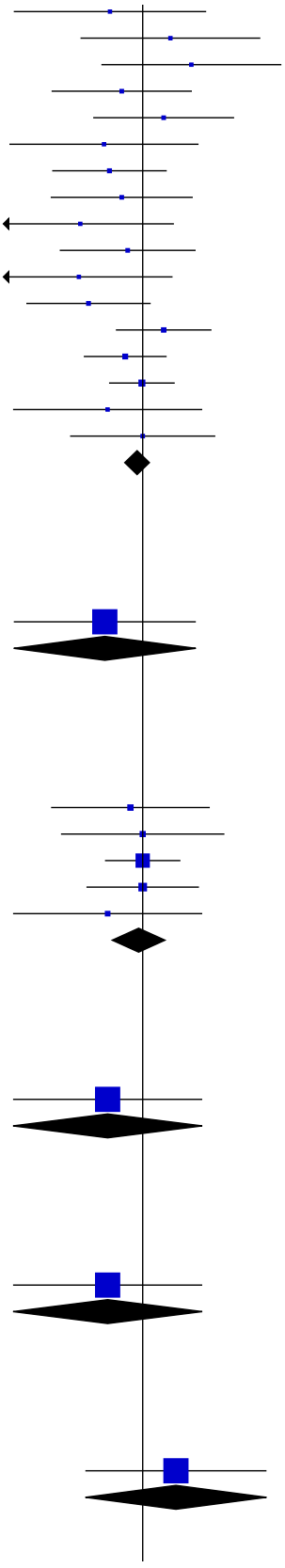
Analysis 14.3. Comparison 14: Experimental versus placebo, Outcome 3: Adverse effects: gastrointestinal



Study or Subgroup	Experimental Events	Experimental Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
14.3.1 Abdominal pain						
Asadabadi 2013	3	20	1	20	3.0%	3.00 [0.34 , 26.45]
Ayatollahi 2020	4	30	4	29	8.4%	0.97 [0.27 , 3.51]
Batebi 2021	4	28	3	27	7.1%	1.29 [0.32 , 5.22]
Behmanesh 2019	4	24	3	24	7.3%	1.33 [0.33 , 5.33]
Ghaleiha 2013b	5	20	2	20	6.1%	2.50 [0.55 , 11.41]
Ghaleiha 2015	3	20	2	20	5.0%	1.50 [0.28 , 8.04]
Ghanizadeh 2013	1	17	0	14	1.4%	2.50 [0.11 , 56.98]
Hollander 2020a	1	10	1	9	2.0%	0.90 [0.07 , 12.38]
Khalaj 2018	2	31	1	31	2.5%	2.00 [0.19 , 20.93]
Lemonnier 2017	1	20	0	7	1.5%	1.14 [0.05 , 25.25]
Lemonnier 2017	1	23	0	7	1.5%	1.00 [0.05 , 22.18]
Lemonnier 2017	2	21	0	7	1.6%	1.82 [0.10 , 33.93]
Moazen-Zadeh 2018	3	33	1	33	2.9%	3.00 [0.33 , 27.38]
Montazmenesh 2020	2	30	3	30	4.7%	0.67 [0.12 , 3.71]
Nikoo 2015	4	20	3	20	7.5%	1.33 [0.34 , 5.21]
Sprengers 2021	17	46	12	43	37.5%	1.32 [0.72 , 2.44]
Subtotal (95% CI)		**393**		**341**	**100.0%**	**1.38 [0.95 , 2.01]**
Total events:	57		36			
Heterogeneity: Tau² = 0.00; Chi² = 3.00, df = 15 (P = 1.00); I² = 0%						
Test for overall effect: Z = 1.70 (P = 0.09)						
14.3.2 Change in bowel habits						
Klaiman 2013	0	23	4	23	43.4%	0.11 [0.01 , 1.95]
Woodard 2007	1	4	1	4	56.6%	1.00 [0.09 , 11.03]
Subtotal (95% CI)		**27**		**27**	**100.0%**	**0.39 [0.05 , 3.26]**
Total events:	1		5			
Heterogeneity: Tau² = 0.59; Chi² = 1.33, df = 1 (P = 0.25); I² = 25%						
Test for overall effect: Z = 0.88 (P = 0.38)						
14.3.3 Constipation						
Arnold 2012a	6	12	2	8	15.0%	2.00 [0.53 , 7.54]
Batebi 2021	4	28	3	27	13.4%	1.29 [0.32 , 5.22]
Dai 2021	5	59	2	60	10.3%	2.54 [0.51 , 12.59]
Ghaleiha 2013b	2	20	2	20	7.6%	1.00 [0.16 , 6.42]
Ghaleiha 2014	0	20	1	20	2.7%	0.33 [0.01 , 7.72]
Ghanizadeh 2013	5	17	1	14	6.4%	4.12 [0.54 , 31.26]
Hajizadeh-Zaker 2018	3	21	3	21	12.0%	1.00 [0.23 , 4.40]
Hollander 2020a	0	5	1	5	2.9%	0.33 [0.02 , 6.65]
Khalaj 2018	2	31	1	31	4.8%	2.00 [0.19 , 20.93]
Moazen-Zadeh 2018	3	33	4	33	13.1%	0.75 [0.18 , 3.09]
Montazmenesh 2020	0	30	3	30	3.1%	0.14 [0.01 , 2.65]
Sprengers 2021	5	46	1	43	5.9%	4.67 [0.57 , 38.41]
Wink 2016	0	16	1	15	2.7%	0.31 [0.01 , 7.15]
Subtotal (95% CI)		**338**		**327**	**100.0%**	**1.29 [0.77 , 2.16]**
Total events:	35		25			
Heterogeneity: Tau² = 0.00; Chi² = 9.15, df = 12 (P = 0.69); I² = 0%						
Test for overall effect: Z = 0.99 (P = 0.32)						
14.3.4 Diarrhoea						
Ayatollahi 2020	5	30	3	29	9.3%	1.61 [0.42 , 6.14]
Batebi 2021	5	28	5	27	13.2%	0.96 [0.31 , 2.96]
Behmanesh 2019	5	24	4	24	11.8%	1.25 [0.38 , 4.10]
Dai 2021	0	59	1	60	1.6%	0.34 [0.01 , 8.15]
Dollfus 1992	1	5	0	4	1.9%	2.50 [0.13 , 48.85]

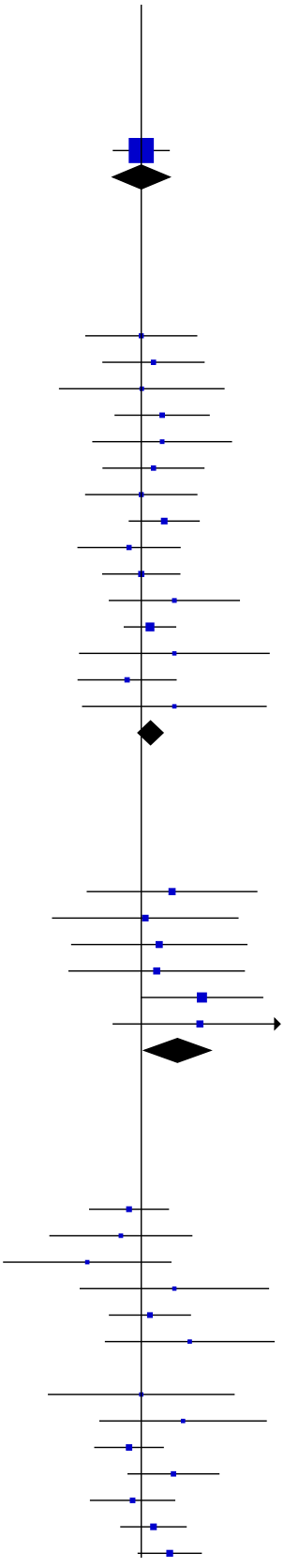
Analysis 14.3. (Continued)

Dal 2021	0	59	1	60	1.6%	0.34 [0.01 , 8.15]
Dollfus 1992	1	5	0	4	1.9%	2.50 [0.13 , 48.85]
Ghaleiha 2013b	2	20	0	20	1.9%	5.00 [0.26 , 98.00]
Ghaleiha 2015	1	20	2	20	3.1%	0.50 [0.05 , 5.08]
Ghaleiha 2016	2	23	1	23	3.1%	2.00 [0.19 , 20.55]
Ghanizadeh 2013	0	17	1	14	1.7%	0.28 [0.01 , 6.33]
Hollander 2020a	1	5	3	5	4.6%	0.33 [0.05 , 2.21]
Khalaj 2018	1	31	2	31	3.0%	0.50 [0.05 , 5.23]
Lemonnier 2017	0	20	1	7	1.7%	0.13 [0.01 , 2.81]
Lemonnier 2017	2	23	1	7	3.3%	0.61 [0.06 , 5.75]
Lemonnier 2017	0	21	1	7	1.7%	0.12 [0.01 , 2.68]
Montazmenesh 2020	1	30	6	30	3.9%	0.17 [0.02 , 1.30]
Nikoo 2015	4	20	2	20	6.6%	2.00 [0.41 , 9.71]
Sprengers 2021	3	46	5	43	8.8%	0.56 [0.14 , 2.21]
Veenstra-VanderWeele 2017	6	76	6	74	14.1%	0.97 [0.33 , 2.88]
Wink 2016	0	16	1	15	1.7%	0.31 [0.01 , 7.15]
Woodard 2007	1	4	1	4	2.9%	1.00 [0.09 , 11.03]
Subtotal (95% CI)		**518**		**464**	**100.0%**	**0.83 [0.55 , 1.25]**
Total events:	40		46			
Heterogeneity: Tau² = 0.00; Chi² = 13.27, df = 19 (P = 0.82); I² = 0%						
Test for overall effect: Z = 0.89 (P = 0.37)						
14.3.5 Drooling						
Campbell 1987	0	6	1	5	100.0%	0.29 [0.01 , 5.79]
Subtotal (95% CI)		**6**		**5**	**100.0%**	**0.29 [0.01 , 5.79]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
14.3.6 Dry mouth						
Arnold 2012a	1	12	1	8	11.0%	0.67 [0.05 , 9.19]
Ghaleiha 2015	1	20	1	20	10.4%	1.00 [0.07 , 14.90]
Hajizadeh-Zaker 2018	4	21	4	21	48.8%	1.00 [0.29 , 3.48]
Nikoo 2015	2	20	2	20	22.0%	1.00 [0.16 , 6.42]
Wink 2016	0	16	1	15	7.8%	0.31 [0.01 , 7.15]
Subtotal (95% CI)		**89**		**84**	**100.0%**	**0.87 [0.37 , 2.09]**
Total events:	8		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 4 (P = 0.97); I² = 0%						
Test for overall effect: Z = 0.30 (P = 0.76)						
14.3.7 Dyspepsia						
Wink 2016	0	16	1	15	100.0%	0.31 [0.01 , 7.15]
Subtotal (95% CI)		**16**		**15**	**100.0%**	**0.31 [0.01 , 7.15]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
14.3.8 Encopresis						
Wink 2016	0	16	1	15	100.0%	0.31 [0.01 , 7.15]
Subtotal (95% CI)		**16**		**15**	**100.0%**	**0.31 [0.01 , 7.15]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
14.3.9 Flatulance						
Hollander 2020a	1	5	0	5	100.0%	3.00 [0.15 , 59.89]
Subtotal (95% CI)		**5**		**5**	**100.0%**	**3.00 [0.15 , 59.89]**
Total events:	1		0			
Heterogeneity: Not applicable						



Analysis 14.3. (Continued)

Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
14.3.10 Increased salivation						
Ghaleiha 2013b	6	20	6	20	100.0%	1.00 [0.39 , 2.58]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**1.00 [0.39 , 2.58]**
Total events:	6		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
14.3.11 Nausea						
Asadabadi 2013	2	20	2	20	5.0%	1.00 [0.16 , 6.42]
Behmanesh 2019	3	24	2	24	6.0%	1.50 [0.27 , 8.19]
Dai 2021	1	59	1	60	2.3%	1.02 [0.07 , 15.88]
Ghaleiha 2013a	4	20	2	20	7.0%	2.00 [0.41 , 9.71]
Ghaleiha 2015	2	20	1	20	3.2%	2.00 [0.20 , 20.33]
Ghaleiha 2016	3	23	2	23	6.1%	1.50 [0.28 , 8.16]
Hajizadeh-Zaker 2018	2	21	2	21	5.0%	1.00 [0.16 , 6.45]
Hardan 2012	6	14	3	15	12.5%	2.14 [0.66 , 6.97]
Mahdavinasab 2019	2	29	3	29	5.9%	0.67 [0.12 , 3.70]
Moazen-Zadeh 2018	4	33	4	33	10.3%	1.00 [0.27 , 3.67]
Nikoo 2015	3	20	1	20	3.7%	3.00 [0.34 , 26.45]
Sprengers 2021	10	46	7	43	22.9%	1.34 [0.56 , 3.19]
Willemsen-Swinkels 1995	1	32	0	32	1.7%	3.00 [0.13 , 71.00]
Wink 2016	2	16	3	15	6.4%	0.63 [0.12 , 3.24]
Woodard 2007	1	8	0	8	1.9%	3.00 [0.14 , 64.26]
Subtotal (95% CI)		**385**		**383**	**100.0%**	**1.36 [0.90 , 2.06]**
Total events:	46		33			
Heterogeneity: Tau² = 0.00; Chi² = 3.93, df = 14 (P = 1.00); I² = 0%						
Test for overall effect: Z = 1.44 (P = 0.15)						
14.3.12 Thirst						
Danforth 2018	2	8	0	4	15.2%	2.78 [0.16 , 47.20]
Lemonnier 2017	1	20	0	7	12.7%	1.14 [0.05 , 25.25]
Lemonnier 2017	2	21	0	7	14.2%	1.82 [0.10 , 33.93]
Lemonnier 2017	2	23	0	7	14.2%	1.67 [0.09 , 31.18]
Sprengers 2021	8	46	1	43	29.3%	7.48 [0.98 , 57.33]
VanAndel 2022	3	19	0	19	14.5%	7.00 [0.39 , 126.92]
Subtotal (95% CI)		**137**		**87**	**100.0%**	**3.32 [1.10 , 10.01]**
Total events:	18		1			
Heterogeneity: Tau² = 0.00; Chi² = 1.71, df = 5 (P = 0.89); I² = 0%						
Test for overall effect: Z = 2.13 (P = 0.03)						
14.3.13 Vomiting						
Arnold 2012a	3	12	3	8	8.7%	0.67 [0.18 , 2.51]
Dai 2021	1	59	2	60	2.7%	0.51 [0.05 , 5.46]
Dollfus 1992	0	5	2	4	2.0%	0.17 [0.01 , 2.73]
Ghaleiha 2013b	1	20	0	20	1.5%	3.00 [0.13 , 69.52]
Ghaleiha 2015	4	20	3	20	8.2%	1.33 [0.34 , 5.21]
Hollander 2020a	2	5	0	5	1.9%	5.00 [0.30 , 83.69]
Lemonnier 2017	0	20	0	7		Not estimable
Lemonnier 2017	1	23	0	7	1.6%	1.00 [0.05 , 22.18]
Lemonnier 2017	5	21	0	7	2.0%	4.00 [0.25 , 64.45]
Mahdavinasab 2019	4	29	6	29	11.4%	0.67 [0.21 , 2.12]
Minshawi 2016	6	34	2	33	6.5%	2.91 [0.63 , 13.41]
Moazen-Zadeh 2018	3	33	4	33	7.6%	0.75 [0.18 , 3.09]
Nikoo 2015	6	20	4	20	12.5%	1.50 [0.50 , 4.52]
Sprengers 2021	11	46	4	43	13.4%	2.57 [0.89 , 7.47]



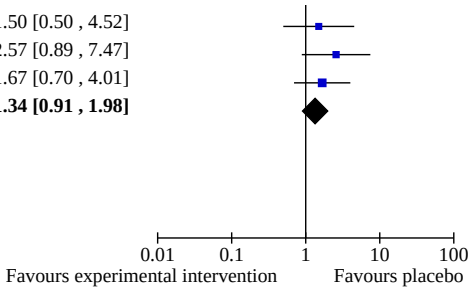
Analysis 14.3. (Continued)

Nikoo 2015	6	20	4	20	12.5%	1.50 [0.50 , 4.52]
Sprengers 2021	11	46	4	43	13.4%	2.57 [0.89 , 7.47]
Veenstra-VanderWeele 2017	12	76	7	74	19.9%	1.67 [0.70 , 4.01]
Subtotal (95% CI)		**423**		**370**	**100.0%**	**1.34 [0.91 , 1.98]**
Total events:	59		37			

Heterogeneity: Tau² = 0.00; Chi² = 10.32, df = 13 (P = 0.67); I² = 0%

Test for overall effect: Z = 1.46 (P = 0.14)

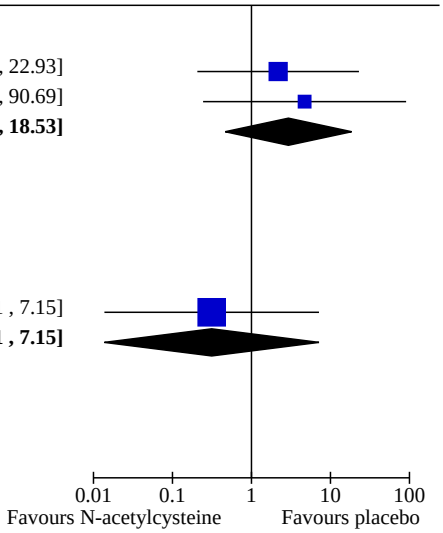
Test for subgroup differences: Chi² = 0.00, df = 12 (P < 0.00001), I² = 0%



Analysis 14.4. Comparison 14: Experimental versus placebo, Outcome 4: Adverse effects: immune system

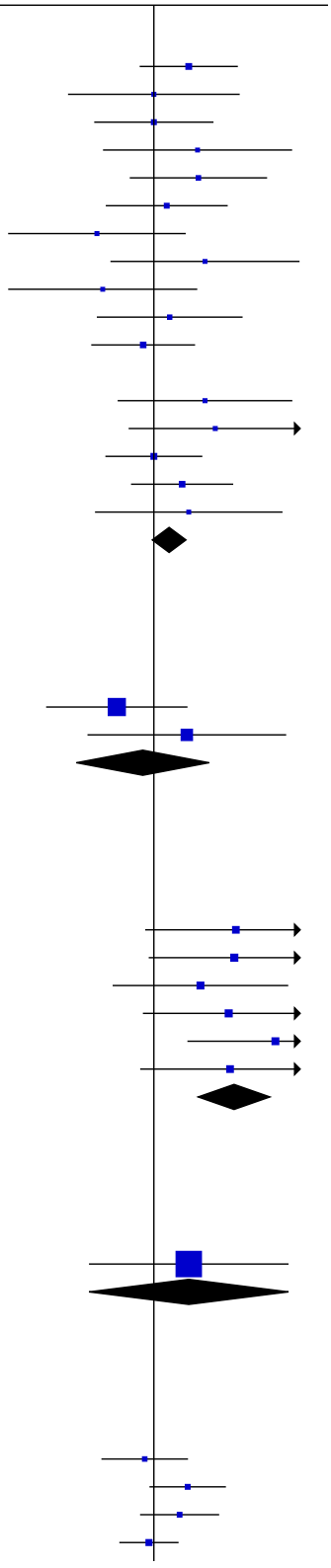
Study or Subgroup	Experimental Events	Experimental Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
14.4.1 Fever						
Dean 2019	2	34	1	37	61.2%	2.18 [0.21 , 22.93]
Wink 2016	2	16	0	15	38.8%	4.71 [0.24 , 90.69]
Subtotal (95% CI)		**50**		**52**	**100.0%**	**2.94 [0.46 , 18.53]**
Total events:	4		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%						
Test for overall effect: Z = 1.15 (P = 0.25)						
14.4.2 Influenza						
Wink 2016	0	16	1	15	100.0%	0.31 [0.01 , 7.15]
Subtotal (95% CI)		**16**		**15**	**100.0%**	**0.31 [0.01 , 7.15]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						

Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%



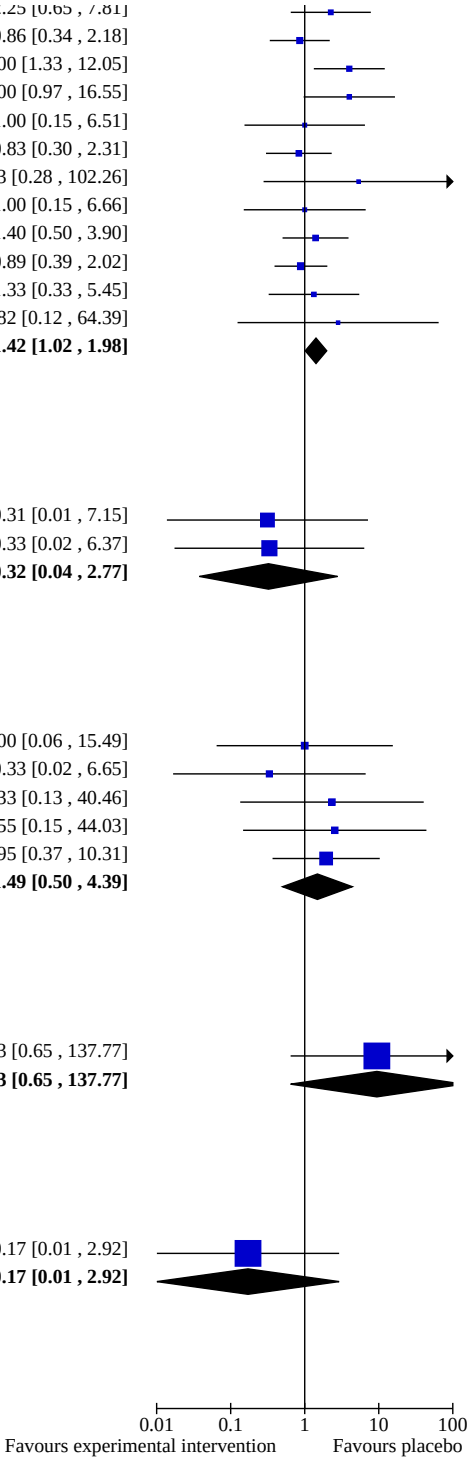
Analysis 14.5. Comparison 14: Experimental versus placebo, Outcome 5: Adverse effects: metabolic (dichotomous)

Study or Subgroup	Experimental Events	Experimental Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
14.5.1 Decreased appetite						
Aran 2021	6	44	2	44	11.8%	3.00 [0.64 , 14.06]
Asadabadi 2013	1	20	1	20	3.9%	1.00 [0.07 , 14.90]
Behmanesh 2019	2	24	2	24	8.0%	1.00 [0.15 , 6.53]
Campbell 1993	2	23	0	18	3.2%	3.96 [0.20 , 77.63]
Dai 2021	4	59	1	60	6.0%	4.07 [0.47 , 35.33]
Danforth 2018	3	8	1	4	7.6%	1.50 [0.22 , 10.22]
Dollfus 1992	0	5	2	4	3.6%	0.17 [0.01 , 2.73]
Ghaleiha 2013b	2	20	0	20	3.2%	5.00 [0.26 , 98.00]
Ghaleiha 2014	0	20	2	20	3.2%	0.20 [0.01 , 3.92]
Ghanizadeh 2013	2	17	1	14	5.3%	1.65 [0.17 , 16.33]
Hardan 2012	2	14	3	15	10.5%	0.71 [0.14 , 3.66]
Lemonnier 2017	0	20	0	7		Not estimable
Lemonnier 2017	7	23	0	7	3.7%	5.00 [0.32 , 78.10]
Lemonnier 2017	9	21	0	7	3.8%	6.91 [0.45 , 105.54]
Moazen-Zadeh 2018	3	33	3	33	12.1%	1.00 [0.22 , 4.60]
Veenstra-VanderWeele 2017	5	76	2	74	10.9%	2.43 [0.49 , 12.16]
Woodard 2007	1	4	0	4	3.2%	3.00 [0.16 , 57.36]
Subtotal (95% CI)		**431**		**375**	**100.0%**	**1.62 [0.95 , 2.75]**
Total events:	49		20			
Heterogeneity: Tau² = 0.00; Chi² = 10.53, df = 15 (P = 0.79); I² = 0%						
Test for overall effect: Z = 1.78 (P = 0.08)						
14.5.2 Hypoglycemia						
Sprengers 2021	1	46	3	43	62.9%	0.31 [0.03 , 2.88]
Wink 2016	1	16	0	15	37.1%	2.82 [0.12 , 64.39]
Subtotal (95% CI)		**62**		**58**	**100.0%**	**0.71 [0.09 , 5.68]**
Total events:	2		3			
Heterogeneity: Tau² = 0.51; Chi² = 1.27, df = 1 (P = 0.26); I² = 21%						
Test for overall effect: Z = 0.33 (P = 0.74)						
14.5.3 Hypokalemia						
Dai 2021	6	59	0	60	15.7%	13.22 [0.76 , 229.47]
Lemonnier 2017	16	20	0	7	17.6%	12.57 [0.85 , 185.77]
Lemonnier 2017	6	23	0	7	16.7%	4.33 [0.27 , 68.67]
Lemonnier 2017	14	21	0	7	17.5%	10.55 [0.71 , 157.00]
Sprengers 2021	24	46	0	43	16.6%	45.87 [2.88 , 731.77]
VanAndel 2022	5	19	0	19	15.9%	11.00 [0.65 , 186.02]
Subtotal (95% CI)		**188**		**143**	**100.0%**	**12.48 [4.04 , 38.62]**
Total events:	71		0			
Heterogeneity: Tau² = 0.00; Chi² = 1.44, df = 5 (P = 0.92); I² = 0%						
Test for overall effect: Z = 4.38 (P < 0.0001)						
14.5.4 Hyponatremia						
VanAndel 2022	1	19	0	19	100.0%	3.00 [0.13 , 69.31]
Subtotal (95% CI)		**19**		**19**	**100.0%**	**3.00 [0.13 , 69.31]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
14.5.5 Increased appetite						
Asadabadi 2013	3	20	4	20	6.0%	0.75 [0.19 , 2.93]
Ayatollahi 2020	9	30	3	29	7.7%	2.90 [0.87 , 9.66]
Batebi 2021	7	28	3	27	7.2%	2.25 [0.65 , 7.81]
Behmanesh 2019	6	24	7	24	12.8%	0.86 [0.34 , 2.18]



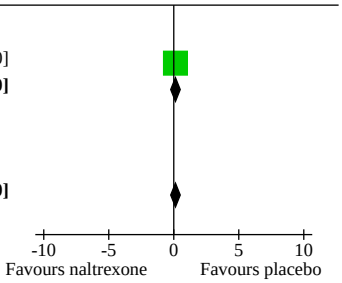
Analysis 14.5. (Continued)

Batebi 2021	7	28	3	27	7.2%	2.25 [0.65 , 7.81]
Behmanesh 2019	6	24	7	24	12.8%	0.86 [0.34 , 2.18]
Ghaleiha 2013b	12	20	3	20	9.1%	4.00 [1.33 , 12.05]
Ghaleiha 2014	8	20	2	20	5.5%	4.00 [0.97 , 16.55]
Ghaleiha 2016	2	23	2	23	3.2%	1.00 [0.15 , 6.51]
Hajizadeh-Zaker 2018	5	21	6	21	10.6%	0.83 [0.30 , 2.31]
Hardan 2012	2	14	0	15	1.3%	5.33 [0.28 , 102.26]
Khalaj 2018	2	31	2	31	3.1%	1.00 [0.15 , 6.66]
Mahdavinasab 2019	7	29	5	29	10.5%	1.40 [0.50 , 3.90]
Moazen-Zadeh 2018	8	33	9	33	16.4%	0.89 [0.39 , 2.02]
Montazmenesh 2020	4	30	3	30	5.6%	1.33 [0.33 , 5.45]
Wink 2016	1	16	0	15	1.1%	2.82 [0.12 , 64.39]
Subtotal (95% CI)		**339**		**337**	**100.0%**	**1.42 [1.02 , 1.98]**
Total events:	76		49			
Heterogeneity: Tau² = 0.00; Chi² = 12.81, df = 13 (P = 0.46); I² = 0%						
Test for overall effect: Z = 2.07 (P = 0.04)						
14.5.6 Weight gain						
Wink 2016	0	16	1	15	47.1%	0.31 [0.01 , 7.15]
Woodard 2007	0	4	1	4	52.9%	0.33 [0.02 , 6.37]
Subtotal (95% CI)		**20**		**19**	**100.0%**	**0.32 [0.04 , 2.77]**
Total events:	0		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 1.03 (P = 0.30)						
14.5.7 Weight loss						
Aran 2021	1	44	1	44	15.7%	1.00 [0.06 , 15.49]
Hollander 2020a	0	5	1	5	13.1%	0.33 [0.02 , 6.65]
Lemonnier 2017	3	23	0	7	14.4%	2.33 [0.13 , 40.46]
Lemonnier 2017	3	21	0	7	14.5%	2.55 [0.15 , 44.03]
Veenstra-VanderWeele 2017	4	76	2	74	42.3%	1.95 [0.37 , 10.31]
Subtotal (95% CI)		**169**		**137**	**100.0%**	**1.49 [0.50 , 4.39]**
Total events:	11		4			
Heterogeneity: Tau² = 0.00; Chi² = 1.37, df = 4 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.71 (P = 0.47)						
14.5.8 Weight loss (0.12-0.67 kg)						
Campbell 1987	5	6	0	5	100.0%	9.43 [0.65 , 137.77]
Subtotal (95% CI)		**6**		**5**	**100.0%**	**9.43 [0.65 , 137.77]**
Total events:	5		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.64 (P = 0.10)						
14.5.9 Weight loss (0.45-2.19 kg)						
Campbell 1987	0	6	2	5	100.0%	0.17 [0.01 , 2.92]
Subtotal (95% CI)		**6**		**5**	**100.0%**	**0.17 [0.01 , 2.92]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.22 (P = 0.22)						
Test for subgroup differences: Chi² = 0.00, df = 8 (P < 0.00001), I² = 0%						



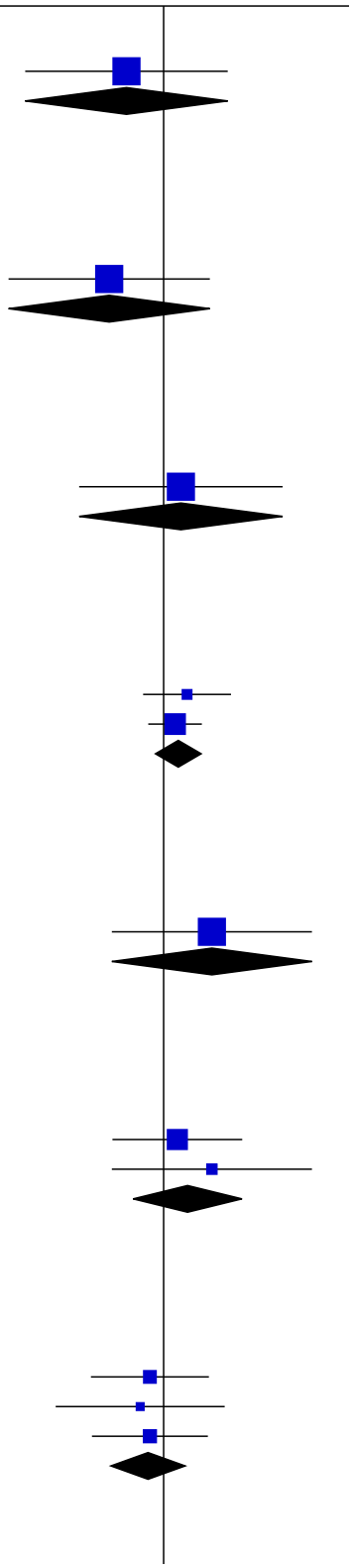
Analysis 14.6. Comparison 14: Experimental versus placebo, Outcome 6: Adverse effects: metabolic (continuous)

Study or Subgroup	Naltrexone Mean	Naltrexone SD	Naltrexone Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
14.6.1 Change in weight (kg)								
Campbell 1993	-0.62	0.29	14	-0.75	0.51	9	100.0%	0.13 [-0.24 , 0.50]
Subtotal (95% CI)			**14**			**9**	**100.0%**	**0.13 [-0.24 , 0.50]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.70 (P = 0.49)								
Total (95% CI)			**14**			**9**	**100.0%**	**0.13 [-0.24 , 0.50]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.70 (P = 0.49)								
Test for subgroup differences: Not applicable								



Analysis 14.7. Comparison 14: Experimental versus placebo, Outcome 7: Adverse effects: musculoskeletal

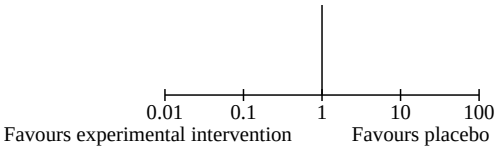
Study or Subgroup	Experimental Events	Experimental Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
14.7.1 Arthralgia						
Hollander 2020a	0	5	1	5	100.0%	0.33 [0.02 , 6.65]
Subtotal (95% CI)		**5**		**5**	**100.0%**	**0.33 [0.02 , 6.65]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
14.7.2 Difficulty walking						
Ghaleiha 2013b	0	20	2	20	100.0%	0.20 [0.01 , 3.92]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.20 [0.01 , 3.92]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
14.7.3 Impaired balance						
Danforth 2018	1	8	0	4	100.0%	1.67 [0.08 , 33.75]
Subtotal (95% CI)		**8**		**4**	**100.0%**	**1.67 [0.08 , 33.75]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
14.7.4 Myalgia						
Moazen-Zadeh 2018	6	33	3	33	27.1%	2.00 [0.55 , 7.33]
Sprengers 2021	12	46	8	43	72.9%	1.40 [0.64 , 3.10]
Subtotal (95% CI)		**79**		**76**	**100.0%**	**1.54 [0.79 , 3.04]**
Total events:	18		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						
14.7.5 Slow movement						
Ghanizadeh 2013	2	17	0	14	100.0%	4.17 [0.22 , 80.25]
Subtotal (95% CI)		**17**		**14**	**100.0%**	**4.17 [0.22 , 80.25]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.95 (P = 0.34)						
14.7.6 Stiffness						
Danforth 2018	3	8	1	4	70.4%	1.50 [0.22 , 10.22]
Ghanizadeh 2013	2	17	0	14	29.6%	4.17 [0.22 , 80.25]
Subtotal (95% CI)		**25**		**18**	**100.0%**	**2.03 [0.41 , 10.15]**
Total events:	5		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.86 (P = 0.39)						
14.7.7 Weakness						
Arnold 2012a	2	12	2	8	39.6%	0.67 [0.12 , 3.81]
Danforth 2018	1	8	1	4	19.3%	0.50 [0.04 , 6.08]
Mahdavinasab 2019	2	29	3	29	41.1%	0.67 [0.12 , 3.70]
Subtotal (95% CI)		**49**		**41**	**100.0%**	**0.63 [0.21 , 1.89]**
Total events:	5		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 2 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.82 (P = 0.41)						



Analysis 14.7. (Continued)

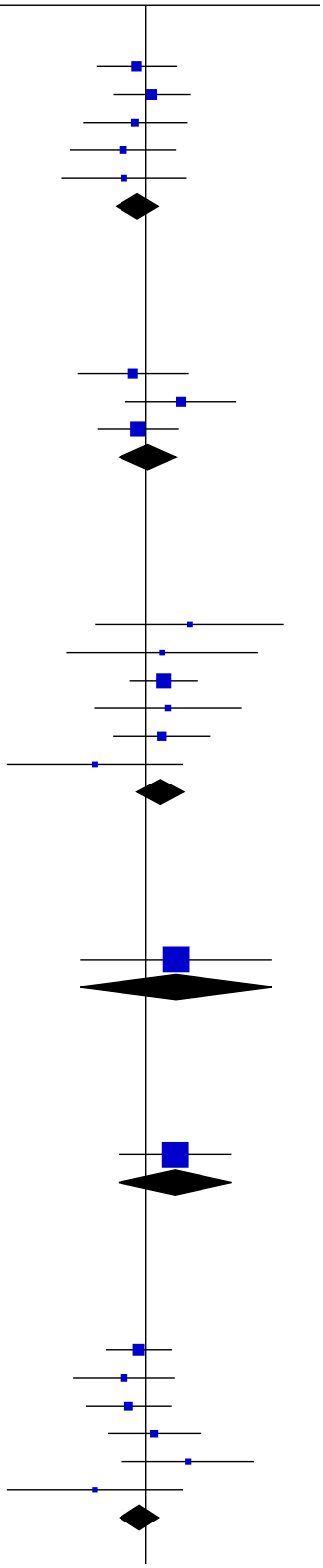
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 2 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)

Test for subgroup differences: Chi² = 0.00, df = 6 (P < 0.00001), I² = 0%



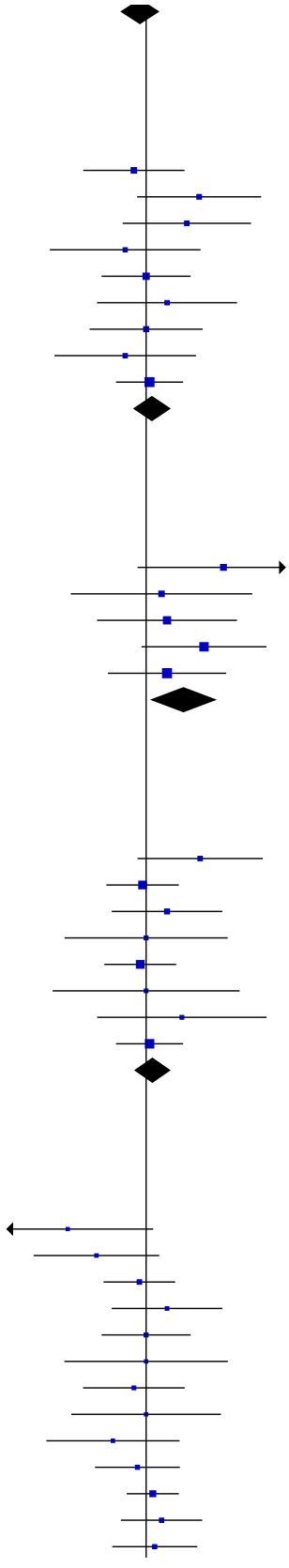
Analysis 14.8. Comparison 14: Experimental versus placebo, Outcome 8: Adverse effects: neurological

Study or Subgroup	Experimental Events	Experimental Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
14.8.1 Agitation/excitement						
Danfors 2005	3	12	4	12	27.2%	0.75 [0.21 , 2.66]
Dollfus 1992	3	5	2	4	29.5%	1.20 [0.36 , 4.04]
Hardan 2012	2	14	3	15	16.3%	0.71 [0.14 , 3.66]
Veenstra-VanderWeele 2017	2	76	4	74	15.7%	0.49 [0.09 , 2.58]
Woodard 2007	1	4	2	4	11.3%	0.50 [0.07 , 3.55]
Subtotal (95% CI)		**111**		**109**	**100.0%**	**0.76 [0.39 , 1.48]**
Total events:	11		15			
Heterogeneity: Tau² = 0.00; Chi² = 1.00, df = 4 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.80 (P = 0.42)						
14.8.2 Anxiety						
Aran 2021	2	44	3	44	25.9%	0.67 [0.12 , 3.80]
Danforth 2018	6	8	1	4	25.8%	3.00 [0.52 , 17.16]
Veenstra-VanderWeele 2017	4	76	5	74	48.3%	0.78 [0.22 , 2.79]
Subtotal (95% CI)		**128**		**122**	**100.0%**	**1.06 [0.44 , 2.57]**
Total events:	12		9			
Heterogeneity: Tau² = 0.00; Chi² = 1.86, df = 2 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.13 (P = 0.90)						
14.8.3 Daytime drowsiness						
Campbell 1993	2	23	0	18	6.1%	3.96 [0.20 , 77.63]
Danforth 2018	1	8	0	4	6.0%	1.67 [0.08 , 33.75]
Ghaleiha 2013b	7	20	4	20	48.1%	1.75 [0.61 , 5.05]
Ghaleiha 2014	2	20	1	20	10.1%	2.00 [0.20 , 20.33]
Ghanizadeh 2013	4	17	2	14	22.7%	1.65 [0.35 , 7.71]
Woodard 2007	0	4	2	4	7.0%	0.20 [0.01 , 3.20]
Subtotal (95% CI)		**92**		**80**	**100.0%**	**1.57 [0.75 , 3.28]**
Total events:	16		9			
Heterogeneity: Tau² = 0.00; Chi² = 2.58, df = 5 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.21 (P = 0.23)						
14.8.4 Dazed						
Campbell 1987	1	6	0	5	100.0%	2.57 [0.13 , 52.12]
Subtotal (95% CI)		**6**		**5**	**100.0%**	**2.57 [0.13 , 52.12]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.54)						
14.8.5 Difficulty concentrating						
Danforth 2018	5	8	1	4	100.0%	2.50 [0.42 , 14.83]
Subtotal (95% CI)		**8**		**4**	**100.0%**	**2.50 [0.42 , 14.83]**
Total events:	5		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
14.8.6 Difficulty sleeping						
Danfors 2005	4	12	5	12	34.1%	0.80 [0.28 , 2.27]
Klaiman 2013	2	23	4	23	14.6%	0.50 [0.10 , 2.47]
Minshawi 2016	3	34	5	33	20.4%	0.58 [0.15 , 2.24]
Veenstra-VanderWeele 2017	4	76	3	74	17.4%	1.30 [0.30 , 5.60]
Wink 2016	4	16	1	15	8.6%	3.75 [0.47 , 29.87]
Woodard 2007	0	4	2	4	4.8%	0.20 [0.01 , 3.20]
Subtotal (95% CI)		**165**		**161**	**100.0%**	**0.81 [0.44 , 1.50]**
Total events:	17		20			



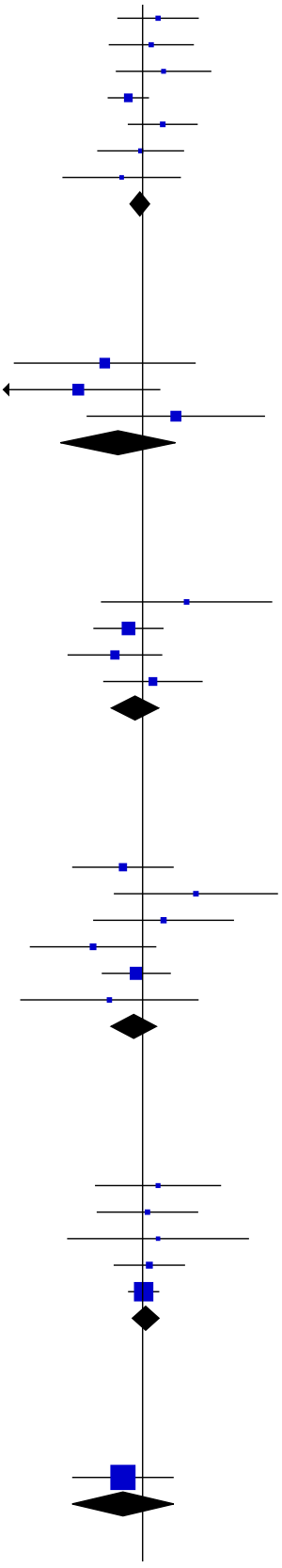
Analysis 14.8. (Continued)

Subtotal (95% CI)		**165**		**161**	**100.0%**	**0.81 [0.44 , 1.50]**
Total events:	17		20			
Heterogeneity: Tau² = 0.00; Chi² = 4.05, df = 5 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.66 (P = 0.51)						
14.8.7 Dizziness						
Asadabadi 2013	2	20	3	20	12.3%	0.67 [0.12 , 3.57]
Ayatollahi 2020	6	30	1	29	8.2%	5.80 [0.74 , 45.26]
Batebi 2021	4	28	1	27	7.6%	3.86 [0.46 , 32.35]
Danforth 2018	1	8	1	4	5.5%	0.50 [0.04 , 6.08]
Ghaleiha 2013b	3	20	3	20	15.9%	1.00 [0.23 , 4.37]
Ghaleiha 2015	2	20	1	20	6.4%	2.00 [0.20 , 20.33]
Ghaleiha 2016	2	23	2	23	9.9%	1.00 [0.15 , 6.51]
Montazmenesh 2020	1	30	2	30	6.3%	0.50 [0.05 , 5.22]
Sprengers 2021	6	46	5	43	28.0%	1.12 [0.37 , 3.41]
Subtotal (95% CI)		**225**		**216**	**100.0%**	**1.21 [0.67 , 2.18]**
Total events:	27		19			
Heterogeneity: Tau² = 0.00; Chi² = 5.19, df = 8 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.64 (P = 0.52)						
14.8.8 Drowsiness						
Aran 2021	6	44	0	44	13.5%	13.00 [0.75 , 223.98]
Danforth 2018	1	8	0	4	12.1%	1.67 [0.08 , 33.75]
Ghaleiha 2014	2	20	1	20	20.4%	2.00 [0.20 , 20.33]
Veenstra-VanderWeele 2017	7	76	1	74	25.5%	6.82 [0.86 , 54.05]
Woodard 2007	2	4	1	4	28.5%	2.00 [0.28 , 14.20]
Subtotal (95% CI)		**152**		**146**	**100.0%**	**3.45 [1.21 , 9.81]**
Total events:	18		3			
Heterogeneity: Tau² = 0.00; Chi² = 1.98, df = 4 (P = 0.74); I² = 0%						
Test for overall effect: Z = 2.32 (P = 0.02)						
14.8.9 Fatigue						
Aran 2021	6	44	1	44	7.5%	6.00 [0.75 , 47.80]
Arnold 2012a	4	12	3	8	22.4%	0.89 [0.27 , 2.95]
Danforth 2018	4	8	1	4	9.6%	2.00 [0.32 , 12.51]
Ghaleiha 2013b	1	20	1	20	4.4%	1.00 [0.07 , 14.90]
Ghanizadeh 2013	4	17	4	14	22.7%	0.82 [0.25 , 2.71]
Lemonnier 2017	1	23	0	7	3.4%	1.00 [0.05 , 22.18]
Lemonnier 2017	4	21	0	7	4.1%	3.27 [0.20 , 54.22]
Sprengers 2021	6	46	5	43	26.1%	1.12 [0.37 , 3.41]
Subtotal (95% CI)		**191**		**147**	**100.0%**	**1.23 [0.70 , 2.17]**
Total events:	30		15			
Heterogeneity: Tau² = 0.00; Chi² = 3.76, df = 7 (P = 0.81); I² = 0%						
Test for overall effect: Z = 0.72 (P = 0.47)						
14.8.10 Headache						
Ayatollahi 2020	0	30	6	29	1.3%	0.07 [0.00 , 1.26]
Batebi 2021	1	28	5	27	2.4%	0.19 [0.02 , 1.55]
Behmanesh 2019	4	24	5	24	7.4%	0.80 [0.24 , 2.62]
Danforth 2018	4	8	1	4	3.1%	2.00 [0.32 , 12.51]
Ghaleiha 2015	3	20	3	20	4.8%	1.00 [0.23 , 4.37]
Ghaleiha 2016	1	23	1	23	1.4%	1.00 [0.07 , 15.04]
Hajizadeh-Zaker 2018	2	21	3	21	3.7%	0.67 [0.12 , 3.59]
Hollander 2020a	1	5	1	5	1.7%	1.00 [0.08 , 11.93]
Khalaj 2018	1	31	3	31	2.1%	0.33 [0.04 , 3.03]
Mahdavinasab 2019	3	29	4	29	5.3%	0.75 [0.18 , 3.06]
Minshawi 2016	9	34	7	33	13.9%	1.25 [0.53 , 2.96]
Moazen-Zadeh 2018	5	33	3	33	5.7%	1.67 [0.43 , 6.41]
Montazmenesh 2020	4	30	3	30	5.2%	1.33 [0.33 , 5.45]



Analysis 14.8. (Continued)

Moazen-Zadeh 2018	5	33	3	33	5.7%	1.67 [0.43 , 6.41]
Montazmenesh 2020	4	30	3	30	5.2%	1.33 [0.33 , 5.45]
Nikoo 2015	4	20	2	20	4.2%	2.00 [0.41 , 9.71]
Sprengers 2021	10	46	15	43	22.3%	0.62 [0.31 , 1.23]
Veenstra-VanderWeele 2017	8	76	4	74	7.8%	1.95 [0.61 , 6.19]
Wink 2016	3	16	3	15	5.0%	0.94 [0.22 , 3.94]
Woodard 2007	1	4	2	4	2.7%	0.50 [0.07 , 3.55]
Subtotal (95% CI)		**478**		**465**	**100.0%**	**0.91 [0.66 , 1.26]**
Total events:	64		71			
Heterogeneity: Tau² = 0.00; Chi² = 12.64, df = 17 (P = 0.76); I² = 0%						
Test for overall effect: Z = 0.57 (P = 0.57)						
14.8.11 Hypoactivity						
Campbell 1987	0	6	1	5	31.2%	0.29 [0.01 , 5.79]
Dollfus 1992	0	5	3	4	36.6%	0.12 [0.01 , 1.80]
Woodard 2007	1	4	0	4	32.2%	3.00 [0.16 , 57.36]
Subtotal (95% CI)		**15**		**13**	**100.0%**	**0.44 [0.07 , 2.95]**
Total events:	1		4			
Heterogeneity: Tau² = 0.65; Chi² = 2.60, df = 2 (P = 0.27); I² = 23%						
Test for overall effect: Z = 0.84 (P = 0.40)						
14.8.12 Increased aggression						
Campbell 1987	2	6	0	5	7.6%	4.29 [0.25 , 72.90]
Campbell 1993	4	23	5	18	45.1%	0.63 [0.20 , 2.00]
Minshawi 2016	2	33	5	33	24.8%	0.40 [0.08 , 1.92]
Wink 2016	3	16	2	15	22.5%	1.41 [0.27 , 7.28]
Subtotal (95% CI)		**78**		**71**	**100.0%**	**0.78 [0.36 , 1.70]**
Total events:	11		12			
Heterogeneity: Tau² = 0.00; Chi² = 2.72, df = 3 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.63 (P = 0.53)						
14.8.13 Increased hyperactivity						
Campbell 1993	2	23	3	18	19.9%	0.52 [0.10 , 2.80]
Dollfus 1992	3	5	0	4	7.6%	5.83 [0.39 , 88.12]
Klaiman 2013	2	23	1	23	10.3%	2.00 [0.19 , 20.55]
Minshawi 2016	1	34	5	33	12.8%	0.19 [0.02 , 1.57]
Veenstra-VanderWeele 2017	5	76	6	74	42.9%	0.81 [0.26 , 2.54]
Woodard 2007	0	4	1	4	6.4%	0.33 [0.02 , 6.37]
Subtotal (95% CI)		**165**		**156**	**100.0%**	**0.75 [0.35 , 1.58]**
Total events:	13		16			
Heterogeneity: Tau² = 0.00; Chi² = 4.96, df = 5 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.77 (P = 0.44)						
14.8.14 Increased irritability						
Campbell 1987	2	6	1	5	4.5%	1.67 [0.21 , 13.43]
Campbell 1993	3	23	2	18	6.9%	1.17 [0.22 , 6.30]
Danforth 2018	1	8	0	4	2.1%	1.67 [0.08 , 33.75]
Klaiman 2013	5	23	4	23	13.9%	1.25 [0.38 , 4.07]
Minshawi 2016	16	34	15	33	72.6%	1.04 [0.62 , 1.74]
Subtotal (95% CI)		**94**		**83**	**100.0%**	**1.11 [0.71 , 1.72]**
Total events:	27		22			
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 4 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.45 (P = 0.65)						
14.8.15 Increased stereotypies						
Campbell 1993	2	23	3	18	100.0%	0.52 [0.10 , 2.80]
Subtotal (95% CI)		**23**		**18**	**100.0%**	**0.52 [0.10 , 2.80]**
Total events:	2		3			
Heterogeneity: Not applicable						

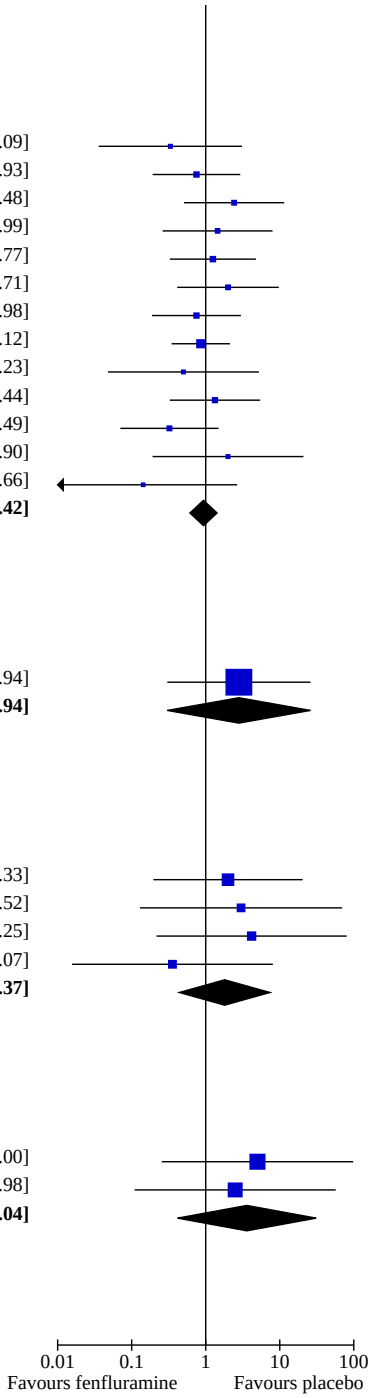


Analysis 14.8. (Continued)

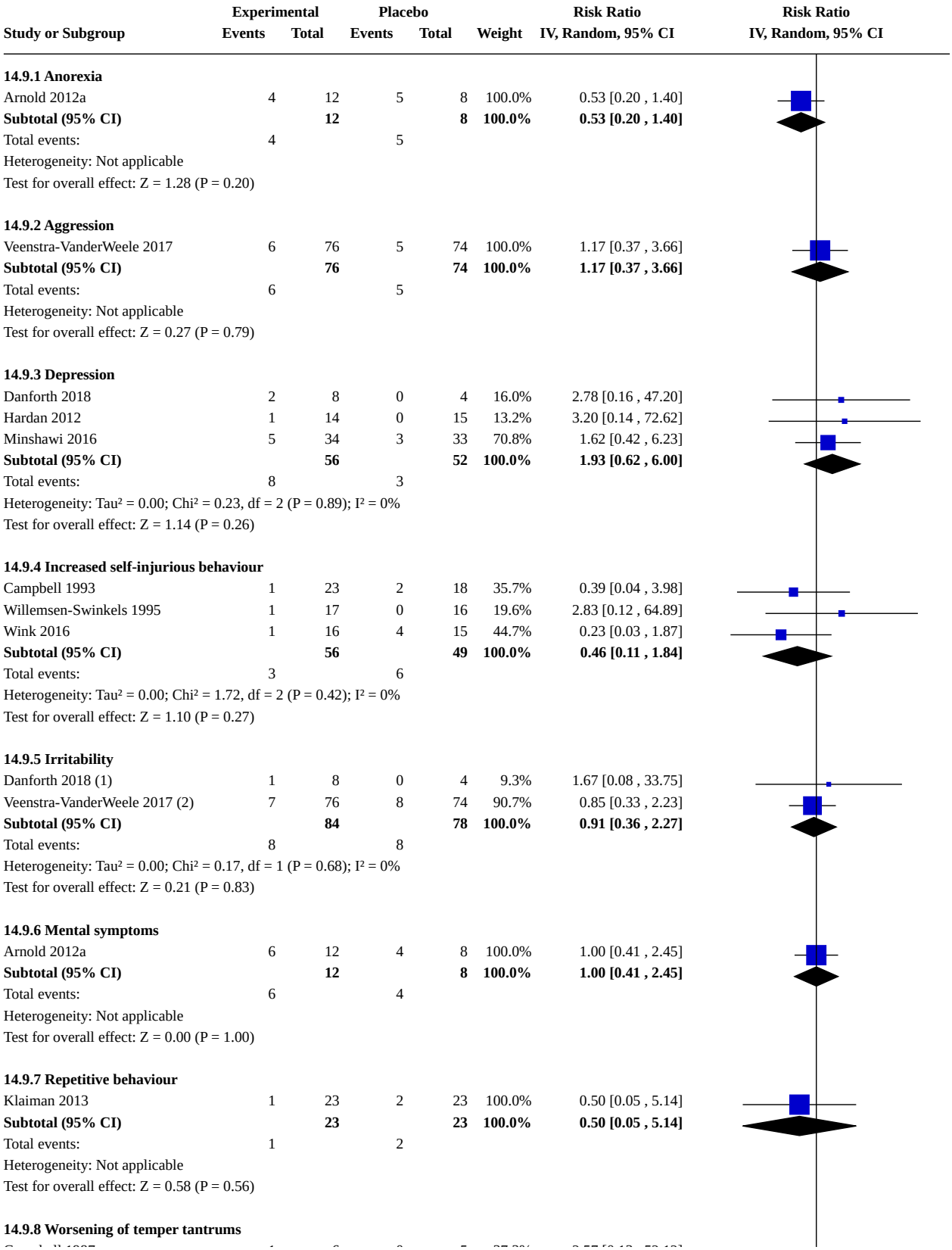
Total events:	2		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.76 (P = 0.45)							
14.8.16 Insomnia							
Asadabadi 2013	2	20	2	20	6.2%	1.00 [0.16 , 6.42]	
Behmanesh 2019	3	24	3	24	9.5%	1.00 [0.22 , 4.47]	
Dollfus 1992	4	5	2	4	18.5%	1.60 [0.55 , 4.68]	
Ghaleiha 2013a	1	20	1	20	2.9%	1.00 [0.07 , 14.90]	
Ghaleiha 2016	2	23	2	23	6.1%	1.00 [0.15 , 6.51]	
Moazen-Zadeh 2018	2	33	3	33	7.2%	0.67 [0.12 , 3.73]	
Sprengers 2021	9	46	6	43	23.9%	1.40 [0.54 , 3.61]	
Veenstra-VanderWeele 2017	7	76	10	74	25.7%	0.68 [0.27 , 1.70]	
Subtotal (95% CI)		**247**		**241**	**100.0%**	**1.04 [0.66 , 1.65]**	
Total events:	30		29				
Heterogeneity: Tau² = 0.00; Chi² = 2.09, df = 7 (P = 0.95); I² = 0%							
Test for overall effect: Z = 0.17 (P = 0.87)							
14.8.17 Migraine							
Hollander 2020a	1	5	0	5	100.0%	3.00 [0.15 , 59.89]	
Subtotal (95% CI)		**5**		**5**	**100.0%**	**3.00 [0.15 , 59.89]**	
Total events:	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.72 (P = 0.47)							
14.8.18 Nervousness							
Behmanesh 2019	4	24	8	24	38.6%	0.50 [0.17 , 1.44]	
Ghaleiha 2013b	3	20	1	20	22.3%	3.00 [0.34 , 26.45]	
Ghaleiha 2014	4	20	1	20	23.1%	4.00 [0.49 , 32.72]	
Ghanizadeh 2013	4	17	0	14	16.0%	7.50 [0.44 , 128.40]	
Subtotal (95% CI)		**81**		**78**	**100.0%**	**1.86 [0.47 , 7.37]**	
Total events:	15		10				
Heterogeneity: Tau² = 0.99; Chi² = 6.15, df = 3 (P = 0.10); I² = 51%							
Test for overall effect: Z = 0.88 (P = 0.38)							
14.8.19 New onset seizures							
Klaiman 2013	0	23	1	23	100.0%	0.33 [0.01 , 7.78]	
Subtotal (95% CI)		**23**		**23**	**100.0%**	**0.33 [0.01 , 7.78]**	
Total events:	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.68 (P = 0.49)							
14.8.20 Restlessness							
Danforth 2018	3	8	1	4	19.1%	1.50 [0.22 , 10.22]	
Ghaleiha 2013b	4	20	1	20	15.9%	4.00 [0.49 , 32.72]	
Ghanizadeh 2013	2	17	2	14	21.0%	0.82 [0.13 , 5.12]	
Minshawi 2016	4	34	3	33	34.9%	1.29 [0.31 , 5.34]	
Woodard 2007	0	4	2	4	9.1%	0.20 [0.01 , 3.20]	
Subtotal (95% CI)		**83**		**75**	**100.0%**	**1.22 [0.53 , 2.82]**	
Total events:	13		9				
Heterogeneity: Tau² = 0.00; Chi² = 3.09, df = 4 (P = 0.54); I² = 0%							
Test for overall effect: Z = 0.47 (P = 0.64)							
14.8.21 Rocking							
Campbell 1987	0	6	1	5	100.0%	0.29 [0.01 , 5.79]	
Subtotal (95% CI)		**6**		**5**	**100.0%**	**0.29 [0.01 , 5.79]**	
Total events:	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.82 (P = 0.41)							

Analysis 14.8. (Continued)

Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
14.8.22 Sedation						
Arnold 2012a	1	12	2	8	3.6%	0.33 [0.04 , 3.09]
Asadabadi 2013	3	20	4	20	9.6%	0.75 [0.19 , 2.93]
Ayatollahi 2020	5	30	2	29	7.3%	2.42 [0.51 , 11.48]
Batebi 2021	3	28	2	27	6.1%	1.45 [0.26 , 7.99]
Campbell 1987	3	6	2	5	9.9%	1.25 [0.33 , 4.77]
Ghaleiha 2013a	4	20	2	20	7.1%	2.00 [0.41 , 9.71]
Ghaleiha 2016	3	23	4	23	9.4%	0.75 [0.19 , 2.98]
Hajizadeh-Zaker 2018	6	21	7	21	21.7%	0.86 [0.35 , 2.12]
Khalaj 2018	1	31	2	31	3.2%	0.50 [0.05 , 5.23]
Mahdavinasab 2019	4	29	3	29	9.0%	1.33 [0.33 , 5.44]
Minshawi 2016	2	34	6	33	7.6%	0.32 [0.07 , 1.49]
Montazmenesh 2020	2	30	1	30	3.2%	2.00 [0.19 , 20.90]
Willemsen-Swinkels 1995	0	32	3	32	2.1%	0.14 [0.01 , 2.66]
Subtotal (95% CI)		**316**		**308**	**100.0%**	**0.93 [0.61 , 1.42]**
Total events:	37		40			
Heterogeneity: Tau² = 0.00; Chi² = 8.17, df = 12 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.32 (P = 0.75)						
14.8.23 Syncope						
Sprengers 2021	3	46	1	43	100.0%	2.80 [0.30 , 25.94]
Subtotal (95% CI)		**46**		**43**	**100.0%**	**2.80 [0.30 , 25.94]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.91 (P = 0.36)						
14.8.24 Tremor						
Ghaleiha 2013b	2	20	1	20	36.9%	2.00 [0.20 , 20.33]
Ghaleiha 2014	1	20	0	20	20.1%	3.00 [0.13 , 69.52]
Ghanizadeh 2013	2	17	0	14	22.7%	4.17 [0.22 , 80.25]
Hardan 2012	0	14	1	15	20.4%	0.36 [0.02 , 8.07]
Subtotal (95% CI)		**71**		**69**	**100.0%**	**1.80 [0.44 , 7.37]**
Total events:	5		2			
Heterogeneity: Tau² = 0.00; Chi² = 1.46, df = 3 (P = 0.69); I² = 0%						
Test for overall effect: Z = 0.82 (P = 0.41)						
14.8.25 Twitching						
Ghaleiha 2013b	2	20	0	20	52.5%	5.00 [0.26 , 98.00]
Ghanizadeh 2013	1	17	0	14	47.5%	2.50 [0.11 , 56.98]
Subtotal (95% CI)		**37**		**34**	**100.0%**	**3.60 [0.42 , 31.04]**
Total events:	3		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 1.16 (P = 0.24)						
Test for subgroup differences: Chi² = 0.00, df = 24 (P < 0.00001), I² = 0%						



Analysis 14.9. Comparison 14: Experimental versus placebo, Outcome 9: Adverse effects: psychological



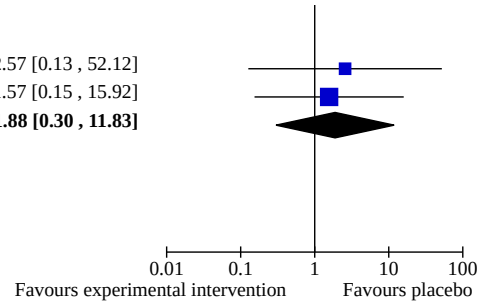
Analysis 14.9. (Continued)

14.9.8 Worsening of temper tantrums						
Campbell 1987	1	6	0	5	37.3%	2.57 [0.13 , 52.12]
Campbell 1993	2	23	1	18	62.7%	1.57 [0.15 , 15.92]
Subtotal (95% CI)		**29**		**23**	**100.0%**	**1.88 [0.30 , 11.83]**
Total events:	3		1			

Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%

Test for overall effect: Z = 0.68 (P = 0.50)

Test for subgroup differences: Chi² = 0.00, df = 7 (P < 0.00001), I² = 0%

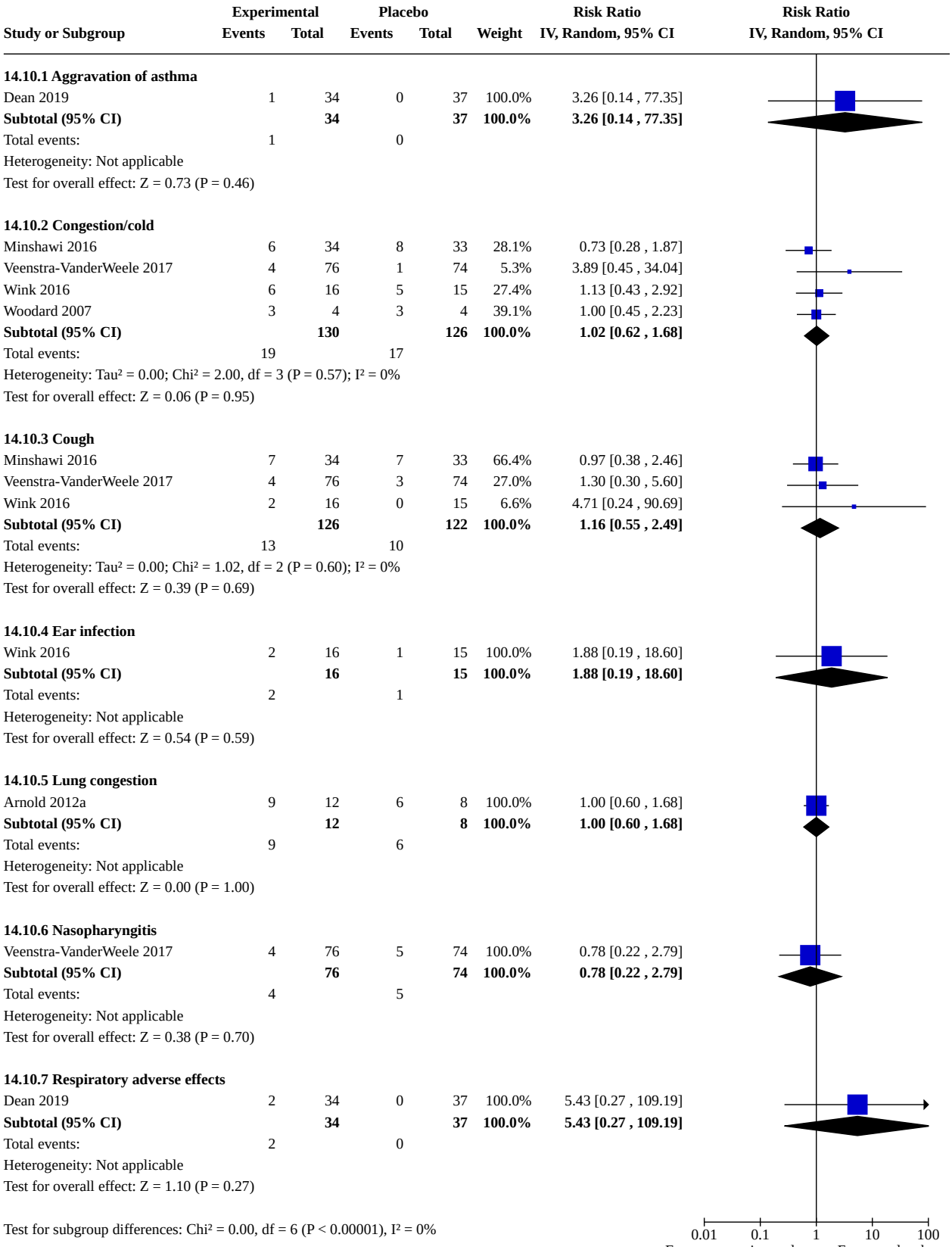


Footnotes

(1) MDMA

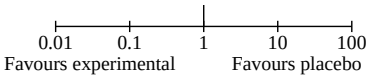
(2) Arbaclofen

Analysis 14.10. Comparison 14: Experimental versus placebo, Outcome 10: Adverse effects: respiratory



Analysis 14.10. (Continued)

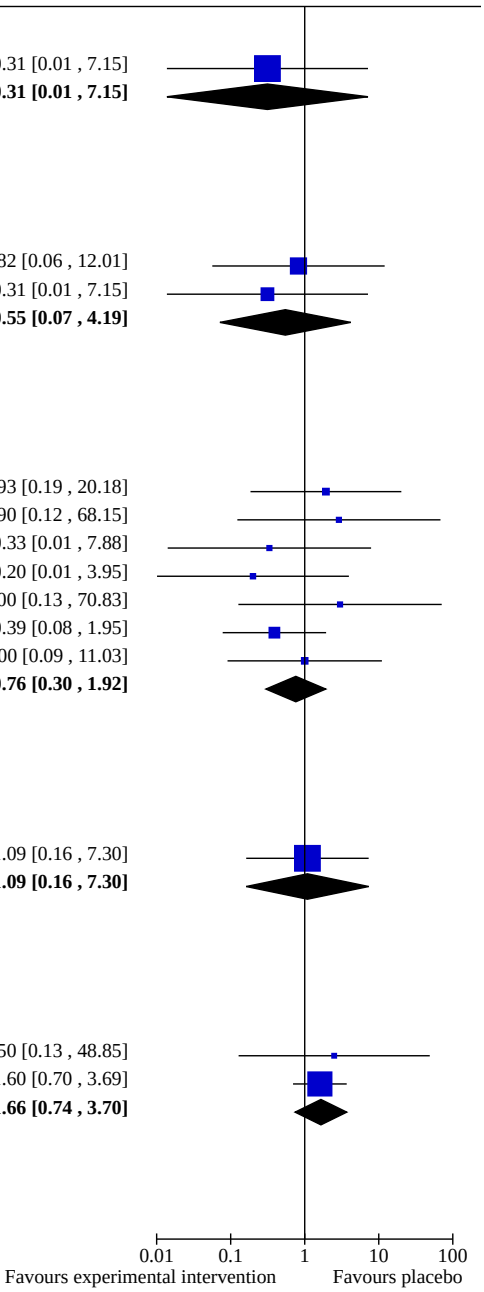
Test for subgroup differences: Chi² = 0.00, df = 6 (P < 0.00001), I² = 0%



Analysis 14.11. Comparison 14: Experimental versus placebo, Outcome 11: Adverse effects: skin

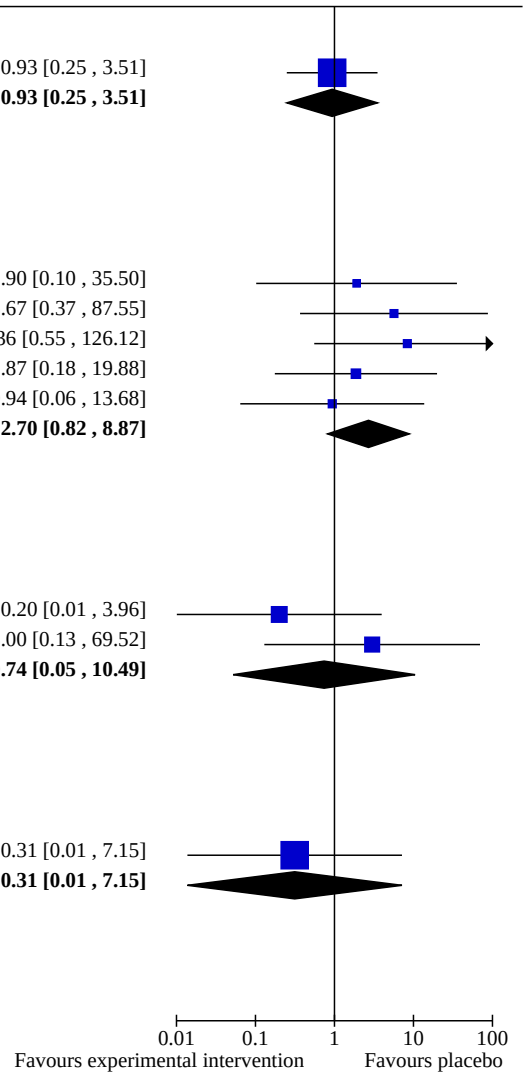
Study or Subgroup	Experimental Events	Experimental Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
14.11.1 Hives						
Wink 2016	0	16	1	15	100.0%	0.31 [0.01 , 7.15]
Subtotal (95% CI)		**16**		**15**	**100.0%**	**0.31 [0.01 , 7.15]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
14.11.2 Itches						
Ghanizadeh 2013	1	17	1	14	57.7%	0.82 [0.06 , 12.01]
Wink 2016	0	16	1	15	42.3%	0.31 [0.01 , 7.15]
Subtotal (95% CI)		**33**		**29**	**100.0%**	**0.55 [0.07 , 4.19]**
Total events:	1		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						
14.11.3 Rash						
Ayatollahi 2020	2	30	1	29	15.7%	1.93 [0.19 , 20.18]
Batebi 2021	1	28	0	27	8.7%	2.90 [0.12 , 68.15]
Khalaj 2018	0	31	1	31	8.7%	0.33 [0.01 , 7.88]
Klaiman 2013	0	23	2	23	9.7%	0.20 [0.01 , 3.95]
Montazmenesh 2020	1	30	0	30	8.7%	3.00 [0.13 , 70.83]
Veenstra-VanderWeele 2017	2	76	5	74	33.5%	0.39 [0.08 , 1.95]
Woodard 2007	1	4	1	4	15.0%	1.00 [0.09 , 11.03]
Subtotal (95% CI)		**222**		**218**	**100.0%**	**0.76 [0.30 , 1.92]**
Total events:	7		10			
Heterogeneity: Tau² = 0.00; Chi² = 3.77, df = 6 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						
14.11.4 Skin adverse effects						
Dean 2019	2	34	2	37	100.0%	1.09 [0.16 , 7.30]
Subtotal (95% CI)		**34**		**37**	**100.0%**	**1.09 [0.16 , 7.30]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.09 (P = 0.93)						
14.11.5 Skin lesion						
Hollander 2020a	1	5	0	4	7.3%	2.50 [0.13 , 48.85]
Sprengers 2021	12	46	7	43	92.7%	1.60 [0.70 , 3.69]
Subtotal (95% CI)		**51**		**47**	**100.0%**	**1.66 [0.74 , 3.70]**
Total events:	13		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 1.23 (P = 0.22)						

Test for subgroup differences: Chi² = 0.00, df = 4 (P < 0.00001), I² = 0%



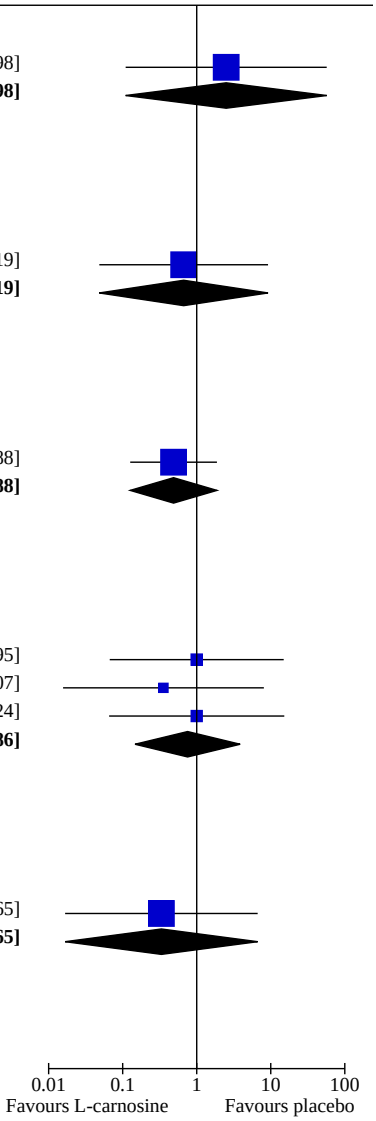
Analysis 14.12. Comparison 14: Experimental versus placebo, Outcome 12: Adverse effects: urinary

Study or Subgroup	Experimental Events	Experimental Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
14.12.1 Diuresis						
Sprengers 2021	4	46	4	43	100.0%	0.93 [0.25 , 3.51]
Subtotal (95% CI)		**46**		**43**	**100.0%**	**0.93 [0.25 , 3.51]**
Total events:	4		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
14.12.2 Enuresis						
Lemonnier 2017	2	20	0	7	16.6%	1.90 [0.10 , 35.50]
Lemonnier 2017	8	23	0	7	18.9%	5.67 [0.37 , 87.55]
Lemonnier 2017	11	21	0	7	19.3%	8.36 [0.55 , 126.12]
Sprengers 2021	2	46	1	43	25.4%	1.87 [0.18 , 19.88]
Wink 2016	1	16	1	15	19.8%	0.94 [0.06 , 13.68]
Subtotal (95% CI)		**126**		**79**	**100.0%**	**2.70 [0.82 , 8.87]**
Total events:	24		2			
Heterogeneity: Tau² = 0.00; Chi² = 1.69, df = 4 (P = 0.79); I² = 0%						
Test for overall effect: Z = 1.63 (P = 0.10)						
14.12.3 Urinary retention						
Behmanesh 2019	0	24	2	24	51.7%	0.20 [0.01 , 3.96]
Ghaleiha 2013b	1	20	0	20	48.3%	3.00 [0.13 , 69.52]
Subtotal (95% CI)		**44**		**44**	**100.0%**	**0.74 [0.05 , 10.49]**
Total events:	1		2			
Heterogeneity: Tau² = 1.22; Chi² = 1.50, df = 1 (P = 0.22); I² = 33%						
Test for overall effect: Z = 0.22 (P = 0.82)						
14.12.4 Urinary tract infection						
Wink 2016	0	16	1	15	100.0%	0.31 [0.01 , 7.15]
Subtotal (95% CI)		**16**		**15**	**100.0%**	**0.31 [0.01 , 7.15]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
Test for subgroup differences: Chi² = 0.00, df = 3 (P < 0.00001), I² = 0%						



Analysis 14.13. Comparison 14: Experimental versus placebo, Outcome 13: Adverse effects: other

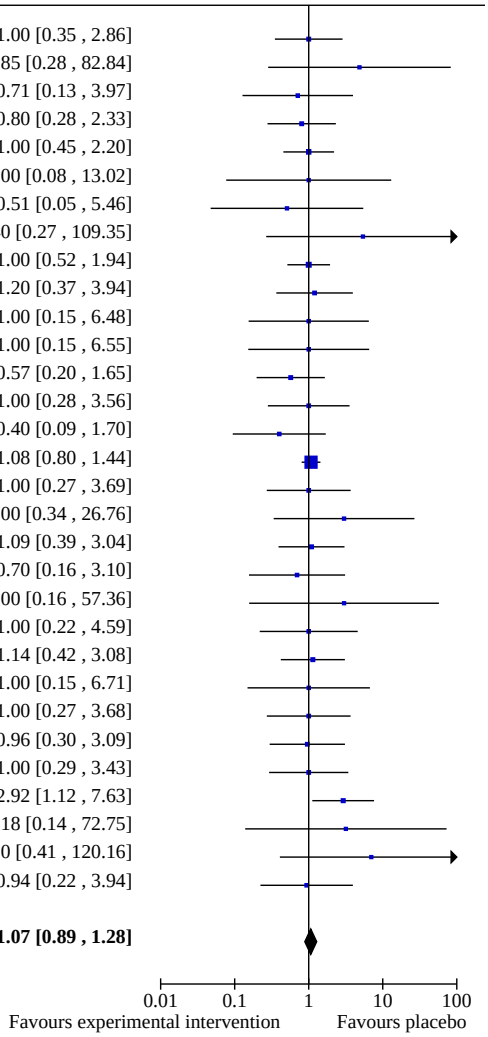
Study or Subgroup	Experimental Events	Experimental Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
14.13.1 Blurred vision						
Ghanizadeh 2013	1	17	0	14	100.0%	2.50 [0.11 , 56.98]
Subtotal (95% CI)		**17**		**14**	**100.0%**	**2.50 [0.11 , 56.98]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
14.13.2 Dilated pupils						
Arnold 2012a	1	12	1	8	100.0%	0.67 [0.05 , 9.19]
Subtotal (95% CI)		**12**		**8**	**100.0%**	**0.67 [0.05 , 9.19]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.30 (P = 0.76)						
14.13.3 Fever						
Veenstra-VanderWeele 2017	3	76	6	74	100.0%	0.49 [0.13 , 1.88]
Subtotal (95% CI)		**76**		**74**	**100.0%**	**0.49 [0.13 , 1.88]**
Total events:	3		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.30)						
14.13.4 Sweating						
Hajizadeh-Zaker 2018	1	21	1	21	36.5%	1.00 [0.07 , 14.95]
Hardan 2012	0	14	1	15	27.4%	0.36 [0.02 , 8.07]
Mahdavinasab 2019	1	29	1	29	36.0%	1.00 [0.07 , 15.24]
Subtotal (95% CI)		**64**		**65**	**100.0%**	**0.75 [0.15 , 3.86]**
Total events:	2		3			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.31$, df = 2 (P = 0.86); $I^2 = 0\%$						
Test for overall effect: Z = 0.34 (P = 0.73)						
14.13.5 Vision: conjunctivitis						
Hollander 2020a	0	5	1	5	100.0%	0.33 [0.02 , 6.65]
Subtotal (95% CI)		**5**		**5**	**100.0%**	**0.33 [0.02 , 6.65]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
Test for subgroup differences: $Chi^2 = 0.00$, df = 4 (P < 0.00001), $I^2 = 0\%$						



Analysis 14.14. Comparison 14: Experimental versus placebo, Outcome 14: Tolerability/acceptability: loss to follow-up

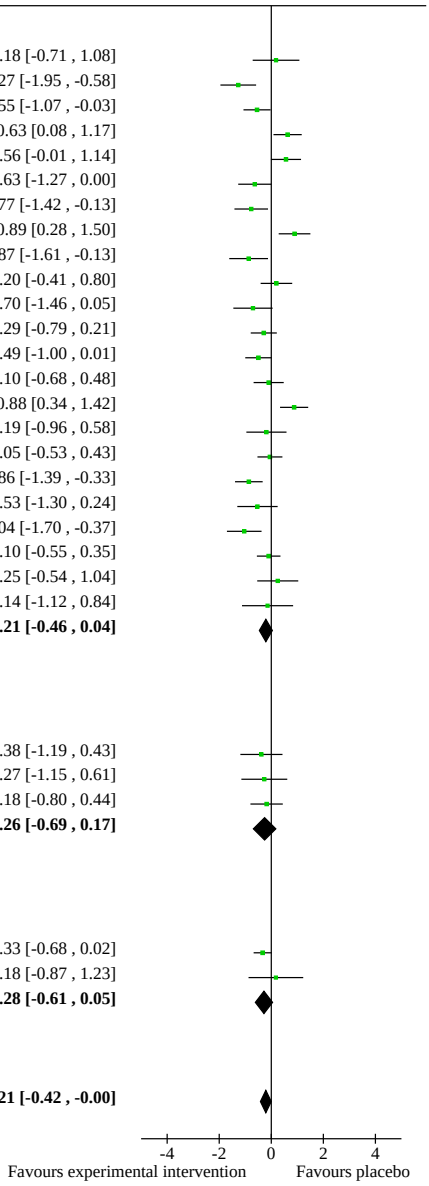
Study or Subgroup	Experimental Events	Experimental Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Aran 2021	6	44	6	44	3.1%	1.00 [0.35 , 2.86]
Arnold 2012a	3	12	0	8	0.4%	4.85 [0.28 , 82.84]
Ayatollahi 2020	2	30	3	32	1.2%	0.71 [0.13 , 3.97]
Batebi 2021	5	28	6	27	3.0%	0.80 [0.28 , 2.33]
Behmanesh 2019	9	33	9	33	5.5%	1.00 [0.45 , 2.20]
Chez 2020	1	7	1	7	0.5%	1.00 [0.08 , 13.02]
Dai 2021	1	59	2	60	0.6%	0.51 [0.05 , 5.46]
Danforth 2018	1	4	0	8	0.4%	5.40 [0.27 , 109.35]
Dean 2019	13	51	13	51	7.7%	1.00 [0.52 , 1.94]
Ghaleiha 2013b	5	25	4	24	2.4%	1.20 [0.37 , 3.94]
Ghaleiha 2015	2	22	2	22	1.0%	1.00 [0.15 , 6.48]
Ghaleiha 2016	2	25	2	25	1.0%	1.00 [0.15 , 6.55]
Ghanizadeh 2013	4	20	7	20	3.0%	0.57 [0.20 , 1.65]
Hajizadeh-Zaker 2018	4	25	4	25	2.1%	1.00 [0.28 , 3.56]
Hardan 2012	2	15	6	18	1.6%	0.40 [0.09 , 1.70]
Jacob 2022	61	163	55	158	40.0%	1.08 [0.80 , 1.44]
Khalaj 2018	4	35	4	35	2.0%	1.00 [0.27 , 3.69]
Klaiman 2013	3	23	1	23	0.7%	3.00 [0.34 , 26.76]
Lemonnier 2017	9	22	3	8	3.2%	1.09 [0.39 , 3.04]
Lemonnier 2017	4	23	2	8	1.5%	0.70 [0.16 , 3.10]
Lewis 2018	1	4	0	4	0.4%	3.00 [0.16 , 57.36]
Mahdavinasab 2019	3	32	3	32	1.5%	1.00 [0.22 , 4.59]
Malek 2020	6	19	5	18	3.4%	1.14 [0.42 , 3.08]
Moazen-Zadeh 2018	2	35	2	35	0.9%	1.00 [0.15 , 6.71]
Montazmenesh 2020	4	34	4	34	2.0%	1.00 [0.27 , 3.68]
Sprengers 2021	5	47	5	45	2.5%	0.96 [0.30 , 3.09]
VanAndel 2022	4	19	4	19	2.2%	1.00 [0.29 , 3.43]
Veenstra-VanderWeele 2017	15	76	5	74	3.7%	2.92 [1.12 , 7.63]
Willemsen-Swinkels 1995	1	16	0	17	0.3%	3.18 [0.14 , 72.75]
Willemsen-Swinkels 1996	3	10	0	10	0.4%	7.00 [0.41 , 120.16]
Wink 2016	3	16	3	15	1.6%	0.94 [0.22 , 3.94]
Total (95% CI)		**974**		**939**	**100.0%**	**1.07 [0.89 , 1.28]**
Total events:	188		161			

Heterogeneity: Tau² = 0.00; Chi² = 14.45, df = 30 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 14.15. Comparison 14: Experimental versus placebo, Outcome 15: Subgroup analyses: age - irritability (option 1)

Study or Subgroup	Experimental Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
14.15.1 Children only								
Arnold 2012a	-3.17	8.76	12	-5	10.78	8	2.7%	0.18 [-0.71 , 1.08]
Asadabadi 2013	-8.5	1.5	20	-5.1	3.4	20	3.4%	-1.27 [-1.95 , -0.58]
Ayatollahi 2020	11.97	3.52	30	14.62	5.8	29	4.1%	-0.55 [-1.07 , -0.03]
Batebi 2021	10.67	4.42	28	8.25	3.04	27	4.0%	0.63 [0.08 , 1.17]
Behmanesh 2019	9.2	3.51	24	6.54	5.53	24	3.9%	0.56 [-0.01 , 1.14]
Ghaleiha 2013b	11.85	5.57	20	16.25	7.86	20	3.6%	-0.63 [-1.27 , 0.00]
Ghaleiha 2015	-10.2	5.87	20	-5.9	5.04	20	3.6%	-0.77 [-1.42 , -0.13]
Ghaleiha 2016	9.17	3.82	23	5.87	3.43	23	3.7%	0.89 [0.28 , 1.50]
Ghanizadeh 2013	9.7	4.1	17	15.1	7.8	14	3.2%	-0.87 [-1.61 , -0.13]
Hajizadeh-Zaker 2018	6.09	8.02	21	4.62	6.5	21	3.8%	0.20 [-0.41 , 0.80]
Hardan 2012	7.2	5.7	14	13.1	9.9	15	3.2%	-0.70 [-1.46 , 0.05]
Hendouei 2019	-8.1	6.5	31	-6.2	6.5	31	4.2%	-0.29 [-0.79 , 0.21]
Khalaj 2018	11.9	3.9	31	14.4	5.9	31	4.2%	-0.49 [-1.00 , 0.01]
Klaiman 2013	10	7.8	23	10.8	7.8	23	3.9%	-0.10 [-0.68 , 0.48]
Mahdavinasab 2019	0	7.87	29	-6.31	6.22	29	4.0%	0.88 [0.34 , 1.42]
Malek 2020	18.61	11.4	13	20.69	10.22	13	3.1%	-0.19 [-0.96 , 0.58]
Minshawi 2016	-1.55	6.11	34	-1.23	6.09	33	4.3%	-0.05 [-0.53 , 0.43]
Montazmenesh 2020	-10.27	4.27	30	-7.1	2.85	30	4.1%	-0.86 [-1.39 , -0.33]
Niederhofer 2002	11.4	7.5	15	15.7	8.3	12	3.1%	-0.53 [-1.30 , 0.24]
Nikoo 2015	-9.25	4.08	20	-5.35	3.23	20	3.5%	-1.04 [-1.70 , -0.37]
Sprengers 2021	10.4	8.5	38	11.2	7.2	37	4.4%	-0.10 [-0.55 , 0.35]
Wink 2016	14.9	14	13	12	7.3	12	3.1%	0.25 [-0.54 , 1.04]
Woodard 2007	11.4	3.59	8	12.1	5.5	8	2.5%	-0.14 [-1.12 , 0.84]
Subtotal (95% CI)			**514**			**500**	**83.5%**	**-0.21 [-0.46 , 0.04]**
Heterogeneity: Tau² = 0.26; Chi² = 82.36, df = 22 (P < 0.00001); I² = 73%								
Test for overall effect: Z = 1.64 (P = 0.10)								
14.15.2 Adults only								
Chez 2020	10.5	10.71	12	14.5	9.67	12	3.0%	-0.38 [-1.19 , 0.43]
Hollander 2020a	-4	18.5	10	-0.14	6.32	10	2.8%	-0.27 [-1.15 , 0.61]
Willemsen-Swinkels 1996	9.82	6.43	20	11.2	8.5	20	3.7%	-0.18 [-0.80 , 0.44]
Subtotal (95% CI)			**42**			**42**	**9.4%**	**-0.26 [-0.69 , 0.17]**
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 2 (P = 0.93); I² = 0%								
Test for overall effect: Z = 1.17 (P = 0.24)								
14.15.3 Children and adults								
Veenstra-VanderWeele 2017	-3.6	0.9	61	-3.3	0.9	69	4.8%	-0.33 [-0.68 , 0.02]
Wink 2018	21.86	10.7	7	20	8.9	7	2.3%	0.18 [-0.87 , 1.23]
Subtotal (95% CI)			**68**			**76**	**7.1%**	**-0.28 [-0.61 , 0.05]**
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 1 (P = 0.37); I² = 0%								
Test for overall effect: Z = 1.67 (P = 0.09)								
Total (95% CI)			**624**			**618**	**100.0%**	**-0.21 [-0.42 , -0.00]**
Heterogeneity: Tau² = 0.20; Chi² = 83.70, df = 27 (P < 0.00001); I² = 68%								
Test for overall effect: Z = 1.99 (P = 0.05)								
Test for subgroup differences: Chi² = 0.13, df = 2 (P = 0.94), I² = 0%								

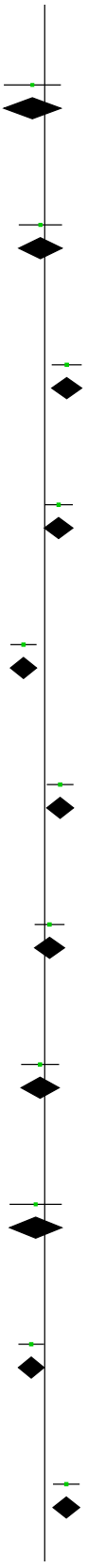


Analysis 14.16. Comparison 14: Experimental versus placebo, Outcome 16: Subgroup analyses: age - irritability (option 2)

Study or Subgroup	Experimental Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
14.16.1 Celecoxib: children only								
Asadabadi 2013	-8.5	1.5	20	-5.1	3.4	20	3.6%	-1.27 [-1.95 , -0.58]
Subtotal (95% CI)			**20**			**20**	**3.6%**	**-1.27 [-1.95 , -0.58]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.63 (P = 0.0003)								
14.16.2 D-cycloserine: children only								
Minshawi 2016	-1.55	6.11	34	-1.23	6.09	33	4.4%	-0.05 [-0.53 , 0.43]
Subtotal (95% CI)			**34**			**33**	**4.4%**	**-0.05 [-0.53 , 0.43]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.21 (P = 0.83)								
14.16.3 Dextromethorphan: children only								
Woodard 2007	11.4	3.59	4	12.1	5.5	4	1.7%	-0.13 [-1.52 , 1.26]
Subtotal (95% CI)			**4**			**4**	**1.7%**	**-0.13 [-1.52 , 1.26]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.18 (P = 0.85)								
14.16.4 Mecamylamine: children only								
Arnold 2012a	-3.17	8.76	12	-5	10.78	8	2.9%	0.18 [-0.71 , 1.08]
Subtotal (95% CI)			**12**			**8**	**2.9%**	**0.18 [-0.71 , 1.08]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.40 (P = 0.69)								
14.16.5 Riluzole: children only								
Ghaleiha 2013b	11.85	5.57	20	16.25	7.86	20	3.8%	-0.63 [-1.27 , 0.00]
Subtotal (95% CI)			**20**			**20**	**3.8%**	**-0.63 [-1.27 , 0.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.95 (P = 0.05)								
14.16.6 Riluzole: children and adults								
Wink 2018	21.86	10.7	7	20	8.9	7	2.4%	0.18 [-0.87 , 1.23]
Subtotal (95% CI)			**7**			**7**	**2.4%**	**0.18 [-0.87 , 1.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.33 (P = 0.74)								
14.16.7 Pioglitazone: children only								
Ghaleiha 2015	-10.2	5.87	20	-5.9	5.04	20	3.8%	-0.77 [-1.42 , -0.13]
Subtotal (95% CI)			**20**			**20**	**3.8%**	**-0.77 [-1.42 , -0.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.34 (P = 0.02)								
14.16.8 N-acetylcysteine: children only								
Ghanizadeh 2013	9.7	4.1	17	15.1	7.8	14	3.4%	-0.87 [-1.61 , -0.13]
Hardan 2012	7.2	5.7	14	13.1	9.9	15	3.4%	-0.70 [-1.46 , 0.05]
Nikoo 2015	-9.25	4.08	20	-5.35	3.23	20	3.7%	-1.04 [-1.70 , -0.37]
Wink 2016	14.9	14	13	12	7.3	12	3.2%	0.25 [-0.54 , 1.04]
Subtotal (95% CI)			**64**			**61**	**13.7%**	**-0.61 [-1.16 , -0.06]**
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 6.65$, df = 3 (P = 0.08); $I^2 = 55\%$								
Test for overall effect: Z = 2.19 (P = 0.03)								
14.16.9 *Trichuris suis* ova: adults only								
Hollander 2020a	-4	18.5	5	-0.14	6.32	5	1.9%	-0.25 [-1.50 , 1.00]
Subtotal (95% CI)			**5**			**5**	**1.9%**	**-0.25 [-1.50 , 1.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.40 (P = 0.69)								
14.16.10 Tetrahydrobiopterin: children only								
Klaiman 2013	10	7.8	23	10.8	7.8	23	4.0%	-0.10 [-0.68 , 0.48]
Subtotal (95% CI)			**23**			**23**	**4.0%**	**-0.10 [-0.68 , 0.48]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.34 (P = 0.73)								

Analysis 14.16. (Continued)

Test for overall effect: Z = 0.34 (P = 0.73)									
14.16.11 Lofexedine: children only									
Niederhofer 2002	11.4	7.5	6	15.7	8.3	6	2.1%	-0.50 [-1.66 , 0.66]	
Subtotal (95% CI)			**6**			**6**	**2.1%**	**-0.50 [-1.66 , 0.66]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.85 (P = 0.40)									
14.16.12 Naltrexone: adults only									
Willemsen-Swinkels 1996	9.82	6.43	10	11.2	8.5	10	2.9%	-0.18 [-1.05 , 0.70]	
Subtotal (95% CI)			**10**			**10**	**2.9%**	**-0.18 [-1.05 , 0.70]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.39 (P = 0.70)									
14.16.13 Minocycline: children only									
Ghaleiha 2016	9.17	3.82	23	5.87	3.43	23	3.9%	0.89 [0.28 , 1.50]	
Subtotal (95% CI)			**23**			**23**	**3.9%**	**0.89 [0.28 , 1.50]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.88 (P = 0.004)									
14.16.14 Propentofylline: children only									
Behmanesh 2019	9.2	3.51	24	6.54	5.53	24	4.0%	0.56 [-0.01 , 1.14]	
Subtotal (95% CI)			**24**			**24**	**4.0%**	**0.56 [-0.01 , 1.14]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.92 (P = 0.06)									
14.16.15 Sulforaphane: children only									
Montazmenesh 2020	-10.27	4.27	30	-7.1	2.85	30	4.2%	-0.86 [-1.39 , -0.33]	
Subtotal (95% CI)			**30**			**30**	**4.2%**	**-0.86 [-1.39 , -0.33]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 3.18 (P = 0.001)									
14.16.16 Folinic acid: children only									
Batebi 2021	10.67	4.42	28	8.25	3.04	27	4.2%	0.63 [0.08 , 1.17]	
Subtotal (95% CI)			**28**			**27**	**4.2%**	**0.63 [0.08 , 1.17]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.26 (P = 0.02)									
14.16.17 L-carnosine: children only									
Hajizadeh-Zaker 2018	6.09	8.02	21	4.62	6.5	21	3.9%	0.20 [-0.41 , 0.80]	
Subtotal (95% CI)			**21**			**21**	**3.9%**	**0.20 [-0.41 , 0.80]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.64 (P = 0.52)									
14.16.18 Prednisolone (steroid): children only									
Malek 2020	18.61	11.4	13	20.69	10.22	13	3.3%	-0.19 [-0.96 , 0.58]	
Subtotal (95% CI)			**13**			**13**	**3.3%**	**-0.19 [-0.96 , 0.58]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.47 (P = 0.64)									
14.16.19 Dextromethorphan/quinidine: adults only									
Chez 2020	10.5	10.71	7	14.5	9.67	7	2.4%	-0.37 [-1.43 , 0.69]	
Subtotal (95% CI)			**7**			**7**	**2.4%**	**-0.37 [-1.43 , 0.69]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.68 (P = 0.50)									
14.16.20 Pregnenolone: children only									
Ayatollahi 2020	11.97	3.52	30	14.62	5.8	29	4.3%	-0.55 [-1.07 , -0.03]	
Subtotal (95% CI)			**30**			**29**	**4.3%**	**-0.55 [-1.07 , -0.03]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.06 (P = 0.04)									
14.16.21 Baclofen: children only									
Mahdavinasab 2019	0	7.87	29	-6.31	6.22	29	4.2%	0.88 [0.34 , 1.42]	
Subtotal (95% CI)			**29**			**29**	**4.2%**	**0.88 [0.34 , 1.42]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 3.18 (P = 0.001)									



Analysis 14.16. (Continued)

Heterogeneity: Not applicable
Test for overall effect: Z = 3.18 (P = 0.001)

14.16.22 Palmitoylethanolamide: children only

Khalaj 2018	11.9	3.9	31	14.4	5.9	31	4.3%	-0.49 [-1.00 , 0.01]
Subtotal (95% CI)			**31**			**31**	**4.3%**	**-0.49 [-1.00 , 0.01]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.91 (P = 0.06)

14.16.23 Bumetanide: children only

Sprengers 2021	10.4	8.5	38	11.2	7.2	37	4.6%	-0.10 [-0.55 , 0.35]
Subtotal (95% CI)			**38**			**37**	**4.6%**	**-0.10 [-0.55 , 0.35]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.66)

14.16.24 Resveratol: children only

Hendouei 2019	-8.1	6.5	31	-6.2	6.5	31	4.4%	-0.29 [-0.79 , 0.21]
Subtotal (95% CI)			**31**			**31**	**4.4%**	**-0.29 [-0.79 , 0.21]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.13 (P = 0.26)

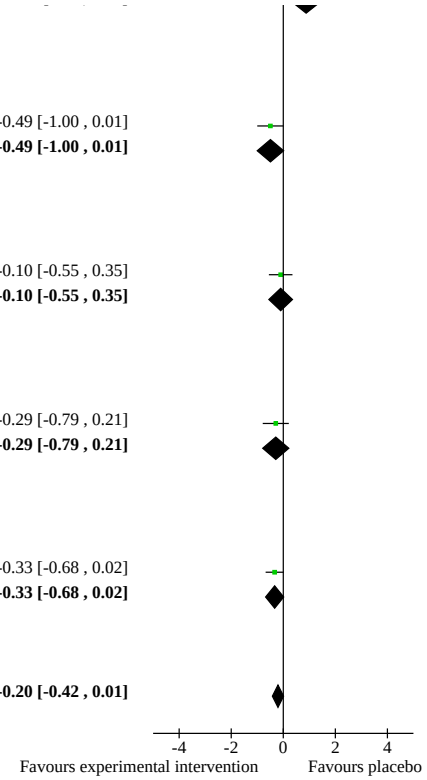
14.16.25 Arbaclofen: children and adults

Veenstra-VanderWeele 2017	-3.6	0.9	61	-3.3	0.9	69	5.0%	-0.33 [-0.68 , 0.02]
Subtotal (95% CI)			**61**			**69**	**5.0%**	**-0.33 [-0.68 , 0.02]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.87 (P = 0.06)

Total (95% CI)			**591**			**588**	**100.0%**	**-0.20 [-0.42 , 0.01]**

Heterogeneity: Tau² = 0.21; Chi² = 83.14, df = 27 (P < 0.00001); I² = 68%
Test for overall effect: Z = 1.86 (P = 0.06)
Test for subgroup differences: Chi² = 72.82, df = 24 (P < 0.00001), I² = 67.0%



Analysis 14.17. Comparison 14: Experimental versus placebo, Outcome 17: Subgroup analyses: age - self-injury (option 1)

Study or Subgroup	Experimental Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
14.17.1 Children only								
Dean 2019	2.2	2.9	48	1.7	2.6	50	66.8%	0.18 [-0.22 , 0.58]
Hardan 2012	2.2	2.3	14	3	3.6	15	19.7%	-0.26 [-0.99 , 0.48]
Subtotal (95% CI)			**62**			**65**	**86.5%**	**0.08 [-0.29 , 0.44]**

Heterogeneity: Tau² = 0.00; Chi² = 1.05, df = 1 (P = 0.30); I² = 5%
Test for overall effect: Z = 0.40 (P = 0.69)

14.17.2 Adults only

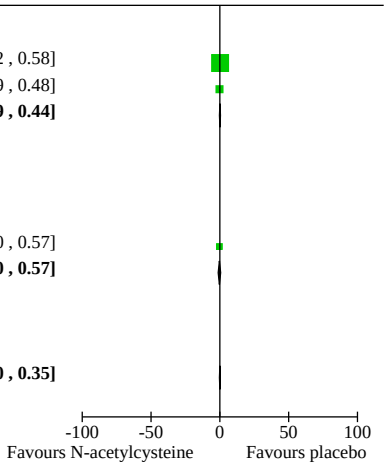
Hollander 2020a	-0.37	2.5	10	0.42	2.31	10	13.5%	-0.31 [-1.20 , 0.57]
Subtotal (95% CI)			**10**			**10**	**13.5%**	**-0.31 [-1.20 , 0.57]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.49)

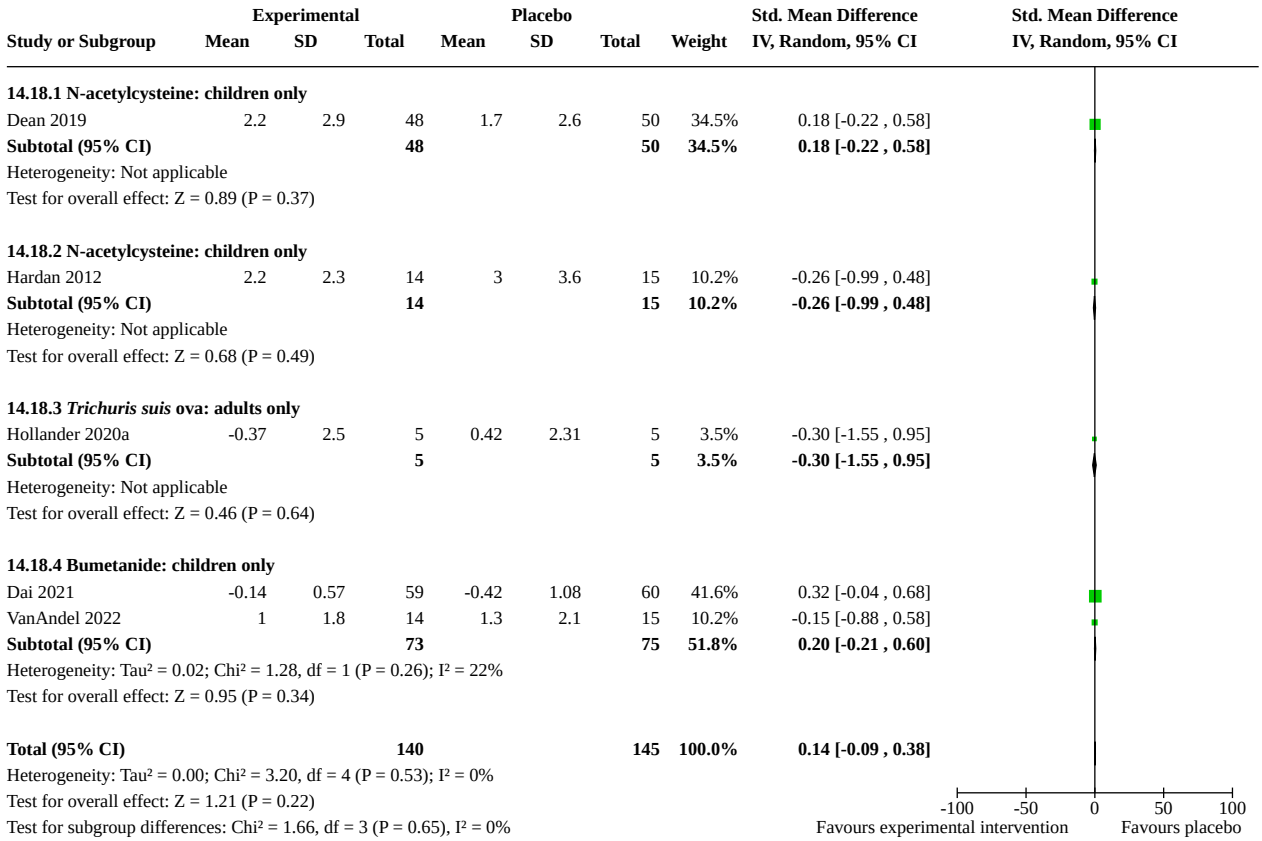
Total (95% CI)			**72**			**75**	**100.0%**	**0.03 [-0.30 , 0.35]**

Heterogeneity: Tau² = 0.00; Chi² = 1.72, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.87)
Test for subgroup differences: Chi² = 0.64, df = 1 (P = 0.42), I² = 0%

Std. Mean Difference IV, Random, 95% CI



Analysis 14.18. Comparison 14: Experimental versus placebo, Outcome 18: Subgroup analyses: age - self-injury (option 2)



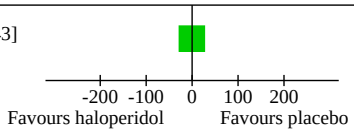
Comparison 15. Typical antipsychotic vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Self-injury	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
15.2 Adverse effects: musculoskeletal	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
15.2.1 Dystonia	1	23	Risk Ratio (IV, Random, 95% CI)	2.36 [0.11, 52.41]
15.3 Adverse effects: neurological	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
15.3.2 Fatigue/lethargy	1	23	Risk Ratio (IV, Random, 95% CI)	8.64 [0.53, 140.05]
15.4 Adverse effects: psychological	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
15.4.1 Behaviour problems	1	23	Risk Ratio (IV, Random, 95% CI)	0.34 [0.16, 0.73]
15.5 Tolerability/acceptabiity: loss to follow-up	2	40	Risk Ratio (IV, Random, 95% CI)	0.46 [0.14, 1.49]

Analysis 15.1. Comparison 15: Typical antipsychotic vs placebo, Outcome 1: Self-injury

Study or Subgroup	Haloperidol Mean	SD	Total	Placebo Mean	SD	Total	Std. Mean Difference IV, Random, 95% CI
Mace 2001	98.8	80.1	8	185.6	194.8	9	-0.54 [-1.52 , 0.43]

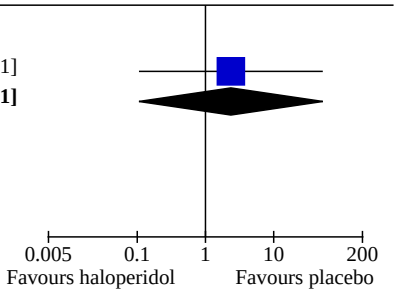
Test for subgroup differences: Not applicable



Analysis 15.2. Comparison 15: Typical antipsychotic vs placebo, Outcome 2: Adverse effects: musculoskeletal

Study or Subgroup	Haloperidol Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
15.2.1 Dystonia						
Remington 2001	1	13	0	10	100.0%	2.36 [0.11 , 52.41]
Subtotal (95% CI)		**13**		**10**	**100.0%**	**2.36 [0.11 , 52.41]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						

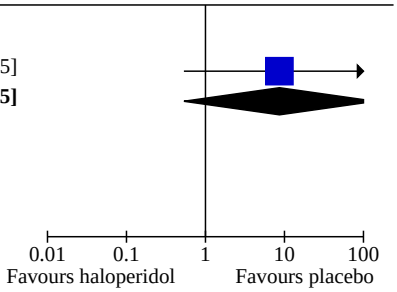
Test for subgroup differences: Not applicable



Analysis 15.3. Comparison 15: Typical antipsychotic vs placebo, Outcome 3: Adverse effects: neurological

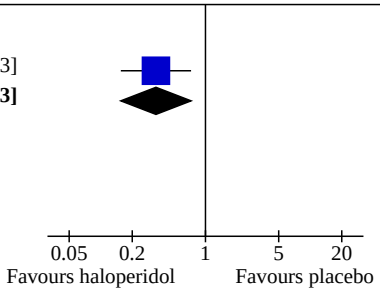
Study or Subgroup	Haloperidol Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
15.3.2 Fatigue/lethargy						
Remington 2001	5	13	0	10	100.0%	8.64 [0.53 , 140.05]
Subtotal (95% CI)		**13**		**10**	**100.0%**	**8.64 [0.53 , 140.05]**
Total events:	5		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.52 (P = 0.13)						

Test for subgroup differences: Not applicable



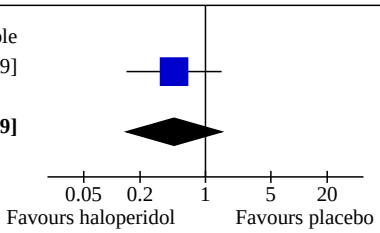
Analysis 15.4. Comparison 15: Typical antipsychotic vs placebo, Outcome 4: Adverse effects: psychological

Study or Subgroup	Haloperidol Events	Haloperidol Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
15.4.1 Behaviour problems						
Remington 2001	4	13	10	10	100.0%	0.34 [0.16 , 0.73]
Subtotal (95% CI)		**13**		**10**	**100.0%**	**0.34 [0.16 , 0.73]**
Total events:	4		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.76 (P = 0.006)						
Test for subgroup differences: Not applicable						



Analysis 15.5. Comparison 15: Typical antipsychotic vs placebo, Outcome 5: Tolerability/acceptabiity: loss to follow-up

Study or Subgroup	Haloperidol Events	Haloperidol Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Mace 2001	0	8	0	9		Not estimable
Remington 2001	3	13	5	10	100.0%	0.46 [0.14 , 1.49]
Total (95% CI)		**21**		**19**	**100.0%**	**0.46 [0.14 , 1.49]**
Total events:	3		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.20)						
Test for subgroup differences: Not applicable						



ADDITIONAL TABLES

Table 1. Antidepressant versus placebo: self-injurious behaviour results that could not be used in meta-analyses

Study name	Short-/ medium-/ long-term outcomes	Group 1	Group 2	Group 1 sample size	Group 2 sample size	Group 1 results	Group 2 results	Other data	Notes
Carminati 2016	Short-term self-injurious behaviour	Venlafaxine 18.75 mg/day	Placebo	6	7	Median 1 (range 0-13)	Median 3 (range 0-8)	-	-
King 2001	Short-term self-injurious behaviour	Citalopram (max 20 mg/day)	Placebo	73	76	2.4 (2.7)	2.0 (2.6)	-	Skewed
Mouti 2014	Short-term self-injurious behaviour	Fluoxetine (max 20-30 mg)	Placebo	53	53	2.09 (3.01)	3.55 (4.59)	-	Skewed

Table 2. Authors contacted

Study ID	Name of contact author	Response from author
Asadabadi 2013	S. Akhonzadeh	No response
Belsito 2001	K. Belsito	No response
Chugani 2016	D. Chugani	No response
Ghaleiha 2013a	S. Akhonzadeh	No response
Ghaleiha 2015	S. Akhonzadeh	No response
Ghaleiha 2016	S. Akhonzadeh	No response
Handen 2000	B. Handen	No response
Handen 2005	B. Handen	No response
Handen 2008	B. Handen	No response
Handen 2011	B. Handen	No response
Mohammadi 2013	S. Akhonzadeh	No response
Nikoo 2015	S. Akhonzadeh	No response
Hollander 2012	E. AnagNostou	No response
	E. Hollander	No response
Kern 2001a	J. Kern	No response
Kern 2002	J. Kern	No response
King 2001	B. King	No response
Mace 2001	N. Blum	No response
McDougle 1996	C. McDougle	Email bounced
Miral 2008	S. Miral	No response
Molloy 2002	C. Molloy	No response
Mouti 2014	M. O'Sullivan	No response
	A. Mouti	Received response but referred to another author
	D. Reddinhough	Was provided with a full-text paper containing the additional data
Munesue 2016	T. Munesue	No response
Novotny 2004	E. Hollander	No response

Table 2. Authors contacted *(Continued)*

Remington 2001	G. Remington	No response
Rezaei 2010	S. Akhonzadeh	No response
Sandler 1999	AD. Sandler	No response
Wasserman 2006	S. Wasserman	No response
Wasserman 2006	E. AnagNostou	No response

Table 3. Summary of all antipsychotic comparisons

Antipsychotics	Placebo	Bromocriptine	Haloperidol	Memantine	Risperidone
Amisulpride		Dollfus 1992 (n = 9)			
Aripiprazole	Findling 2014 (n = 85) Ichikawa 2017 (n = 92) Marcus 2009 (n = 105) NCT00198107 (n = 81) NCT00468130 (n=15) Owen 2009 (n = 98) 6 studies (n = 476)				DeVane 2019 (n = 61) Ghanizadeh 2014 (n = 59)
Haloperidol	Mace 2001 (n = 7) Remington 2001 (n = 36)				
Lurasidone	Loebel 2016 (n = 148)				
Olanzapine	Hollander 2006b (n = 11)		Malone 2001 (n = 30)		
Risperidone	Kent 2013 (n = 66) Luby 2006 (n = 23) McCracken 2002 (n = 101) McDougle 1998 (n = 31) Research Units 2005 (n = 32) NCT01624675 (n = 39) Shea 2004 (n = 79) Troost 2005 (n = 24) 8 studies (n = 395)		Miral 2008 (n = 30)	Nikvarz 2017 (n = 30)	

n: number of participants

Table 4. Atypical antipsychotics versus placebo: irritability results that could not be used in meta-analyses

Study name	Short-/medium-/long-term outcomes	Group 1	Group 2	Group 1 sample size	Group 2 sample size	Group 1 results Mean (standard deviation)	Group 2 results Mean (standard deviation)	Other data	Notes
Findling 2014	Short-term irritability	Aripiprazole (max 15 mg/day)	Placebo	39	43	5.2 (10.05)	9.6 (10.23)	-	Skewed

Table 5. Atypical antipsychotic versus placebo: aggression results that could not be used in meta-analyses

Study name	Short-/medium-/ long-term outcomes	Group 1	Group 2	Group sample size	Group 2 sample size	Group 1 results	Group 2 results	Other data	Notes
Hollander 2006a	Short-term aggression	Olanzapine max 20 mg/day	Placebo	6	5	Not provided	Not provided	-	"we did not find any evidence for significant change on the CY-BOCS, the OAS-M irritability measure, or the OAS-M aggression measure"

CY-BOCS: Children's Yale Bown Obsessive compulsive Scale; **OAS-M:** Overt Aggression Scale - Modified

Table 6. Atypical antipsychotic versus placebo: self-injurious behaviour results that could not be used in the meta-analyses

Study name	Short-/medium-/long-term outcomes	Group 1	Group 2	Group sample size	Group 2 sample size	Group 1 results Mean (standard deviation)	Group 2 results Mean (standard deviation)	Other data	Notes
Shea 2004	Short-term self-injurious behaviour	Risperidone maximum 0.02 mg/kg/day	Placebo	39	38	−2.6 (3.3)	−1.3 (2.8)	-	Skewed

Table 7. Atypical antipsychotics versus placebo: adverse effects data that could not be used in the meta-analyses

Study name	Short-/medium-/long-	Group 1	Group 2	Group 1 sample size	Group 2 sample size	Group 1 results	Group 2 results	Other data	Notes

Table 7. Atypical antipsychotics versus placebo: adverse effects data that could not be used in the meta-analyses *(Continued)*

	term outcomes					**Mean (standard deviation)**	**Mean (standard deviation)**		
Malone 2001	Short-term weight gain	Olanzapine 2.5-2 mg/day	Placebo	Not described. 33 in total	Not described. 33 in total	Not outlined for each group. Weight gain was described as change in BMI category from baseline to endpoint and summarised as a group BMI change. AEs were measured at baseline and after week 12 (not after blinded phase)	Not outlined for each group. See Group 1	At baseline, 70.3% of children were at a healthy weight, 21.6% were overweight, 2.7% were obese, and 5.4% were underweight. By week 12, 42.4% were healthy weight, 21.2% were overweight, and 36.4% were obese.	
Marcus 2009	Short-term weight gain (kg)	Aripiprazole 5 mg/day	Placebo	44	13	1.5 (2.65)	0.4 (1.85)	"All aripiprazole treatment groups were associated with significantly greater change in weight compared with the placebo at endpoint. Aripiprazole 5 mg/day and aripiprazole 15 mg/day were associated with a greater prevalence of clinically significant weight gain than the placebo, and aripiprazole 15 mg/day was also associated with significantly greater increases in body mass index than the placebo"	Skewed
		Aripiprazole 10 mg/day	Placebo	49	13	1.4 (2.1)	0.4 (1.85)		
		Aripiprazole 15 mg/day	Placebo	47	13	1.6 (2.06)	0.4 (1.85)		
Owen 2009	Short-term weight gain (kg)	Aripiprazole (2-15 mg/day)	Placebo	47	50	2.0 (12.15)	0.8 (12.15)	"Aripiprazole treatment was associated with significantly greater mean weight change compared with placebo at endpoint (LOCF: 2.0 vs 0.8 kg (P .005); observed case: 1.9 vs 0.5 kg (P .01)). Aripiprazole was also associated with a greater incidence of clinically significant weight gain (>7% increase from baseline) than placebo (LOCF: 28.9% vs 6.1%; P.01)"	Skewed

Table 7. Atypical antipsychotics versus placebo: adverse effects data that could not be used in the meta-analyses *(Continued)*

AE: adverse effect; **BMI:** body mass index; **LOCF:** Last observation carried forward

Table 8. Atypical antipsychotics versus placebo: quality-of-life results that could not be used in the meta-analyses

Study name	Short-/medium-/long-term outcomes	Group 1	Group 2	Group 1 sample size	Group 2 sample size	Group 1 results Mean (standard deviation)	Group 2 results Mean (standard deviation)	Other data	Notes
Marcus 2009	Short-term QoL	Aripiprazole 5 mg/day	Placebo	43	12	14 (15.74)	10.6 (15.82)	-	"Although patients receiving aripiprazole 5 and 10 mg/day had improvement in these 3 (QoL) scale scores compared with those receiving placebo, the 95% CIs of the treatment differences included zero"
		Aripiprazole 10 mg/day	Placebo	41	12	10.4 (15.4)	10.6 (15.82)	-	

QoL: Quality of Life

Table 9. Neurohormones versus placebo: irritability results that could not be used in the meta-analyses

Study name	Short-/medium-/long-term outcomes	Group 1 sample size	Group 2 sample size	Group 1 results Mean (standard deviation)	Group 2 results Mean (standard deviation)	Other data	Notes
Levy 2003	Short-term (single-dose secretin (2 CU/kg))	31	31	0.01 (1.35)	−0.18 (0.79)	-	Skewed
Squassante 2018	Short-term balovaptan 1.5 mg	32	23	−1.99 (14.92)	−2.85 (24.29)	-	Skewed
	Short-term balovaptan 4 mg	77	22	−1.64 (24.15)	−1.07 (4.95)		
	Short-term balovaptan 10 mg	39	22	−3.42 (34.79)	−2.99 (9.49)		
Unis 2002	Short-term synthetic secretin (single infusion of 0.4 µg/kg)	23	15	−1.3 (3.93)	−1.5 (3.38)	-	Skewed

Table 10. Neurohormones versus placebo: adverse effects data that could not be used in the meta-analysis

Name of study	Short-/medium-/long-term outcomes	Group 1 sample size	Group 1 sample size	Group 1 results Mean (standard deviation)	Group 2 results Mean (standard deviation)	Other data	Notes
Sikich 2013	Short-term oxytocin (max 24 IU children 3-10 years or max 32 IU children 11-17 years) adverse effects (metabolic)	11	13	0.64 (1.95)	1.09 (1.14)	-	Skewed

Table 11. Neurohormones versus placebo: quality-of-life results that could not be used in the meta-analyses

Study name	Short-/medium-/long-term outcomes	Group 1 sample size	Group 2 sample size	Results Group 1 Mean (standard deviation)	Results Group 2 Mean (standard deviation)	Other data	Notes
Bernaerts 2020	Short-term oxytocin (24 IU once daily)	22	17	1.77 (8.04)	-1.35 (6.74)	-	Skewed
Jacob 2022	Short-term balovaptan (10 mg once daily)	106	92	8.0 (13.7)	6.0 (11.6)	-	Skewed
NCT01908205 (2013)	Short-term oxytocin (twice daily dose of max 24 IUs)	25	29	14.2 (17.4)	7.6 (21.3)	-	Skewed
NCT02940574 (2016)	Short-term oxytocin (24 IU once daily)	22	17	1.14 (5.48)	0.35 (4.53)	-	Skewed
Squassante 2018	Short-term balovaptan (1.5 mg)	26	22	2.0 (13.7)	3.9 (13.0)	-	Skewed
	Short-term balovaptan (4 mg)	69	22	6.2 (10.8)	3.9 (13)	-	
	Short-term balovaptan (10 mg)	30	23	9.8 (10.0)	3.98 (13.0)	-	

Table 12. ADHD versus placebo: adverse effects data that could not be used in the meta-analyses

Study name	Short-/medium-/long-term outcomes	Group 1 sample size	Group 2 sample size	Group 1 results	Group 2 results	Other data	Notes

Table 12. ADHD versus placebo: adverse effects data that could not be used in the meta-analyses *(Continued)*

				Mean (standard deviation)	Mean (standard deviation)		
Jaselskis 1992	Short-term adverse effects (increased thirst) clonidine (0.15-0.20 mg/day)	8	8	0.5 (0.8)	0.3 (0.5)	-	Skewed
	Short-term adverse effects (appetite change) clonidine (0.15-0.20 mg/day)	8	8	1.6 (2.1)	0.6 (0.7)		
	Short-term adverse effects (sleep disturbance) clonidine (0.15-0.20 mg/day)	8	8	1.6 (2.7)	1.4 (2.3)		
	Short-term adverse effects (depression) clonidine (0.15-0.20 mg/day)	8	8	1.4 (2.0)	1.3 (1.4)		

Table 13. Antidepressant versus placebo: irritability results that could not be used in the meta-analyses

Study name Short-/medium-/ long-term outcomes		Group 1	Group 2	Group 3	Group 1 sample size	Group 2 sample size	Group 3 sample size	Group 1 results Mean (standard deviation)	Group 2 results Mean (standard deviation)	Group 3 results Mean (standard deviation)	Notes
Carminati 2016	Short-term irritability	Venlafaxine (18.75 mg/day)	Placebo	NA	6	7	NA	Median 10 (range 0-40)	Median 9 (range 5-17)	NA	Results presented as median and range
Gordon 1993	Short-term irritabilty	Clomipromine mean dose 4.3 mg/kg/day	Placebo	NA	24	12	NA	ABC-I data not reported	ABC-I data not reported	NA	Data not reported
Hollander 2012	Short-term Irritability	Fluoxetine (max 80 mg/day)	Placebo	Fluoxetine	22	15	NA	Not reported	Not reported	NA	Irritability was an outcome; however, it was not reported

Table 13. Antidepressant versus placebo: irritability results that could not be used in the meta-analyses *(Continued)*

NCT00183339	Medium-term irritability	Fluoxetine (max 20 mg/day)	Placebo	NA	8	10	NA	ABC-I -8.5 (10.6)	ABC-I -0.7 (2.9)	NA	Skewed
Remington 2001	Short-term irritability	Clompramine (max 150 mg/day)	Haloperidol (max 150 mg/day)	Placebo	13	13	10	Mean 16	Mean 12	17.5	Results presented graphically without SD

ABC-I: Aberrant Behaviour Checklist - Irritability; **SD:** standard deviation

Table 14. Antidepressant versus placebo: aggression results that could not be used in the meta-analyses

Study name	Short-/ medium-/ long-term outcomes	Group 1	Group 2	Group 1 sample size	Group 2 sample size	Group 1 results	Group 2 results	Other data	Notes
Carminati 2016	Short-term aggression	Venlafaxine 18.75 mg/day	Placebo	6	7	Median 3.5 (range 0-18)	Median 4 (range 1-9)	-	Only median and range provided
McDougle 1996	Short-term aggression	Fluvoxamine max 300 mg/day	Placebo	15	15	Not reported; only t scores and P value	Not reported; only t scores and P value	As measured by total score on the Brown Aggression Scale, fluvoxamine was superior to placebo in reducing aggression (F = 4.57; d = 3.84; P < 0.03).	-

Table 15. Experimental versus placebo: irritability results that could not be used in the meta-analyses

Study name	Short-/medium-/long-term outcomes	Group 1 sample size	Group 2 sample size	Group 1 results Mean (standard deviation)	Group 2 results Mean (standard deviation)	Other data	Notes

Table 15. Experimental versus placebo: irritability results that could not be used in the meta-analyses *(Continued)*

Arnold 2012a	Short-term mecamylamine (max 5 mg/day)	12	8	−3.17 (8.76)	−5.0 (10.78)	"No significant differences were found for age, weight, sex, diagnosis, IQ, or entry scores for the OACIS, RBS, ABC Irritability, ABC Hyperactivity, ABC Lethargy/ Social Withdrawal, ABC Inappropriate Speech, ADI-R Qualitative Abnormalities in Reciprocal Social Interaction or ADI-R Qualitative Abnormalities in Communication"	Skewed
Hollander 2020a	Short-term *Trichuris suis* ova (a dose of 2500 *Trichurissuis* ova every 2 weeks)	10	10	−4.0 (18.5)	−0.14 (6.32)	P = 0.0687, 95% CI −4.82 to 91.32	Skewed
Minshawi 2016	Short-term D-cycloserine (50 mg once weekly)	34	33	−1.55 (6.11)	−1.23 (6.09)	"teacher-rated ABC data was returned for 23.5 % of the DCS group, and 30.3 % of the placebo group with no significant difference noted for any of the ABC subscales (irritability p = 0.623, social withdrawal p = 0.845"	Skewed

ABC: Aberrant Behaviour checklist; **DCS:** D-cycloserine; **OACIS:** Ohio Autism Clinical Impressions Scale; **RBS:** Repetitive Behaviour Scale

Table 16. Experimental versus placebo: self-injurious behaviour results that could not be used in the meta-analysis

Study name	Short-/medium-/long-term outcomes	Group 1 sample size	Group 2 sample size	Group 1 results Mean (standard deviation)	Group 2 results Mean (standard deviation)	Other data	Notes
Dean 2019	Short-term self-injurious behaviour (N-acetylcysteine 500 mg/day)	48	50	2.2 (2.9)	1.7 (2.6)	"There were no differences between N-acetyl cysteine and placebo-treated groups on any of the outcome measures for either primary or secondary endpoints. There was no significant difference in the number and severity of adverse events between groups"	Skewed
Hardan 2012	Short-term self-injurious behaviour (N-	14	15	2.2 (2.3)	3.0 (3.6)	"Compared with placebo, NAC resulted in significant improvements on ABC ir-	Skewed

Table 16. Experimental versus placebo: self-injurious behaviour results that could not be used in the meta-analysis *(Continued)*

	acetylcysteine maz 900 mg/day 3 times daily)					ritability subscale (F= 6.80; P <.001;d.= 0.96)"	
Hollander 2020a	Short-term self-injurious behaviour (*Trichuris suis* ova, dose of 2500 ova every 2 weeks)	10	10	−0.37 (2.5)	0.42 (2.31)	"Trending improvements were observed in irritability using the overall percent change from baseline to endpoint on the Aberrant Behavior Checklist (ABC)–Irritability subscale"	Skewed

NAC: N-acetylcysteine

Table 17. Experimental versus placebo: adverse effects data that could not be used in the meta-analysis

Study name	Short-/medium-/long-term outcomes	Group 1	Group 2	Group 1 sample size	Group 2 sample size	Group 1 results Mean (standard deviation)	Group 2 results Mean (standard deviation)	Other data	Notes
Ghanizadeh 2013	Short-term adverse effects (NAC 1200 mg/day, risperidone 2-3 mg/day depending on weight). 20+ AEs included fatigue, increased appetite, decreased appetite, diarrhoea, and constipation.	N-acetylcysteine + risperidone	Placebo + risperidone	17	14				AEs were reported for each group although percentage was out of total number of participants, not participants for each group.

AE: adverse effect; **NAC:** N-acetylcysteine

APPENDICES

Appendix 1. Search strategies used

CENTRAL

#1 [mh "child development disorders, pervasive"]
#2 [mh ^"Developmental Disabilities"]
#3 [mh ^"Neurodevelopmental disorders"]
#4 (pervasive NEAR/3 child*)
#5 pervasive NEXT development* NEXT disorder*
#6 (PDD or PDDs or PDD NEXT NOS or ASD or ASDs)
#7 autis*
#8 asperger*
#9 kanner*
#10 childhood next schizophrenia
#11 Rett*
#12 {OR #1-#11}
#13 [mh ^"Drug therapy"]
#14 ((pharma* or drug) NEAR/1 (intervention* or therap* or treat*))
#15 pharmacotherap*
#16 [mh ^Psychopharmacology]
#17 (psychopharmacol* or psycho next pharmacol*)
#18 [mh ^"Off-Label Use"]
#19 (off next label)
#20 (novel NEAR/1 (drug* or medication* or pharma* or treatment*))
#21 (acetylcholinesterase or acetyl NEXT cholinesterase)
#22 [mh ^Amisulpride]
#23 (Analeptics or (Analeptic near agent*) or (Analeptic near drug*))
#24 [mh ^"Anti-Anxiety Agents"]
#25 (anxiolytic* or antianxiety NEXT agent* or antianxiety NEXT drug* or anti NEXT anxiety NEXT agent* or anti NEXT anxiety NEXT drug*)
#26 [mh Anticonvulsants]
#27 (Anticonvulsant* or anti next convulsant*)
#28 (antiepileptic* or anti next epileptic*)
#29 [mh "Antidepressive Agents"]
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#31 [mh "Antipsychotic Agents"]
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#33 [mh "Antihypertensive Agents"]
#34 [mh "Antiparkinson Agents"]
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#37 [mh ^"Atomoxetine Hydrochloride"]
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#46 [mh Clonidine]
#47 [mh Fluoxetine]
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#49 [mh guanfacine]
#50 [mh Haloperidol]
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#52 [mh Levetiracetam]
#53 [mh "Lurasidone Hydrochloride"]
#54 [mh memantine]
#55 [mh methylphenidate]
#56 [mh Milnacipran]

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#61 [mh oxytocin]
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#63 [mh "Paliperidone Palmitate"]
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#65 [mh "Quetiapine Fumarate"]
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#67 [mh Rivastigmine]
#68 [mh Secretin]
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#74 Tetracyclic*
#75 [mh Topiramate]
#76 Tricyclic*
#77 [mh "Venlafaxine Hydrochloride"]
#78 [mh "Valproic Acid"]
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#80 {or #13-#79}
#81 #12 and #80 in Trials

Ovid MEDLINE

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3 Neurodevelopmental disorders/
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8 asperger$.tw,kf.
9 kanner$.tw,kf.
10 childhood schizophrenia.tw,kf.
11 Rett$.tw,kf.
12 or/1-11
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15 pharmacotherap$.tw,kf.
16 Psychopharmacology/
17 (psychopharmacol$ or psycho-pharmacol$).tw,kf.
18 "Off-Label Use"/
19 (off label or "off-label").tw,kf.
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22 Amisulpride/
23 (Analeptics or (Analeptic adj agent$) or (Analeptic adj drug$)).tw,kf.
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25 (anxiolytic$ or antianxiety agent$ or antianxiety drug$ or anti anxiety agent$ or anti anxiety drug$).tw,kf.
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27 (Anticonvulsant$ or anti-convulsant$).mp.
28 (antiepileptic$ or anti-epileptic$).mp.

29 exp Antidepressive Agents/
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31 exp Antipsychotic Agents/
32 (antipsychotic$ or anti-psychotic$).mp.
33 exp Antihypertensive Agents/
34 exp Antiparkinson Agents/
35 (antiparkinson or anti-parkinson).mp.
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37 Atomoxetine Hydrochloride/
38 Bromocriptine/
39 Buspirone/
40 Central Nervous System Stimulants/
41 CNS Stimulant$.tw,kf.
42 Cholinesterase Inhibitors/
43 Cholinesterase Inhibitor$.tw,kf.
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45 Clomipramine/
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47 Fluoxetine/
48 Fluvoxamine/
49 guanfacine/
50 Haloperidol/
51 Imipramine/
52 Levetiracetam/ (2193)
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54 memantine/
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56 Milnacipran/
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63 Paliperidone Palmitate/
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67 Rivastigmine/
68 Secretin/
69 "Serotonin and Noradrenaline Reuptake Inhibitors"/
70 Serotonin Uptake Inhibitors/
71 ((Serotonin adj3 Uptake Inhibitor$) or (Serotonin adj3 reuptake Inhibitor$) or (Serotonin adj3 re-uptake Inhibitor$)).tw,kf.
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74 Tetracyclic$.tw,kf.
75 Topiramate/
76 Tricyclic$.tw,kf.
77 Venlafaxine Hydrochloride/
78 Valproic Acid/
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87 randomly.ab.
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91 exp animals/ not humans.sh.
92 90 not 91
93 81 and 92

MEDLINE In-Process and Other Non-Indexed Citations

1 pervasive development$ disorder$.tw,kf.
2 Developmental Disabilit$.tw,kf.
3 neurodevelopmental disorder$.tw,kf.
4 (pervasive adj3 child$).tw,kf.
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35 or/12-34
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38 36 and 37

MEDLINE EPub Ahead of Print

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32 (SSRI or SSRIs).tw,kf.
33 Tricyclic$.tw,kf.
34 (amantadine or amisulpride or aripiprazole or atomoxetine or bromocriptine or buspirone or Centedrin or Concerta or Daytrana or citalopram or clomipramine or clozapine or divalproex or donepezil or Equasym or escitalopram or fluoxetine or fluvoxamine or gabapentin or guanfacine or Haloperidol or imipramine or iamotrigine or lamotrigine or levetiracetam or lurasidone or memantine or Metadate or Methylin or Methylphenidat$ or milnacipran or mirtazapine or nortriptyline or olanzapine or oxytocin or paliperidone or paroxetine or Phenidylate or quetiapine or risperidone or Ritalin$ or rivastigmine or secretin or Sertraline or Tianeptine or Topiramate or Tsentedrin or valproate or Venlafaxine or Ziprasidone).tw,kf.
35 or/12-34
36 11 and 35
37 (random$ or trial$ or control$ or group$ or placebo$ or blind$ or prospectiv$ or longitudinal$ or meta-analys$ or systematic review $).tw.
38 36 and 37

Embase Ovid

1 exp autism/
2 developmental disorder/
3 pervasive development$ disorder$.tw.
4 (PDD or PDDs or ASD or ASDs).tw.
5 autis$.tw.
6 asperger$.tw.
7 kanner$.tw.
8 childhood schizophreni$.tw.
9 Rett$.tw.
10 (pervasive adj3 child$).tw.
11 or/1-10
12 drug therapy/
13 ((pharma$ or drug) adj1 (intervention$ or therap$ or treat$)).tw,kw.
14 pharmacotherap$.tw,kw.
15 psychopharmacology/
16 (psychopharmacol$ or psycho-pharmacol$).tw,kw.
17 "off label drug use"/
18 (off label or "off-label").tw,kw.
19 (novel adj1 (drug$ or medication$ or pharma$ or treatment$)).tw,kw.
20 (acetylcholinesterase or acetyl-cholinesterase).mp.

21 amisulpride/
22 central stimulant agent/
23 (Analeptics or (Analeptic adj agent$) or (Analeptic adj drug$)).tw,kw.
24 anxiolytic agent/
25 (anxiolytic$ or antianxiety agent$ or antianxiety drug$ or anti anxiety agent$ or anti anxiety drug$).tw,kw.
26 anticonvulsive agent/
27 (Anticonvulsant$ or anti-convulsant$).mp.
28 (antiepileptic$ or anti-epileptic$).mp.
29 exp antidepressant agent/
30 (antidepress$ or anti-depress$).mp.
31 (antipsychotic$ or anti-psychotic$).mp.
32 exp antihypertensive agent/
33 exp antiparkinson agent/
34 (antiparkinson or anti-parkinson).mp.
35 adrenergic receptor affecting agent/ (
36 atomoxetine/
37 bromocriptine/
38 buspirone/
39 central stimulant agent/
40 ((CNS or central nervous system) adj Stimulant$).tw,kw.
41 cholinesterase inhibitor/
42 Cholinesterase Inhibitor$.tw,kw.
43 citalopram/
44 clomipramine/
45 clonidine/
46 fluoxetine/
47 fluvoxamine/
48 fluvoxamine maleate/
49 guanfacine/
50 Haloperidol/
51 imipramine/
52 levetiracetam/
53 lurasidone/
54 memantine/
55 methylphenidate/
56 milnacipran/
57 mood stabilizer/
58 mood stabili#er$.tw,kw.
59 neurohormone/
60 (neurohormone$ or neuro hormone$).tw,kw.
61 (NMDA adj1 (antagonist$ or receptor$)).tw,kw.
62 nortriptyline/
63 neuroleptic agent/
64 oxytocin/
65 Olanzapine/
66 paliperidone/
67 paroxetine/
68 quetiapine/
69 risperidone/
70 rivastigmine/
71 secretin/
72 serotonin noradrenalin reuptake inhibitor/
73 serotonin uptake inhibitor/
74 ((Serotonin adj3 Uptake Inhibitor$) or (Serotonin adj3 reuptake Inhibitor$) or (Serotonin adj3 re-uptake Inhibitor$)).tw,kw.
75 (SSRI or SSRIs).tw,kw.
76 sertraline/
77 Tetracyclic$.tw,kw.
78 topiramate/
79 Tricyclic$.tw,kw.
80 venlafaxine/
81 valproic acid/

82 (amantadine or amisulpride or aripiprazole or atomoxetine or bromocriptine or buspirone or Centedrin or Concerta or Daytrana or citalopram or clomipramine or clozapine or divalproex or donepezil or Equasym or escitalopram or fluoxetine or fluvoxamine or gabapentin or guanfacine or Haloperidol or imipramine or iamotrigine or lamotrigine or levetiracetam or lurasidone or memantine or Metadate or Methylin or Methylphenidat$ or milnacipran or mirtazapine or nortriptyline or olanzapine or oxytocin or paliperidone or paroxetine or Phenidylate or quetiapine or risperidone or Ritalin$ or rivastigmine or secretin or Sertraline or Tianeptine or Topiramate or Tsentedrin or valproate or Venlafaxine or Ziprasidone).mp.
83 or/12-82
84 11 and 83
85 Randomized controlled trial/
86 Controlled clinical study/
87 random$.ti,ab.
88 randomization/
89 intermethod comparison/
90 placebo.ti,ab.
91 (compare or compared or comparison).ti.
92 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
93 (open adj label).ti,ab.
94 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
95 double blind procedure/
96 parallel group$1.ti,ab.
97 (crossover or cross over).ti,ab.
98 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant $1)).ti,ab.
99 (assigned or allocated).ti,ab.
100 (controlled adj7 (study or design or trial)).ti,ab.
101 (volunteer or volunteers).ti,ab.
102 human experiment/
103 trial.ti.
104 or/85-103
105 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)
106 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)
107 (((case adj control$) and random$) not randomi?ed controlled).ti,ab.
108 (Systematic review not (trial or study)).ti.
109 (nonrandom$ not random$).ti,ab.
110 "Random field$".ti,ab.
111 (random cluster adj3 sampl$).ti,ab.
112 (review.ab. and review.pt.) not trial.ti.
113 "we searched".ab. and (review.ti. or review.pt.)
114 "update review".ab.
115 (databases adj4 searched).ab.
116 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/
117 Animal experiment/ not (human experiment/ or human/)
118 or/105-117
119 104 not 118
120 84 and 119

CINAHL EBSCOhost

S1 (MH "Child Development Disorders, Pervasive+")
S2 (MH "Rett Syndrome")
S3 (MH "Developmental Disabilities")
S4 (MH "Mental Disorders Diagnosed in Childhood")
S5 TI(autis* or asperger* or kanner* or "childhood schizophrenia" or Rett* or "pervasive development* disorder*" or PDD or PDDs or PDD-NOS or ASD or ASDs) OR AB(autis* or asperger* or kanner* or "childhood schizophrenia" or Rett* or "pervasive development* disorder*" or PDD or PDDs or PDD-NOS or ASD or ASDs)
S6 S1 OR S2 OR S3 OR S4 OR S5
S7 (MH "Drug Therapy")
S8 TI((pharma* or drug) N1 (intervention* or therap* or treat*)) OR AB((pharma* or drug) N1 (intervention* or therap* or treat*))

S9 TI(pharmacotherap* OR psychopharmacol* or psycho-pharmacol*) OR AB(pharmacotherap* OR psychopharmacol* or psycho-pharmacol*)
S10 (MH "Psychopharmacology")
S11 (MH "Drugs, Off-Label")
S12 TI("off label" or (novel N1 (drug* or medication* or pharma* or treatment*))) OR AB("off label" or (novel N1 (drug* or medication* or pharma* or treatment*)))
S13 TI(acetylcholinesterase or acetyl-cholinesterase) OR AB(acetylcholinesterase or acetyl-cholinesterase)
S14 (MH "Antianxiety Agents") OR (MH "Anticonvulsants") OR (MH "Antidepressive Agents+") OR (MH "Antipsychotic Agents+") OR (MH "Central Nervous System Stimulants+")
S15 (MH "Antihypertensive Agents+")
S16 (MH "Antiparkinson Agents")
S17 (MH "Adrenergic Uptake Inhibitors") OR (MH "Serotonin Uptake Inhibitors") OR(MH "Cholinesterase Inhibitors")
S18 (MH "Atomoxetine")
S19 (MH "Bromocriptine")
S20 (MH "Buspirone")
S21 (MH "Citalopram")
S22 (MH "Clomipramine")
S23 (MH "Clonidine")
S24 (MH "Fluoxetine")
S25 (MH "Fluvoxamine Maleate")
S26 (MH "Haloperidol")
S27 (MH "Imipramine")
S28 (MH "Memantine")
S29 (MH "Methylphenidate")
S30 (MH "Milnacipran Hydrochloride")
S31 (MH "Nortriptyline")
S32 (MH "Oxytocin")
S33 (MH "Olanzapine")
S34 (MH "Paliperidone")
S35 (MH "Paroxetine")
S36 (MH "Quetiapine")
S37 (MH "Risperidone")
S38 (MH "Rivastigmine")
S39 (MH "Secretin")
S40 (MH "Topiramate")
S41 (MH "Venlafaxine")
S42 (MH "Valproic Acid")
S43 (MH "Sertraline Hydrochloride")
S44 "(acetylcholinesterase or acetyl-cholinesterase)"
S45 (Analeptics or ("Analeptic agent*") or ("Analeptic Drug*"))
S46 (anxiolytic* or "antianxiety agent*" or "antianxiety drug*" or "anti anxiety agent*" or "anti anxiety drug*")
S47 (Anticonvulsant* or "anti convulsant*")
S48 (antiepileptic* or "anti epileptic*")
S49 (antiepileptic* or "anti epileptic*")
S50 (antidepress* or "anti depress*")
S51 (antipsychotic* or "anti psychotic*")
S52 (antiparkinson or "anti-parkinson")
S53 ("antiparkinson or "anti-parkinson")
S54 (CNS or "central nervous Stimulant*")
S55 "Cholinesterase Inhibitor*"
S56 ("mood stabili*er*")
S57 neurohormone* or neuro-hormone*
S58 (NMDA N1 (antagonist* or receptor*))
S59 ((Serotonin N3 "Uptake Inhibitor*") or (Serotonin N3 "reuptake Inhibitor*") or ("Serotonin N3 "re-uptake Inhibitor*"))
S60 (SSRI or SSRIs)
S61 Tricyclic*
S62 (amantadine or amisulpride or aripiprazole or atomoxetine or bromocriptine or buspirone or Centedrin or Concerta or Daytrana or citalopram or clomipramine or clozapine or divalproex or donepezil or Equasym or escitalopram or fluoxetine or fluvoxamine or gabapentin or guanfacine or Haloperidol or imipramine or iamotrigine or lamotrigine or levetiracetam or lurasidone or memantine or Metadate or Methylin or Methylphenidat* or milnacipran or mirtazapine or nortriptyline or olanzapine or oxytocin or paliperidone or paroxetine or Phenidylate or quetiapine or risperidone or Ritalin* or rivastigmine or secretin or Sertraline or Tianeptine or Topiramate or Tsentedrin or valproate or Venlafaxine or Ziprasidone)

S63 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62
S64 S6 AND S63
S65 MH ("Randomized Controlled Trials")
S66 (MH "Double-Blind Studies")
S67 (MH "Single-Blind Studies")
S68 (MH "Random Assignment")
S69 (MH "Pretest-Posttest Design")
S70 MH ("Cluster Sample")
S71 TI (randomised OR randomized)
S72 AB (random*)
S73 TI (trial)
S74 (MH "Sample Size") AND AB (assigned OR allocated OR control)
S75 MH (Placebos)
S76 PT (Randomized Controlled Trial)
S77 AB (control W5 group)
S78 MH ("Crossover Design") OR MH ("Comparative Studies")
S79 AB (cluster W3 RCT)
S80 (MH "Animals+")
S81 MH ("Animal Studies")
S82 TI (animal model*)
S83 S80 OR S81 OR S82
S84 MH ("Human")
S85 S83 NOT S84
S86 S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79
S87 S86 NOT S85
S88 S64 AND S87

APA PsycInfo

1 exp autism spectrum disorders/
2 neurodevelopmental disorders/
3 Developmental disabilities/
4 pervasive development$ disorder$.tw.
5 (pervasive adj3 child$).tw.
6 autis$.tw.
7 asperger$.tw.
8 (autis$ or ASD or ASDs).tw.
9 Rett$.tw.
10 Kanner$.tw.
11 (PDD or PDDs or PDD-NOS or ASD or ASDs).tw.
12 childhood schizophreni$.tw.
13 or/1-12
14 Drug Therapy/
15 ((pharma$ or drug) adj1 (intervention$ or therap$ or treat$)).tw.
16 pharmacotherap$.tw.
17 psychopharmacology/
18 (psychopharmacol$ or psycho-pharmacol$).tw.
19 (off label or "off-label").tw.
20 (novel adj1 (drug$ or medication$ or pharma$ or treatment$)).tw.
21 "prescribing (drugs)"/
22 exp Acetylcholinesterase/ or exp Acetylcholine/
23 (acetylcholinesterase or acetyl-cholinesterase).mp.
24 analeptic drugs/
25 (Analeptics or (Analeptic adj agent$) or (Analeptic adj drug$)).tw.
26 (anxiolytic$ or antianxiety agent$ or antianxiety drug$ or anti anxiety agent$ or anti anxiety drug$).tw.
27 Tranquilizing Drugs/ or sedatives/
28 Anticonvulsive Drugs/
29 (Anticonvulsant$ or anti-convulsant$).tw.
30 (antiepileptic$ or anti-epileptic$).tw.

31 Antidepressant Drugs/ or tricyclic antidepressant drugs/
32 (antidepress$ or anti-depress$).tw.
33 exp Neuroleptic Drugs/
34 (antipsychotic$ or anti-psychotic$).tw.
35 antihypertensive drugs/
36 exp antihypertensive drugs/
37 exp antitremor drugs/
38 (antiparkinson or anti-parkinson).tw.
39 atomoxetine/
40 bromocriptine/
41 buspirone/
42 Cns stimulating drugs/
43 ((Central Nervous System or CNS) adj stimulant$).tw.
44 cholinesterase inhibitors/
45 Cholinesterase Inhibitor$.tw.
46 citalopram/
47 chlorimipramine/
48 clonidine/
49 fluoxetine/
50 fluvoxamine/
51 haloperidol/
52 imipramine/
53 methylphenidate/
54 mood stabilizers/
55 mood stabili#er$.tw.
56 (neurohormone$ or neuro hormone$).tw.
57 (NMDA adj1 (antagonist$ or receptor$)).tw.
58 nortriptyline/
59 oxytocin/
60 olanzapine/
61 paroxetine/
62 quetiapine/
63 risperidone/
64 exp Serotonin Reuptake Inhibitors/ or exp Serotonin Norepinephrine Reuptake Inhibitors/
65 neurotransmitter uptake inhibitors/
66 ((Serotonin adj3 Uptake Inhibitor$) or (Serotonin adj3 reuptake Inhibitor$) or (Serotonin adj3 re-uptake Inhibitor$)).tw.
67 (SSRI or SSRIs).tw.
68 Sertraline/
69 Tetracyclic$.tw.
70 Venlafaxine/
71 Valproic Acid/
72 (amantadine or amisulpride or aripiprazole or atomoxetine or bromocriptine or buspirone or Centedrin or Concerta or Daytrana or citalopram or clomipramine or clozapine or divalproex or donepezil or Equasym or escitalopram or fluoxetine or fluvoxamine or gabapentin or guanfacine or Haloperidol or imipramine or iamotrigine or lamotrigine or levetiracetam or lurasidone or memantine or Metadate or Methylin or Methylphenidat$ or milnacipran or mirtazapine or nortriptyline or olanzapine or oxytocin or paliperidone or paroxetine or Phenidylate or quetiapine or risperidone or Ritalin$ or rivastigmine or secretin or Sertraline or Tianeptine or Topiramate or Tsentedrin or valproate or Venlafaxine or Ziprasidone).mp.
73 or/14-72
74 13 and 73
75 clinical trials/
76 longitudinal studies/
77 exp program evaluation/
78 exp Treatment Effectiveness Evaluation/
79 random$.tw.
80 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
81 (crossover$ or "cross over$").tw.
82 trial$.tw.
83 group$.ab.
84 treatment effectiveness evaluation/
85 ((singl$ or doubl$ or tripl$ or trebl$) adj1 (blind$ or mask$)).tw.
86 prospective.tw. (60764)
87 factorial$.tw.

88 random$.tw.
89 (assign$ or allocat$).ab.
90 control.ab.
91 treatment as usual.ab.
92 placebo.ab.
93 (crossover or cross-over).tw.
94 ((effectiveness or evaluat$) adj3 (stud$ or research$)).tw.
95 or/75-94
96 74 and 95

ERIC EBSCOhost

S1 DE "Developmental Disabilities"
S2 DE "Pervasive Developmental Disorders" OR DE "Asperger Syndrome" OR DE "Autism"
S3 (pervasive development* disorder* or PDD or PDDs)
S4 (autis* or ASD or ASDs)
S5 Asperger*
S6 Rett*
S7 Kanner*
S8 childhood schizophren*
S9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S10 DE "Pharmacology"
S11 (anxiolytic* or "antianxiety agent*" or "antianxiety drug*" or "anti anxiety agent*" or "anti anxiety drug*")
S12 (Anticonvulsant* or "anti convulsant*")
S13 (antiepileptic* or "anti epileptic*")
S14 (antidepress* or "anti depress*")
S15 (antipsychotic* or "anti psychotic*")
S16 (antiparkinson or "anti-parkinson")
S17 (CNS or "central nervous Stimulant*")
S18 "Cholinesterase Inhibitor*"
S19 ("mood stabili*er*")
S20 neurohormone* or neuro-hormone*
S21 (NMDA N1 (antagonist* or receptor*))
S22 ((Serotonin N3 "Uptake Inhibitor*") or (Serotonin N3 "reuptake Inhibitor*") or ("Serotonin N3 "re-uptake Inhibitor*"))
S23 (SSRI or SSRIs)
S24 Tricyclic*
S25 (amantadine or amisulpride or aripiprazole or atomoxetine or bromocriptine or buspirone or Centedrin or Concerta or Daytrana or citalopram or clomipramine or clozapine or divalproex or donepezil or Equasym or escitalopram or fluoxetine or fluvoxamine or gabapentin or guanfacine or Haloperidol or imipramine or iamotrigine or lamotrigine or levetiracetam or lurasidone or memantine or Metadate or Methylin or Methylphenidat* or milnacipran or mirtazapine or nortriptyline or olanzapine or oxytocin or paliperidone or paroxetine or Phenidylate or quetiapine or risperidone or Ritalin* or rivastigmine or secretin or Sertraline or Tianeptine or Topiramate or Tsentedrin or valproate or Venlafaxine or Ziprasidone)
S26 S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25
S27 S9 AND S26
S28 DE "Randomized Controlled Trials"
S29 RCT*
S30 *randomly or randomi*ed) N3 (allocated* or assign* or group*)
S31 control group* or experimental group*
S32 placebo* or "treatment as usual" or TAU
S33 S28 OR S29 OR S30 OR S31 OR S32
S34 S27 AND S33

Epistemonikos

title:((amantadine OR amisulpride OR aripiprazole OR atomoxetine OR bromocriptine OR buspirone OR Centedrin OR Concerta OR Daytrana OR citalopram OR clomipramine OR clozapine OR divalproex OR donepezil OR Equasym OR escitalopram OR fluoxetine OR fluvoxamine OR gabapentin OR guanfacine OR Haloperidol OR imipramine OR iamotrigine OR lamotrigine OR levetiracetam OR lurasidone OR memantine OR Metadate OR Methylin OR Methylphenidat$ OR milnacipran OR mirtazapine OR nortriptyline OR olanzapine OR oxytocin OR paliperidone OR paroxetine OR Phenidylate OR quetiapine OR risperidone OR Ritalin$ OR rivastigmine OR secretin OR Sertraline OR Tianeptine OR Topiramate OR Tsentedrin OR valproate OR Venlafaxine OR Ziprasidone)) OR abstract:((amantadine OR amisulpride OR aripiprazole OR atomoxetine OR bromocriptine OR buspirone OR Centedrin OR Concerta OR Daytrana OR citalopram OR clomipramine OR clozapine OR divalproex OR donepezil OR Equasym OR escitalopram OR fluoxetine OR fluvoxamine OR gabapentin OR guanfacine OR Haloperidol OR imipramine OR iamotrigine OR lamotrigine OR levetiracetam OR lurasidone OR memantine OR Metadate OR Methylin

OR Methylphenidat$ OR milnacipran OR mirtazapine OR nortriptyline OR olanzapine OR oxytocin OR paliperidone OR paroxetine OR Phenidylate OR quetiapine OR risperidone OR Ritalin$ OR rivastigmine OR secretin OR Sertraline OR Tianeptine OR Topiramate OR Tsentedrin OR valproate OR Venlafaxine OR Ziprasidone))) OR title:(drug* OR pharma* OR medic*) AND (title:(ASD OR autis* OR asperg* OR rett* OR pervasive OR PDD*) OR abstract:(ASD OR autis* OR asperg* OR rett* OR pervasive OR PDD*))

Science Citation Index- Expanded Web of Science, Clarivate

26 #25 AND #22
25 #24 OR #23
24 ab=(randomi*sed or randomly or trial* or control* or RCT or placebo* or blind* or "treatment as usual" or TAU)
23 ti=(random* or trial* or control* or RCT)
22 #21 AND #1
21 #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2
20 ti=(amantadine or amisulpride or aripiprazole or atomoxetine or bromocriptine or buspirone or Centedrin or Concerta or Daytrana or citalopram or clomipramine or clozapine or divalproex or donepezil or Equasym or escitalopram or fluoxetine or fluvoxamine or gabapentin or guanfacine or Haloperidol or imipramine or iamotrigine or lamotrigine or levetiracetam or lurasidone or memantine or Metadate or Methylin or Methylphenidat* or milnacipran or mirtazapine or nortriptyline or olanzapine or oxytocin or paliperidone or paroxetine or Phenidylate or quetiapine or risperidone or Ritalin* or rivastigmine or secretin or Sertraline or Tianeptine or Topiramate or Tsentedrin or valproate or Venlafaxine or Ziprasidone) OR ab=(amantadine or amisulpride or aripiprazole or atomoxetine or bromocriptine or buspirone or Centedrin or Concerta or Daytrana or citalopram or clomipramine or clozapine or divalproex or donepezil or Equasym or escitalopram or fluoxetine or fluvoxamine or gabapentin or guanfacine or Haloperidol or imipramine or iamotrigine or lamotrigine or levetiracetam or lurasidone or memantine or Metadate or Methylin or Methylphenidat* or milnacipran or mirtazapine or nortriptyline or olanzapine or oxytocin or paliperidone or paroxetine or Phenidylate or quetiapine or risperidone or Ritalin* or rivastigmine or secretin or Sertraline or Tianeptine or Topiramate or Tsentedrin or valproate or Venlafaxine or Ziprasidone)
19 ti=(Tricyclic*) or ab=(Tricyclic*)
18 ti=(SSRI or SSRIs) or ab=(SSRI or SSRIs)
17 ti=((Serotonin Near/3 "Uptake Inhibitor*") or (Serotonin Near/3 "reuptake Inhibitor*") or (Serotonin Near/3 "re-uptake Inhibitor*")) or ab=((Serotonin Near/3 "Uptake Inhibitor*") or (Serotonin Near/3 "reuptake Inhibitor*") or (Serotonin Near/3 "re-uptake Inhibitor*"))
16 ti=(NMDA Near/0 (antagonist* or receptor*)) or ab=(NMDA Near/0 (antagonist* or receptor*))
15 ti=(neurohormone* or "neuro hormone*") or ab=(neurohormone* or "neuro hormone*")
14 ti=("mood stabili*er*") or ab=("mood stabili*er*")
13 ti=("Cholinesterase Inhibitor*") or ab=("Cholinesterase Inhibitor*")
12 ti=("central nervous system stimulant*" or "CNS stimulant*") or ab=("central nervous system stimulant*" or "CNS stimulant*")
11 ti=(antiparkinson or "anti parkinson") or ab=(antiparkinson or "anti parkinson")
10 ti=(antipsychotic* or "anti psychotic*") or ab=(antipsychotic* or "anti psychotic*")
9 ti=(antidepress* or "anti depress*") or ab=(antidepress* or "anti depress*")
8 ti=(Anticonvulsant* or "anti convulsant*") or ab=(Anticonvulsant* or "anti convulsant*")
7 ti=(anxiolytic* or "antianxiety agent*" or "antianxiety drug*" or "anti anxiety agent*" or "anti anxiety drug*") or ab=(anxiolytic* or "antianxiety agent*" or "antianxiety drug*" or "anti anxiety agent*" or "anti anxiety drug*")
6 ti=(Analeptics or "Analeptic agent*" or "Analeptic drug*") or ab=(Analeptics or "Analeptic agent*" or "Analeptic drug*")
5 ti=(acetylcholinesterase or "acetyl cholinesterase") or ab=(acetylcholinesterase or "acetyl cholinesterase")
4 ti=("off label" or (novel NEAR/0 (drug* or medication* or pharma* or treatment*))) OR ab=("off label" or (novel NEAR/0 (drug* or medication* or pharma* or treatment*)))
3 TI=(pharmacotherap* or psychopharmacol* or "psycho-pharmacol*") or AB=(pharmacotherap* or psychopharmacol* or "psycho-pharmacol*")
2 TI=((pharma* or drug) Near/1 (intervention* or therap* or treat*)) or AB=((pharma* or drug) Near/1 (intervention* or therap* or treat*))
1 ti=(autis* or asperg* or Rett* or kanner* or "childhood schizophrenia" or "pervasive development* disorder*" or PDD or PDDs or "PDD-NOS" or ASD or ASDs) OR ab=(autis* or asperg* or Rett* or kanner* or "childhood schizophrenia" or "pervasive development* disorder*" or PDD or PDDs or "PDD-NOS" or ASD or ASDs)

Conference Proceedings Citation Index (Science), Web of Science, Clarivate

26 #25 AND #22
25 #24 OR #23
24 ab=(randomi*sed or randomly or trial* or control* or RCT or placebo* or blind* or "treatment as usual" or TAU)
23 ti=(random* or trial* or control* or RCT)
22 #21 AND #1
21 #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2
20 ti=(amantadine or amisulpride or aripiprazole or atomoxetine or bromocriptine or buspirone or Centedrin or Concerta or Daytrana or citalopram or clomipramine or clozapine or divalproex or donepezil or Equasym or escitalopram or fluoxetine or fluvoxamine or gabapentin or guanfacine or Haloperidol or imipramine or iamotrigine or lamotrigine or levetiracetam or lurasidone or memantine or Metadate or Methylin or Methylphenidat* or milnacipran or mirtazapine or nortriptyline or olanzapine or oxytocin or paliperidone or paroxetine or Phenidylate or quetiapine or risperidone or Ritalin* or rivastigmine or secretin or Sertraline or Tianeptine or Topiramate or Tsentedrin or

valproate or Venlafaxine or Ziprasidone) OR ab=(amantadine or amisulpride or aripiprazole or atomoxetine or bromocriptine or buspirone or Centedrin or Concerta or Daytrana or citalopram or clomipramine or clozapine or divalproex or donepezil or Equasym or escitalopram or fluoxetine or fluvoxamine or gabapentin or guanfacine or Haloperidol or imipramine or iamotrigine or lamotrigine or levetiracetam or lurasidone or memantine or Metadate or Methylin or Methylphenidat* or milnacipran or mirtazapine or nortriptyline or olanzapine or oxytocin or paliperidone or paroxetine or Phenidylate or quetiapine or risperidone or Ritalin* or rivastigmine or secretin or Sertraline or Tianeptine or Topiramate or Tsentedrin or valproate or Venlafaxine or Ziprasidone)
19 ti=(Tricyclic*) or ab=(Tricyclic*)
18 ti=(SSRI or SSRIs) or ab=(SSRI or SSRIs)
17 ti=((Serotonin Near/3 "Uptake Inhibitor*") or (Serotonin Near/3 "reuptake Inhibitor*") or (Serotonin Near/3 "re-uptake Inhibitor*")) or ab=((Serotonin Near/3 "Uptake Inhibitor*") or (Serotonin Near/3 "reuptake Inhibitor*") or (Serotonin Near/3 "re-uptake Inhibitor*"))
16 ti=(NMDA Near/0 (antagonist* or receptor*)) or ab=(NMDA Near/0 (antagonist* or receptor*))
15 ti=(neurohormone* or "neuro hormone*") or ab=(neurohormone* or "neuro hormone*")
14 ti=("mood stabili*er*") or ab=("mood stabili*er*")
13 ti=("Cholinesterase Inhibitor*") or ab=("Cholinesterase Inhibitor*")
12 ti=("central nervous system stimulant*" or "CNS stimulant*") or ab=("central nervous system stimulant*" or "CNS stimulant*")
11 ti=(antiparkinson or "anti parkinson") or ab=(antiparkinson or "anti parkinson")
10 ti=(antipsychotic* or "anti psychotic*") or ab=(antipsychotic* or "anti psychotic*")
9 ti=(antidepress* or "anti depress*") or ab=(antidepress* or "anti depress*")
8 ti=(Anticonvulsant* or "anti convulsant*") or ab=(Anticonvulsant* or "anti convulsant*")
7 ti=(anxiolytic* or "antianxiety agent*" or "antianxiety drug*" or "anti anxiety agent*" or "anti anxiety drug*") or ab=(anxiolytic* or "antianxiety agent*" or "antianxiety drug*" or "anti anxiety agent*" or "anti anxiety drug*")
6 ti=(Analeptics or "Analeptic agent*" or "Analeptic drug*") or ab=(Analeptics or "Analeptic agent*" or "Analeptic drug*")
5 ti=(acetylcholinesterase or "acetyl cholinesterase") or ab=(acetylcholinesterase or "acetyl cholinesterase")
4 ti=("off label" or (novel NEAR/0 (drug* or medication* or pharma* or treatment*))) OR ab=("off label" or (novel NEAR/0 (drug* or medication* or pharma* or treatment*)))
3 TI=(pharmacotherap* or psychopharmacol* or "psycho-pharmacol*") or AB=(pharmacotherap* or psychopharmacol* or "psycho-pharmacol*")
2 TI=((pharma* or drug) Near/1 (intervention* or therap* or treat*)) or AB=((pharma* or drug) Near/1 (intervention* or therap* or treat*))
1 ti=(autis* or asperg* or Rett* or kanner* or "childhood schizophrenia" or "pervasive development* disorder*" or PDD or PDDs or "PDD-NOS" or ASD or ASDs) OR ab=(autis* or asperg* or Rett* or kanner* or "childhood schizophrenia" or "pervasive development* disorder*" or PDD or PDDs or "PDD-NOS" or ASD or ASDs)

Cochrane Database of Systematic Reviews

ID Search
#1 [mh "child development disorders, pervasive"]
#2 [mh ^"Developmental Disabilities"]
#3 [mh ^"Neurodevelopmental disorders"]
#4 (pervasive NEAR/3 child*):ti,ab,kw
#5 (pervasive NEXT development* NEXT disorder*):ti,ab,kw
#6 (PDD or PDDs or PDD NEXT NOS or ASD or ASDs):ti,ab,kw
#7 autis*:ti,ab,kw
#8 asperger*:ti,ab,kw
#9 kanner*:ti,ab,kw
#10 childhood next schizophrenia:ti,ab,kw
#11 Rett*:ti,ab,kw
#12 {OR #1-#11}
#13 [mh ^"Drug therapy"]
#14 ((pharma* or drug) NEAR/1 (intervention* or therap* or treat*)):ti,ab,kw
#15 pharmacotherap*:ti,ab,kw
#16 [mh ^Psychopharmacology]
#17 (psychopharmacol* or psycho next pharmacol*):ti,ab,kw
#18 [mh ^"Off-Label Use"]
#19 (off next label):ti,ab,kw
#20 (novel NEAR/1 (drug* or medication* or pharma* or treatment*)):ti,ab,kw
#21 (acetylcholinesterase or acetyl NEXT cholinesterase):ti,ab,kw
#22 [mh ^Amisulpride]
#23 (Analeptics or (Analeptic near agent*) or (Analeptic near drug*)):ti,ab,kw
#24 [mh ^"Anti-Anxiety Agents"]
#25 (anxiolytic* or antianxiety NEXT agent* or antianxiety NEXT drug* or anti NEXT anxiety NEXT agent* or anti NEXT anxiety NEXT drug*):ti,ab,kw
#26 [mh Anticonvulsants]

#27 (Anticonvulsant* or anti next convulsant*):ti,ab,kw
#28 (antiepileptic* or anti next epileptic*):ti,ab,kw
#29 [mh "Antidepressive Agents"]
#30 (antidepress* or anti NEXT depress*)
#31 [mh "Antipsychotic Agents"]
#32 (antipsychotic* or anti next psychotic*):ti,ab,kw
#33 [mh "Antihypertensive Agents"]
#34 [mh "Antiparkinson Agents"]
#35 (antiparkinson or anti next parkinson):ti,ab,kw
#36 [mh ^"Adrenergic Uptake Inhibitors"]
#37 [mh ^"Atomoxetine Hydrochloride"]
#38 [mh Bromocriptine]
#39 [mh Buspirone]
#40 [mh "Central Nervous System Stimulants"]
#41 ((CNS or central next nervous) next Stimulant*):ti,ab,kw
#42 [mh "Cholinesterase Inhibitors"]
#43 (Cholinesterase next Inhibitor*):ti,ab,kw
#44 [mh citalopram]
#45 [mh Clomipramine]
#46 [mh Clonidine]
#47 [mh Fluoxetine]
#48 [mh Fluvoxamine]
#49 [mh guanfacine]
#50 [mh Haloperidol]
#51 [mh Imipramine]
#52 [mh Levetiracetam]
#53 [mh "Lurasidone Hydrochloride"]
#54 [mh memantine]
#55 [mh methylphenidate]
#56 [mh Milnacipran]
#57 (mood next stabili*er*):ti,ab,kw
#58 (neurohormone* or neuro NEXT hormone*):ti,ab,kw
#59 (NMDA NEAR/1 (antagonist* or receptor*)):ti,ab,kw
#60 [mh Nortriptyline]
#61 [mh oxytocin]
#62 [mh Olanzapine]
#63 [mh "Paliperidone Palmitate"]
#64 [mh Paroxetine]
#65 [mh "Quetiapine Fumarate"]
#66 [mh Risperidone]
#67 [mh Rivastigmine]
#68 [mh Secretin]
#69 [mh "Serotonin and Noradrenaline Reuptake Inhibitors"]
#70 [mh "Serotonin Uptake Inhibitors"]
#71 ((Serotonin NEAR/3 Uptake NEXT Inhibitor*) or (Serotonin NEAR/3 reuptake NEXT Inhibitor*) or (Serotonin NEAR/3 re NEXT uptake NEXT Inhibitor*)):ti,ab,kw
#72 (SSRI or SSRIs):ti,ab,kw
#73 [mh Sertraline]
#74 Tetracyclic*:ti,ab,kw
#75 [mh Topiramate]
#76 Tricyclic*:ti,ab,kw
#77 [mh "Venlafaxine Hydrochloride"]
#78 [mh "Valproic Acid"]
#79 (amantadine or amisulpride or aripiprazole or atomoxetine or bromocriptine or buspirone or Centedrin or Concerta or Daytrana or citalopram or clomipramine or clozapine or divalproex or donepezil or Equasym or escitalopram or fluoxetine or fluvoxamine or gabapentin or guanfacine or Haloperidol or imipramine or iamotrigine or lamotrigine or levetiracetam or lurasidone or memantine or Metadate or Methylin or Methylphenidat* or milnacipran or mirtazapine or nortriptyline or olanzapine or oxytocin or paliperidone or paroxetine or Phenidylate or quetiapine or risperidone or Ritalin* or rivastigmine or secretin or Sertraline or Tianeptine or Topiramate or Tsentedrin or valproate or Venlafaxine or Ziprasidone):ti,ab,kw
#80 {or #13-#79}
#81 #12 and #80 in Cochrane Reviews, Cochrane Protocols

LILACS (lilacs.bvsalud.org/en/)

(ti:((drug* OR pharma* OR medic*) AND (asd OR autis* OR asperg* OR rett* OR pervasive OR pdd*))) OR ((amantadine OR amisulpride OR aripiprazole OR atomoxetine OR bromocriptine OR buspirone OR centedrin OR concerta OR daytrana OR citalopram OR clomipramine OR clozapine OR divalproex OR donepezil OR equasym OR escitalopram OR fluoxetine OR fluvoxamine OR gabapentin OR guanfacine OR haloperidol OR imipramine OR iamotrigine OR lamotrigine OR levetiracetam OR lurasidone OR memantine OR metadate OR methylin OR methylphenidat* OR milnacipran OR mirtazapine OR nortriptyline OR olanzapine OR oxytocin OR paliperidone OR paroxetine OR phenidylate OR quetiapine OR risperidone OR ritalin* OR rivastigmine OR secretin OR sertraline OR tianeptine OR topiramate OR tsentedrin OR valproate OR venlafaxine OR ziprasidone) AND (asd OR autis* OR asperg* OR rett* OR pervasive OR pdd*)) AND (db:("LILACS") AND type_of_study:("clinical_trials"))

Sociological Abstracts (Proquest)

(SU.EXACT("Medications") OR(Psychopharmacology OR Amantadine OR Anticonvulsants OR Antidepressive Agents OR Antipsychotic Agents OR Antihypertensive Agents OR Antiparkinson Agents OR Central Nervous System Agents OR Cholinesterase Inhibitors OR Citalopram OR Clomipramine OR Clonidine OR Clozapine OR Fluoxetine OR Fluvoxamine OR Gabapentin OR Guanfacine OR Haloperidol OR Imipramine OR Memantine OR Nortriptyline OR Paroxetine OR Risperidone OR Serotonin Uptake Inhibitors OR Sertraline) OR (pharmacotherap* OR Amantadine OR Aripiprazole OR Cholinesterase Inhibitor* OR Citalopram OR Citalopram OR Clomipramine OR Clonidine OR Clozapine OR Divalproex OR Donepezil OR Escitalopram OR Fluoxetine OR Fluvoxamine OR Gabapentin OR Guanfacine OR Haloperidol OR Imipramine OR Lamotrigine OR Memantine OR Mirtazapine OR Nortriptyline OR Olanzapine OR Paliperidone OR Paroxetine OR Quetiapine OR Risperidone OR Rivastigmine OR Serotonin OR Sertraline OR Tetracyclic* OR Tianeptine OR Tricyclic* OR Venlafaxine OR Ziprasidone) OR ((pharma* OR drug) NEAR/1 (intervention* OR therap* OR treat*)) OR (psychopharmacol* OR psycho-pharmacol*) OR (off label OR "off-label") OR (novel NEAR/1 (drug* OR medication* OR pharma* OR treatment*)) OR (Anticonvulsant* OR anti-convulsant* OR antiepileptic* OR anti-epileptic* OR antidepress* OR anti-depress* OR antipsychotic* OR anti-psychotic* OR antiparkinson OR anti-parkinson OR acetylcholinesterase OR acetyl-cholinesterase) OR ("mood stabiliser" OR "mood stabilizer") OR (mood stabiliser) OR (mood stabilizer) OR (NMDA NEAR/1 (antagonist* OR receptor*)) OR (NMDA NEAR/1 antagonist*) OR (SSRI OR SSRIs)) AND ((randomized controlled trial) OR (controlled clinical trial) OR (randomised OR randomized) OR placebo* OR (drug therapy) OR ab(randomly) OR ab(trial) OR ab(groups)) AND (su(child development disorders, pervasive) OR su(Developmental Disabilities) OR (PDD OR PDDs OR PDD-NOS OR ASD OR ASDs) OR (pervasive development* disorder*) OR (pervasive NEAR/3 child*) OR (autis* OR asperger* OR kanner* OR Rett*) OR (childhood schizophrenia))

ClinicalTrials.gov

Advanced search

53 Studies found for: Interventional Studies | Autism OR Autism Spectrum Disorder OR ASPERGER OR RETT OR PDD-NOS OR PERVASIVE DEVELOPMENT DISORDER | amantadine OR amisulpride OR aripiprazole OR atomoxetine OR bromocriptine OR buspirone OR Centedrin OR Concerta OR Daytrana OR citalopram OR clomipramine OR clozapine OR divalproex OR donepezil OR Equasym OR escitalopram OR fluoxetin

26 Studies found for: Interventional Studies | Autism OR Autism Spectrum Disorder OR ASPERGER OR RETT OR PDD-NOS OR PERVASIVE DEVELOPMENT DISORDER | fluvoxamine OR gabapentin OR guanfacine OR Haloperidol OR imipramine OR iamotrigine OR lamotrigine OR levetiracetam OR lurasidone OR memantine OR Metadate OR Methylin OR Methylphenidate OR milnacipran OR mirtazapine OR nortriptyline

78 Studies found for: Interventional Studies | Autism OR Autism Spectrum Disorder OR ASPERGER OR RETT OR PDD-NOS OR PERVASIVE DEVELOPMENT DISORDER | olanzapine OR oxytocin OR paliperidone OR paroxetine OR Phenidylate OR quetiapine OR risperidone OR Ritalin* OR rivastigmine OR secretin OR Sertraline OR Tianeptine OR Topiramate OR Tsentedrin OR valproate OR Venlafaxine OR Ziprasidone

29 Studies found for: Interventional Studies | Autism OR Autism Spectrum Disorder OR ASPERGER OR RETT OR PDD-NOS OR PERVASIVE DEVELOPMENT DISORDER | drug OR pharmacological OR medicine

WHO ICTRP

The WHO ICTRP site was affected by heavy search traffic in November 2020 due to COVID, therefore an abbreviated form of the search was used.

BASIC SEARCH

autism AND amantadine OR autism AND amisulpride OR autism AND aripiprazole OR autism AND atomoxetine OR autism AND bromocriptine OR autism AND buspirone OR autism AND Centedrin OR autism AND Concerta OR autism AND Daytrana OR autism AND citalopram OR autism AND clomipramine OR autism AND clozapine OR autism AND divalproex OR autism AND donepezil OR autism AND Equasym OR autism AND escitalopram OR autism AND fluoxetin [49 RECORDS]

Autism AND fluvoxamine OR Autism AND gabapentin OR Autism AND guanfacine OR Autism AND Haloperidol OR Autism AND imipramine OR Autism AND iamotrigine OR Autism AND lamotrigine OR Autism AND levetiracetam OR Autism AND lurasidone OR Autism AND

memantine OR Autism AND Metadate OR Autism AND Methylin OR Autism AND Methylphenidate OR Autism AND milnacipran OR Autism AND mirtazapine OR Autism AND nortriptyline [34 records]

Autism AND olanzapine OR Autism AND oxytocin OR Autism AND paliperidone OR Autism AND paroxetine OR Autism AND Phenidylate OR Autism AND quetiapine OR Autism AND risperidone OR Autism AND Ritalin OR Autism AND rivastigmine OR Autism AND secretin OR Autism AND Sertraline OR Autism AND Tianeptine OR Autism AND Topiramate OR Autism AND Tsentedrin OR Autism AND valproate OR Autism AND Venlafaxine OR Autism AND Ziprasidone [145 records]

Searching other resources

We contacted study authors when outcomes relevant to this review were either not reported fully or were reported using data not suitable for use in systematic reviews. Where contact details were no longer valid (such as an email bouncing) we made further attempts to find up-to-date details of the relevant researchers. We tried to contact study authors at least twice to request further information and noted if a reply had not been received. We requested information regarding the following studies.

Study ID	Contact person
Asabadadi 2013	Shahin Akhondzadeh
Belsito 2001	Karin Belsito
Chugani 2016	Diane Chugani
Ghaleiha 2013	Shahin Akhondzadeh
Ghaleiha 2015	Shahin Akhondzadeh
Ghaleiha 2016	Shahin Akhondzadeh
Handen 2000	Benjamin Handen
Handen 2005	Benjamin Handen
Handen 2008	Benjamin Handen
Handen 2011	Benjamin Handen
Hollander 2012	Eric Hollander
	Evdokia Anagnostou
Kern 2001a	Janet Kern
Kern 2002	Janet Kern
KIng 2001	Bryan King
Mace 2001	Nathan Blum
McDougle 1996	Christopher McDougle
Miral 2008	Suha Miral
Mohammadi 2013	Shahin Akhondzadeh
Molloy 2002	Cynthia Molloy

(Continued)

Mouti 2014	Molly O'Sullivan
	Dinah Reddihough
Munesue 2016	Toshio Munesue
Nagaraj 2006	Ravishankar Nagaraj
Nikoo 2015	Shahin Akhondzadeh
Noone 2014	Rachel Noone
Novotny 2004	Eric Hollander
Posey 2005	David Posey
Remington 2001	Gary Remington
Rezaei 2010	Shahin Akhondzadeh
Sandler 1999	Adrian Sandler
Wasserman 2006	Stacey Wasserman
	Evdokia Anagnostou

Appendix 2. Original search strategy

Ovid MEDLINE search strategy

1 exp child development disorders, pervasive/

2 Developmental Disabilities/

3 pervasive development$ disorder$.tw.

4 (pervasive adj3 child$).tw.

5 (PDD or PDDs or PDD-NOS or ASD or ASDs).tw.

6 autis$.tw.

7 asperger$.tw.

8 kanner$.tw.

9 childhood schizophrenia.tw.

10 Rett$.tw.

11 or/1-10

12 Drug Therapy/

13 ((pharma$ or drug) adj1 (intervention$ or therap$ or treat$)).tw.

14 pharmacotherap$.tw.
15 Psychopharmacology/
16 (psychopharmacol$ or psycho-pharmacol$).tw.
17 "Off-Label Use"/

18 (off label or “off-label”).tw.
19 (novel adj1 (drug$ or medication$ or pharma$ or treatment$)).tw.
20 Amantadine/
21 Amantadine.mp.
22 exp Anticonvulsants/
23 (Anticonvulsant$ or anti-convulsant$).mp.
24 (antiepileptic$ or anti-epileptic$).mp.
25 exp Antidepressive Agents/
26 (antidepress$ or anti-depress$).mp.
27 exp Antipsychotic Agents/
28 (antipsychotic$ or anti-psychotic$).mp.
29 exp Antihypertensive Agents/
30 exp Antiparkinson Agents/
31 (antiparkinson or anti-parkinson).mp.
32 Aripiprazole.mp.
33 Central Nervous System Agents/
34 Cholinesterase Inhibitors/
35 Cholinesterase Inhibitor$.mp.
36 (acetylcholinesterase or acetyl-cholinesterase).mp.
37 citalopram/
38 citalopram.mp.
39 Clomipramine/
40 Clomipramine.mp.
41 Clonidine/
42 Clonidine.mp.
43 Clozapine/
44 Clozapine.mp.
45 divalproex.mp.
46 donepezil.mp.
47 Escitalopram.mp.
48 Fluoxetine/
49 Fluoxetine.mp.
50 Fluvoxamine/
51 Fluvoxamine.mp.
52 gabapentin.mp.
53 guanfacine/
54 guanfacine.mp.
55 Haloperidol/
56 Haloperidol.mp.
57 Imipramine/
58 Imipramine.mp.
59 lamotrigine.mp.
60 memantine/
61 memantine.mp.
62 Mirtazapine.mp.
63 mood stabili#er$.mp.
64 (NMDA adj1 (antagonist$ or receptor$)).mp.
65 Nortriptyline/
66 Nortriptyline.mp.

67 Olanzapine.mp.
68 Paliperidone.mp.
69 Paroxetine/
70 Paroxetine.mp.
71 Quetiapine.mp.
72 Risperidone/
73 Risperidone.mp.
74 Rivastigmine.mp.
75 exp Serotonin Uptake Inhibitors/
76 (SSRI or SSRIs).tw.
77 serotonin.mp.
78 Sertraline/

79 Sertraline.mp.
80 Tetracyclic$.mp.
81 Tianeptine.mp.
82 Tricyclic$.mp.
83 Venlafaxine.mp.
84 Ziprasidone.mp.
85 or/12-84
86 randomized controlled trial.pt.
87 controlled clinical trial.pt.
88 randomi#ed.ab.
89 placebo$.ab.
90 drug therapy.fs.
91 randomly.ab.
92 trial.ab.
93 groups.ab.
94 or/86-93
95 exp animals/ not humans.sh.
96 94 not 95
97 11 and 85 and 96

Appendix 3. Unused methods

We did not use the following methods for a range of reasons including insufficient details to conduct the planned subgroup analyses, the characteristics of included studies, and following advice from a statistician we decided that a network meta-analysis (NMA) was not feasible.

Criteria for considering studies for this review

Types of interventions

Had there been sufficient studies with direct comparisons of two or more interventions we would have primarily used these studies. However, the majority of studies compared one or more interventions to a placebo.

In the case of direct comparisons of two or more interventions, we would have assessed the plausibility of transitivity, and made indirect comparisons by including primary studies that compare relevant interventions to either placebo treatment, wait-list or no-treatment conditions, or an active common comparator. Transitivity requires the assumption that any patient that meets the inclusion criteria could reasonably be randomised among any selection of eligible interventions.

Measures of treatment effect

Relative treatment effects

We would have presented results from the network meta-analysis (NMA) as summary relative effect sizes (standardised mean difference (SMD) or odds ratio (OR)) for each possible pair of treatments.

Relative treatment ranking

We would have estimated the ranking probabilities for each treatment. This is the probability that each treatment is the first, second, third, etc. best in the network. We would have obtained a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA; Chaimani 2013), and mean ranks. SUCRA can also be expressed as a percentage and interpreted as the percentage of efficacy or safety of treatment that would be ranked first without uncertainty.

Unit of analysis issues

Studies with multiple intervention groups were anticipated in this area. Had we performed an NMA, data from any relevant multi-arm trial could have been retained in their original form and entered into the model accordingly.

Dealing with missing data

Had continuous data been missing, we would have imputed data using a 'last observation carried forward' approach. Had cases been missing from the first outcome measure, we would have analysed only the available data.

Assessment of heterogeneity

We would have assessed the assumption of transitivity visually, by examining the distribution of potential effect modifiers extracted; for example, whether antidepressants were administered the same way in studies comparing antidepressants to placebo and in those comparing antidepressants to antipsychotics.

Assessment of reporting biases

Had we conducted an NMA, and had data been sufficient, we would have used the comparison-adjusted funnel plot technique (Chaimani 2013).

Data synthesis

Methods for indirect and mixed comparisons

Had direct and indirect comparisons appeared to be in agreement, and had the assessment of transitivity seemed reasonable, we would have combined direct and indirect evidence to create mixed estimates of the relative effects of the different types of pharmacological interventions. We would have performed the NMA in STATA (Stata 2013), using the 'mvmeta' command (White 2012), and self-programmed STATA routines (Chaimani 2013).

Assessment of statistical heterogeneity

Assumptions when estimating the heterogeneity

Had we conducted an NMA, we would have assumed a common estimate for heterogeneity variance across different comparisons.

Measures and tests for heterogeneity

The assessment of statistical heterogeneity in the NMA would have been based on the magnitude of the heterogeneity variance parameter (τ^2) estimated from the NMA models. For dichotomous outcomes, the magnitude of the heterogeneity variance can then be compared with the empirical distribution described by meta-epidemiological studies (Savović 2012; Turner 2012).

Assessment of statistical inconsistency

Local approaches for evaluating inconsistency

We would have used the loop-specific approach to evaluate the presence of inconsistency locally. This method separately evaluates consistency in each closed loop of the network, where consistency is defined as the difference between direct and indirect estimates for a specific comparison in that loop (inconsistency factor). Then, the magnitude of the inconsistency factors and their 95% confidence intervals (CIs) can be used to infer the presence of inconsistency in each loop. We would have assumed a common heterogeneity estimate and presented the results of this approach graphically in a forest plot using the 'ifplot' command in STATA (Chaimani 2013).

Global approaches for evaluating inconsistency

Had we conducted a NMA, we would have conducted the following: check the assumption of consistency in the entire network, by using the 'design-by-treatment' model described by Higgins and colleagues (Higgins 2012). This method assesses different sources of inconsistency that can occur when studies with different designs (e.g. two-arm trials versus three-arm trials) give different results as well as disagreement between direct and indirect evidence. Using this approach, we would have inferred the presence of inconsistency from any source in the entire network based on a Chi^2 test. We would have performed the design-by-treatment model in STATA using the 'mvmeta' command.

Sensitivity analysis

Although we conducted some sensitivity analyses to assess whether the findings of this review are robust to the decisions made in the process of obtaining them, we could not perform some sensitivity analyses. Specifically, we could not conduct the following:

- Reanalysis excluding studies according to study quality issues, including those with low sample size, high risk of bias, or high attrition and dropout rate
- Reanalysis without imputing data for the missing participants
- Reanalysis using a fixed-effect model

Multiple treatment groups

If some studies had included more than one control group, each undergoing different yet equally eligible forms of 'management as usual' we would have combined the control groups to create a single pair-wise comparison. Had this strategy posed a problem for the investigation of heterogeneity, we would have compared each group separately as part of the subgroup analyses.

Cluster-randomised trials

We did not anticipate cluster-randomised trials, in which allocation to the intervention group has occurred by school, hospital or by community as opposed to by individual, in this research area.

Had this review included cluster-randomised trials we would have conducted the following: in the event that we had identified relevant cluster-randomised trials, it is likely that study authors would have controlled for a clustering effect when presenting their results. When this information was unclear, we would contact study authors for further information. If the clustering effect was not controlled for, we would have requested individual participant data to calculate an estimate of the intracluster correlation coefficient (ICC). If individual participant data were not available, we would have searched for external estimates of the ICC from similar studies or available resources.

If we could not find an appropriate ICC from any available resources, we would have sought statistical advice to obtain an estimate of the ICC and used this to reanalyse the trial data to obtain approximate correct analyses. We would then have entered these data into Review Manager Web software (RevMan Web 2021) to analyse effect sizes and CIs using the generic inverse variance method (Higgins 2022b).

HISTORY

Protocol first published: Issue 7, 2015

CONTRIBUTIONS OF AUTHORS

- Conception of the review: NL and authors of the protocol
- Design of the review: NL and authors of the protocol
- Co-ordination of the review: NL, DG
- Search and selection of studies for inclusion in review: DG, MI, MJ, NL
- Collection of data for the review: DG, MI, MJ, NL
- Assessment of the risk of bias, DG, MI, NL, MJ
- Analysis of data: MI, NL, DG
- Assessment of the certainty of the evidence: MI, DG, NL
- Interpretation of data: MI, DG, NL
- Writing of review: MI, DG, NL
- Author of protocol and revising final draft: PH
- All review authors contributed to the drafting and revising of the draft for important intellectual content.

DECLARATIONS OF INTEREST

Michelle Iffland is a Research Officer with the NDIS Quality and Safeguards Commission, NSW. The NDIS Quality and Safeguards Commission is committed to reducing and eliminating the use of restrictive practices in people with a disability.

Donna Gillies is the Director for Research and Practice Evidence with the NDIS Quality and Safeguards Commission, Penrith, NSW. The NDIS Quality and Safeguards Commission is committed to reducing and eliminating the use of restrictive practices in people with a disability.

Nuala Livingstone is a Quality Assurance Editor with the Cochrane Evidence Production and Methods Directorate, Central Editorial Service, and an Editor with Cochrane Developmental, Psychosocial and Developmental Problems (DPLP); UK. Nuala Livingstone was not involved in the editorial process for this article

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Philip Hazell (PH) reports payments for lectures, for Lilly, Janssen, Pfizer and Shire, and advisory boards for Lilly, Janssen and Shire related to the pharmacological management of child and adolescent mental disorders in general; paid to Sydney Local Health District; PH is a Consultant Psychiatrist for Sydney Local Health District, NSW, and an Editor with Cochrane Developmental, Psychosocial and Learning Problems, UK. PH reports being involved in a study eligible for inclusion in this review: *Multisite randomised control trail of fluoxetine for children and adolescents with autism;* the study was funded by NHMRC and hosted by Murdoch Children's Research Institute, VIC. The researchers retained complete control over the study design, methods, data analysis and reporting. PH was not involved in assessing the studies for eligibility, extracting data from the studies, or assessing the risk of bias or grading the certainty of the evidence; these methods were completed by two independent review authors (DG, MI, MJ, NL).

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Description of the intervention

The original classifications of medications for this review were to include: antidepressants, antipsychotics, cholinesterase inhibitors, mood stabilisers, and N-methyl-D-aspartate (NMDA) receptor antagonists. However, because these categories were based on both function and pharmacological receptor activity, we modified these categories based on function and, where possible, conducted subgroup analyses based on pharmacological action. The major drug classes that were used, therefore, were typical and atypical antipsychotics, ADHD-related drugs (both stimulant and non-stimulant), anticonvulsants, antidementia drugs, antidepressants, antiparkinsonian drugs, anxiolytics, neurohormones, and a number of drugs that did not fall into any of these classes that we grouped under an experimental category.

Objectives

"To generate a clinically useful ranking of available pharmacological interventions for BoC in autism, according to their safety, efficacy, and tolerability." After consultation with a statistician (who was not involved in the review in any other way), it was decided that a network meta-analysis was not feasible.

Unit of analysis issues

We originally planned to only include data from the first phase of cross-over trials in the analysis. We found that only a very small percentage of cross-over trials reported phase one data and as such, we decided to include data from all cross-over trials provided the participants were randomised. This was due to the large number of studies that would have been excluded from the review had we only included trials that reported phase data.

As the majority of cros-sover studies did not differentiate data from first and second phases we undertook sensitivity analyses to identify whether inclusion of these data had a differential effect on meta-analytic estimates.

Types of outcome measures

Due to the wide range of adverse effect data that we collected during this review, a post-protocol decision was made to categorise available data into the following groups; neurological, psychological, metabolic, musculoskeletal, cardiovascular, gastrointestinal, immune system, respiratory system, skin, urinary, and other.

We also decided to include improvement and relapse as outcomes because a few study authors reported either at least a 25% decrease (improvement) or a 25% increase (relapse) in ABC-Irritability scores. We included these outcomes because they are related to the primary outcome of irritability.

Summary of findings and assessment of the certainty of the evidence

During the course of this review, a very large number of different types of 'adverse effects' were found to be reported by the included studies. To make the summary of findings table more readable and useful, the clinical content experts on the review team were asked to prioritise the list of available adverse effects, to decide which should be presented in the summary of findings table. The clinical experts were blinded to the type or availability of evidence available for each type of adverse effect when they made this decision, to ensure their choice was based on clinical importance and not data availability. As a result of this prioritisation exercise, the decision was made to present a narrative summary of the most important adverse effects in the four most clinically important categories: neurological, psychological, metabolic, and musculoskeletal.

INDEX TERMS

Medical Subject Headings (MeSH)

Aggression; Antidepressive Agents [therapeutic use]; *Antipsychotic Agents [therapeutic use]; *Autism Spectrum Disorder [drug therapy]; Fatigue; Neurotransmitter Agents [pharmacology]; Quality of Life; *Self-Injurious Behavior [drug therapy]

MeSH check words

Adolescent; Adult; Child; Humans