Cochrane Library

Cochrane Database of Systematic Reviews

Pharmacological interventions for people with borderline personality disorder (Review)

Stoffers-Winterling JM, Storebø OJ, Pereira Ribeiro J, Kongerslev MT, Völlm BA, Mattivi JT, Faltinsen E, Todorovac A, Jørgensen MS, Callesen HE, Sales CP, Schaug JP, Simonsen E, Lieb K

Stoffers-Winterling JM, Storebø OJ, Pereira Ribeiro J, Kongerslev MT, Völlm BA, Mattivi JT, Faltinsen E, Todorovac A, Jørgensen MS, Callesen HE, Sales CP, Schaug JP, Simonsen E, Lieb K.
Pharmacological interventions for people with borderline personality disorder.
Cochrane Database of Systematic Reviews 2022, Issue 11. Art. No.: CD012956.
DOI: 10.1002/14651858.CD012956.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Pharmacological interventions for people with borderline personality disorder

Jutta M Stoffers-Winterling[1], Ole Jakob Storebø[2,3,4a], Johanne Pereira Ribeiro[2,4], Mickey T Kongerslev[4,5], Birgit A Völlm[6], Jessica T Mattivi[1], Erlend Faltinsen[2], Adnan Todorovac[2], Mie S Jørgensen[2], Henriette E Callesen[2], Christian P Sales[7,8], Julie Perrine Schaug[9], Erik Simonsen[10b], Klaus Lieb[1]

[1]Department of Psychiatry and Psychotherapy, University Medical Center Mainz, Mainz, Germany. [2]Psychiatric Research Unit, Psychiatry Region Zealand, Slagelse, Denmark. [3]Child and Adolescent Psychiatric Department, Region Zealand, Roskilde, Denmark. [4]Department of Psychology, University of Southern Denmark, Odense, Denmark. [5]District Psychiatric Services Roskilde, Region Zealand Mental Health Services, Roskilde, Denmark. [6]Department of Forensic Psychiatry, Center for Neurology, University Rostock, Rostock, Germany. [7]Duncan MacMillan House, Nottinghamshire Healthcare NHS Foundation Trust, Nottingham, UK. [8]Institute of Mental Health, Department of Psychiatry & Applied Psychology, Nottingham, UK. [9]Region Zealand Psychiatry, Center for Evidence Based Psychiatry, Slagelse, Denmark. [10]Research Unit, Mental Health Services, Copenhagen University Hospital, Psychiatry Region Zealand, Roskilde, Denmark

[a]Shares first authorship.. [b]Shares last authorship.

Contact: Ole Jakob Storebø, ojst@regionsjaelland.dk.

Editorial group: Cochrane Developmental, Psychosocial and Learning Problems Group.
Publication status and date: New, published in Issue 11, 2022.

Citation: Stoffers-Winterling JM, Storebø OJ, Pereira Ribeiro J, Kongerslev MT, Völlm BA, Mattivi JT, Faltinsen E, Todorovac A, Jørgensen MS, Callesen HE, Sales CP, Schaug JP, Simonsen E, Lieb K. Pharmacological interventions for people with borderline personality disorder. *Cochrane Database of Systematic Reviews* 2022, Issue 11. Art. No.: CD012956. DOI: 10.1002/14651858.CD012956.pub2.

ABSTRACT

Background

Among people with a diagnosis of borderline personality disorder (BPD) who are engaged in clinical care, prescription rates of psychotropic medications are high, despite the fact that medication use is off-label as a treatment for BPD. Nevertheless, people with BPD often receive several psychotropic drugs at a time for sustained periods.

Objectives

To assess the effects of pharmacological treatment for people with BPD.

Search methods

For this update, we searched CENTRAL, MEDLINE, Embase, 14 other databases and four trials registers up to February 2022. We contacted researchers working in the field to ask for additional data from published and unpublished trials, and handsearched relevant journals. We did not restrict the search by year of publication, language or type of publication.

Selection criteria

Randomised controlled trials comparing pharmacological treatment to placebo, other pharmacologic treatments or a combination of pharmacologic treatments in people of all ages with a formal diagnosis of BPD. The primary outcomes were BPD symptom severity, self-harm, suicide-related outcomes, and psychosocial functioning. Secondary outcomes were individual BPD symptoms, depression, attrition and adverse events.

Data collection and analysis

At least two review authors independently selected trials, extracted data, assessed risk of bias using Cochrane's risk of bias tool and assessed the certainty of the evidence using the GRADE approach. We performed data analysis using Review Manager 5 and quantified the statistical reliability of the data using Trial Sequential Analysis.

Main results

We included 46 randomised controlled trials (2769 participants) in this review, 45 of which were eligible for quantitative analysis and comprised 2752 participants with BPD in total. This is 18 more trials than the 2010 review on this topic. Participants were predominantly female except for one trial that included men only. The mean age ranged from 16.2 to 39.7 years across the included trials. Twenty-nine different types of medications compared to placebo or other medications were included in the analyses. Seventeen trials were funded or partially funded by the pharmaceutical industry, 10 were funded by universities or research foundations, eight received no funding, and 11 had unclear funding.

For all reported effect sizes, negative effect estimates indicate beneficial effects by active medication. Compared with placebo, no difference in effects were observed on any of the primary outcomes at the end of treatment for any medication.

Compared with placebo, medication may have little to no effect on BPD symptom severity, although the evidence is of very low certainty (antipsychotics: SMD -0.18, 95% confidence interval (CI) -0.45 to 0.08; 8 trials, 951 participants; antidepressants: SMD −0.27, 95% CI −0.65 to 1.18; 2 trials, 87 participants; mood stabilisers: SMD −0.07, 95% CI −0.43 to 0.57; 4 trials, 265 participants).

The evidence is very uncertain about the effect of medication compared with placebo on self-harm, indicating little to no effect (antipsychotics: RR 0.66, 95% CI 0.15 to 2.84; 2 trials, 76 participants; antidepressants: MD 0.45 points on the Overt Aggression Scale-Modified-Self-Injury item (0-5 points), 95% CI −10.55 to 11.45; 1 trial, 20 participants; mood stabilisers: RR 1.08, 95% CI 0.79 to 1.48; 1 trial, 276 participants).

The evidence is also very uncertain about the effect of medication compared with placebo on suicide-related outcomes, with little to no effect (antipsychotics: SMD 0.05, 95 % CI −0.18 to 0.29; 7 trials, 854 participants; antidepressants: SMD −0.26, 95% CI −1.62 to 1.09; 2 trials, 45 participants; mood stabilisers: SMD −0.36, 95% CI −1.96 to 1.25; 2 trials, 44 participants).

Very low-certainty evidence shows little to no difference between medication and placebo on psychosocial functioning (antipsychotics: SMD −0.16, 95% CI −0.33 to 0.00; 7 trials, 904 participants; antidepressants: SMD −0.25, 95% CI -0.57 to 0.06; 4 trials, 161 participants; mood stabilisers: SMD −0.01, 95% CI -0.28 to 0.26; 2 trials, 214 participants).

Low-certainty evidence suggests that antipsychotics may slightly reduce interpersonal problems (SMD −0.21, 95% CI −0.34 to -0.08; 8 trials, 907 participants), and that mood stabilisers may result in a reduction in this outcome (SMD −0.58, 95% CI -1.14 to -0.02; 4 trials, 300 participants). Antidepressants may have little to no effect on interpersonal problems, but the corresponding evidence is very uncertain (SMD −0.07, 95% CI -0.69 to 0.55; 2 trials, 119 participants).

The evidence is very uncertain about dropout rates compared with placebo by antipsychotics (RR 1.11, 95% CI 0.89 to 1.38; 13 trials, 1216 participants). Low-certainty evidence suggests there may be no difference in dropout rates between antidepressants (RR 1.07, 95% CI 0.65 to 1.76; 6 trials, 289 participants) and mood stabilisers (RR 0.89, 95% CI 0.69 to 1.15; 9 trials, 530 participants), compared to placebo.

Reporting on adverse events was poor and mostly non-standardised. The available evidence on non-serious adverse events was of very low certainty for antipsychotics (RR 1.07, 95% CI 0.90 to 1.29; 5 trials, 814 participants) and mood stabilisers (RR 0.84, 95% CI 0.70 to 1.01; 1 trial, 276 participants). For antidepressants, no data on adverse events were identified.

Authors' conclusions

This review included 18 more trials than the 2010 version, so larger meta-analyses with more statistical power were feasible. We found mostly very low-certainty evidence that medication may result in no difference in any primary outcome. The rest of the secondary outcomes were inconclusive. Very limited data were available for serious adverse events. The review supports the continued understanding that no pharmacological therapy seems effective in specifically treating BPD pathology. More research is needed to understand the underlying pathophysiologic mechanisms of BPD better. Also, more trials including comorbidities such as trauma-related disorders, major depression, substance use disorders, or eating disorders are needed. Additionally, more focus should be put on male and adolescent samples.

PLAIN LANGUAGE SUMMARY

What are the benefits and risks of medication for people with borderline personality disorder?

Key messages

This review is an update of a previous review on the same topic published in 2010. Although this review includes an additional 18 studies, the conclusions remain the same: there are probably no benefits and risks of medications for borderline personality disorder (BDP), but the evidence is unclear.

Better and larger studies comparing the effects of medication with placebo are needed. Such studies should focus on men, adolescents and those with additional psychiatric diagnoses.

What is BPD?

BPD affects how a person interacts with others and understands one's self. Although its exact causes are unclear, it is thought to result from a combination of genetic and environmental factors (e.g. stressful or traumatic life events when growing up). Approximately 2% of adults and 3% of adolescents are affected.

The symptoms of BPD can be grouped into four categories.

Instability in mood: People with BPD may experience intense feelings that change rapidly and are difficult to control. They may also feel empty and abandoned much of the time.

Cognitive distortions (disturbed patterns of thinking): People with BPD often have upsetting thoughts (e.g. they may think that they are a terrible person). They can have brief episodes of strange experiences (e.g. paranoid ideations or stress-induced dissociative experiences (i.e. feeling detached from the world around them).

Impulsive behaviour: People with BPD may act impulsively and do things that could harm themselves (e.g. when sad and depressed, they may self-harm or have suicidal feelings). They might also engage in reckless behaviour (e.g. drug misuse).

Intense but unstable relationships: People with BPD may find it difficult to keep stable relationships (e.g. they may feel very worried about being abandoned and might constantly text or call, or make threats to harm or kill themselves if the person leaves them).

A person only needs to experience five out of nine criteria across these categories to be given a diagnosis of BPD.

How is BPD treated?

No medication has been approved for the treatment of BPD. Nonetheless, a large proportion of people with BPD are given medications for sustained periods of time to alleviate their symptoms. The type of medication given is chosen based on its known effects on other disorders with similar symptoms.

Review question

We wanted to find out whether medications to treat BPD work better or worse than placebo; whether one medication works better than another; or whether one combination of medications work better than another combination of medications.

We wanted to look at how well medications worked on BPD severity, self-harm, suicide-related outcomes, and functioning (how well a person performs in everyday life).

We also wanted to find out if medications are associated with any unwanted side effects.

What did we do?

We searched for studies that compared the effects of different medications with placebo, another medication, or a combination of medications, in people diagnosed with BPD.

We compared and summarised the results and rated our confidence in the evidence based on factors such as sample size and methods used. Below, we present the findings from our key comparison: medication versus placebo.

What did we find?

We found 46 studies that involved 2769 people with BPD. The smallest study had 13 participants and the largest 451 participants. There were four studies with more than 100 participants. Except for one study that included men only, all studies included women. The average age of the participants ranged from 16 years to 39 years. Most studies were conducted in outpatient settings (31 studies) in Europe (20 studies) and lasted between four and 52 weeks. Pharmaceutical companies fully or partially funded 16 studies.

The studies looked at the effects of 27 different medications, mostly classified as: 1) antipsychotics (drugs to treat psychosis where a person’s thoughts and mood are so impaired that the person has lost contact with reality); 2) antidepressants (drugs to treat depression); or 3) mood stabilisers (drugs to control and even out mood swings, reducing both high moods (mania) and low moods (depression)).

Compared with placebo, medications seem to make little to no difference to BPD severity, self-harm, suicide-related outcomes, and psychosocial functioning. They may make little to no difference as to whether a person continues in a study or drops out. Compared to placebo, antipsychotics and mood stabilisers may make little to no difference to the occurrence of unwanted or harmful effects. No study reported on the side effects of antidepressants.

What are the limitations of the evidence?

Our confidence in the evidence varied between very low and low. The results of future research could differ from the results of this review. Four main factors reduced our confidence in the evidence. First, not all of the studies provided data about everything that we were interested in. Second, the results were very inconsistent across the different studies. Third, there were not enough studies to be certain about the results of our outcomes. Fourth, many studies did not clearly report how they were conducted.

How up-to-date is this evidence?

The evidence is up-to-date to February 2022.

Summary of findings 1. Antipsychotics compared with placebo for people with borderline personality disorder

Antipsychotics compared with placebo for people with borderline personality disorder

Patient or population: people with borderline personality disorder

Settings: inpatient and outpatient

Intervention: antipsychotics

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Antipsychotics				
BPD symptom severity Timing of outcome assessment: end of treatment (5 to 12 weeks treatment duration)	-	The mean score in the intervention groups was **0.18 SD lower** (0.45 lower to 0.08 higher, I^2 = 70%) than in the placebo group	-	951 (8 trials)	⊕⊖⊖⊖ **Very Low[a,b]**	An SMD of 0.18 represents a small effect. **TSA-adjusted CI is −3.27 to 0.86 on the Zanarini BPD scale. Z value in futility area TSA DARIS = 951 TSA in futility area
Self-harm Timing of outcome assessment: end of treatment (8 to 24 weeks treatment duration)	**310 per 1000**	**208 per 1000** (211 less to 127 more self-harm incidents than in the placebo group)	**RR 0.66** (95% CI 0.15 to 2.84, I^2 = 67%)	76 (2 trials)	⊕⊖⊖⊖ **Very Low[c,d]**	-
Suicide-related outcomes Timing of outcome assessment: end of treatment (6 to 12 weeks treatment duration)	-	The mean score in the intervention groups was **0.05 SD higher** (0.18 lower to 0.29 higher, I^2 = 55%) than in the placebo group	-	854 (7 trials)	⊕⊖⊖⊖ **Very Low[a,e]**	A SMD of 0.05 represents a marginal effect. RR 0.73 (95% CI 0.31 to 1.73; 2 trials, 61 participants), low-certainty evidence

Psychosocial functioning Timing of outcome assessment: end of treatment (5 to 12 weeks treatment duration)	-	The mean score in the intervention groups was **0.16 SD lower** (0.33 lower to 0.00 lower, I^2 = 75%) than in the placebo group	-	904 (7 trials)	⊕⊖⊖⊖ **Very Low[a,f,g]**	A SMD of 0.16 represents a small effect.
Interpersonal problems Timing of outcome assessment: end of treatment (5 to 12 weeks treatment duration)	-	The mean score in the intervention groups was **0.21 SD lower** (0.34 lower to 0.08 lower, I^2 = 0%) than in the placebo group	-	907 (8 trials)	⊕⊕⊖⊖ **Low[a]**	A SMD of 0.21 represents a small effect. TSA-adjusted CI is −0.60 to 0.08 on Zanarini BPD Scale -Interpersonal Problem Index TSA DARIS = 386
Attrition Timing of outcome assessment: end of treatment (5 weeks to 6 months treatment duration)	**325 per 1000**	**361 per 1000** (36 less to 123 more than in the placebo group dropped out)	**RR 1.11** (0.89 to 1.38; I^2 = 35%)	1216 (13 trials)	⊕⊖⊖⊖ **Very Low[a,h]**	TSA-adjusted CI is 0.74 to 2.13 TSA DARIS = 2008
Non-serious adverse events Timing of outcome assessment: end of treatment (8 to 12 weeks treatment duration)	**560 per 1000**	**599 per 1000** (56 less to 162 more than in the placebo group dropped out)	**RR 1.07** (0.90 to 1.29; I^2 = 57%)	814 (5 trials)	⊕⊖⊖⊖ **Very Low[a,i]**	TSA-adjusted CI is 0.79 to 1.47 TSA DARIS = 1250 TSA in futility area

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**TSA did not include cross-over trials.
CI: Confidence interval; **RR:** Risk Ratio; **BPD**: Borderline Personality Disorder; **SD**: standard deviation; **SMD**: Standardised mean difference **TSA** Trial Sequential Analysis, **DARIS**: Diversity-adjusted required information size

GRADE Working Group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

[a]We downgraded the evidence two levels due to risk of bias of the included studies (indication of selective outcome reporting, indication of incomplete outcome data presented in the included studies) (rated by HEC and OJS (E))
[b]We downgraded the evidence one level due to inconsistency (I^2= 70%) (rated by HEC and OJS)

[c] We downgraded the evidence two levels due to imprecision (wide CI around the pooled effect estimate suggest both an appreciable effect and no effect; few participants included in the studies) (rated by HEC and OJS)
[d] We downgraded the evidence one level due to inconsistency (I^2 = 67%) (rated by HEC and OJS (D))
[e] We downgraded the evidence one level due to inconsistency (I^2 = 55%) (rated by HEC and OJS)
[f] We downgraded the evidence one level due to inconsistency (I^2 = 75%) (rated by HEC and OJS)
[g] We downgraded the evidence one level due to imprecision (wide CI around the pooled effect estimate suggest both an appreciable effect and no effect) (rated by HEC and OJS)
[h] We downgraded the evidence one level due to imprecision (wide CI around the pooled effect estimate suggest both an appreciable effect and no effect; the TSA that did not reach the required information size (RIS)) (rated by HEC and OJS)
[i] We downgraded the evidence one level due to inconsistency (I^2= 57%) (rated by HEC and OJS)

Summary of findings 2. Antidepressants compared with placebo for people with borderline personality disorder

Antidepressants compared with placebo for people with borderline personality disorder

Patient or population: people with borderline personality disorder

Settings: inpatient, outpatient, partial inpatient and partial outpatient

Intervention: antidepressants

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Antidepressant				
BPD symptom severity Timing of outcome assessment: end of treatment (5 to 6 weeks treatment duration)	-	The mean score in the intervention group was **0.27 SD lower** (0.65 lower to 1.18 higher, I^2= 73) than in the placebo group	-	87 (2 trials)	⊕⊖⊖⊖ **Very low[a,b]**	-
Self-harm Assessed with: OAS-M (Self-injury; scale range: 0-40 (0 = no aggression, 40 = maximum grade of aggression) Timing of outcome assessment: end of treatment (12 weeks treatment duration)	The mean reduction in self-harm was 6.55 in the control group	The mean score in the intervention group was**0.45 points higher** (10.55 lower to 11.45 higher) than in the placebo group	-	20 (1 trial)	⊕⊖⊖⊖ **Very low[a,c]**	-

Suicide-related outcomes Timing of outcome assessment: end of treatment (6 to 12 weeks treatment duration)	-	The mean score in the intervention groups was **0.26 SD lower** (1.62 lower to 1.09 higher, I^2 = 80%) than in the placebo group	-	45 (2 trials)	⊕⊖⊖⊖ **Very low[a,c,d]**	-RR 1.00 (95% CI 0.71 to 1.4; 1 trial, 49 participants). Very low-certainty evidence
Psychosocial functioning Timing of outcome assessment: end of treatment (5 to 12 weeks treatment duration)	-	The mean score in the intervention groups was **0.25 SD lower** (0.57 lower to 0.06 higher, I^2 = 0%) than in the placebo group	-	161 (4 trials)	⊕⊖⊖⊖ **Very low[a,e]**	-
Interpersonal problems Timing of outcome assessment: end of treatment (5 weeks treatment duration)	-	The mean score in the intervention groups was **0.07 SD lower** (0.69 lower to 0.55 higher, I^2 = 66%) than in the placebo group	-	119 (2 trials)	⊕⊖⊖⊖ **Very low[a,f]**	-
Attrition Timing of outcome assessment: end of treatment (5 weeks to 6 months treatment duration)	**170 per 1000**	**182 per 1000** (59 less to 129 more than in the placebo group dropped out)	**RR 1.07** (95% CI 0.65 to 1.76; I^2 = 0%)	289 (6 trials)	⊕⊕⊖⊖ **Low[c, g]**	TSA-adjusted CI is 0.07 to 14.98 TSA DARIS = 1816
Non-serious adverse events Timing of outcome assessment: end of treatment	no data available	no data available	no data available	no data available	no data available	no data available

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk Ratio; **BPD**: Borderline Personality Disorder;**OAS-M:** Modified Overt Agression Scale; **SD**: standard deviation; **TSA** Trial Sequential Analysis, **DARIS**: Diversity-adjusted required information size

GRADE Working Group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

[a]We downgraded the evidence by two levels due to imprecision (wide CI around the pooled effect estimate suggest both an appreciable effect and no effect; few patients included) (rated by HEC and OJS)
[b]We downgraded the evidence one level due to inconsistency (a high I^2 score of 73%) (rated by HEC and OJS)

[c]We downgraded the evidence one level due to risk of bias (indication selective outcome reporting in the included study) (rated by HEC and OJS)
[d]We downgraded the evidence one level due to inconsistency (a high I^2 score of 80%) (rated by HEC and OJS)
[e]We downgraded the evidence one level due to risk of bias (indication of incomplete outcome data) (rated by JSW and OJS)
[f]We downgraded the evidence one level due to inconsistency (a high I^2 score of 66%) (rated by HEC and OJS)
[g]We downgraded the evidence one level due to imprecision (wide CI around the pooled effect estimate suggest both an appreciable effect and no effect; TSA not reaching required information size (RIS)) (rated by HEC and OJS)

Summary of findings 3. Mood stabilisers compared with placebo for people with borderline personality disorder

Mood stabilisers compared with placebo for people with borderline personality disorder

Patient or population: people with borderline personality disorder

Settings: inpatient, outpatient, inpatient and outpatient

Intervention: mood stabilisers

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Mood stabilisers				
BPD symptom severity Timing of outcome assessment: end of treatment (6 to 52 weeks treatment duration)	-	The mean score in the intervention groups was **0.07 SD lower** than in the placebo group (0.43 lower to 0.57 higher, I^2 = 55%)	-	265 (4 trials)	⊕⊖⊖⊖ **Very low[a,b,c]**	A SMD of 0.07 represents a marginal effect.
Self-harm Timing of outcome assessment: end of treatment (52 weeks treatment duration)	**345 per 1000**	**373 per 1000** (72 less to 166 more self-harm incidents than in the placebo group)	**RR 1.08** (95% CI 0.79 to 1.48)	276 (1 trial)	⊕⊖⊖⊖ **Very low[d,e]**	-
Suicide-related outcomes Timing of outcome assessment: end of treatment (6 to 10 weeks treatment duration)	-	The mean score in the intervention group was **0.36 SD lower** than in the placebo group (1.96 lower to 1.25 higher, I^2 = 81%)	-	44 (2 trials)	⊕⊖⊖⊖ **Very low[d,e,f]**	-

Psychosocial functioning Timing of outcome assessment: end of treatment (32 days to 6 weeks treatment duration)	-	The mean score in the intervention groups was **0.01 SD lower** than in the placebo group (-0.28 lower to 0.26 higher, I^2 = 0%)	-	214 (2 trials)	⊕⊖⊖⊖ **Very low**[d,e,g]	A SMD of 0.01 represents a marginal effect. RR 0.64 (95% CI 0.37 to 1.11; 1 trial, 16 participants).Very low-certainty evidence
Interpersonal problems Timing of outcome assessment: end of treatment (32 days to 24 weeks)	-	The mean score in the intervention groups was **0.58 SD lower** than in the placebo group (1.14 lower to 0.02 lower, I^2 = 73%)	-	300 (4 trials)	⊕⊕⊖⊖ **Low**[g,h]	A SMD of 0.58 represents a moderate effect.
Attrition Timing of outcome assessment: end of treatment (32 days to 24 weeks treatment duration)	**260 per 1000**	**208 per 1000** (6 less to 154 more than in the placebo group dropped out)	**RR 0.89** (95% CI 0.69 to 1.15; I^2 = 0%)	530 (9 trials)	⊕⊕⊖⊖ **Low**[a,i]	TSA-adjusted CI is 0.37 to 2.23 TSA DARIS = 1300
Non-serious adverse events Timing of outcome assessment: end of treatment (6 weeks treatment duration)	**670 per 1000**	**563 per 1000** (201 less to 7 more than in the placebo group dropped out)	**RR 0.84** (95% CI 0.70 to 1.01; I^2 = 0%)	276 (1 trial)	⊕⊖⊖⊖ **Very low**[a,e]	-

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk Ratio; **BPD**: Borderline Personality Disorder; **NA:** not applicable; **OAS-M**: Modified Overt Agression Scale; **CGI-I**: Clinical Global Impression scale - Improvement **SD**: standard deviation; **SMD**: Standardised mean difference; **TSA** Trial Sequential Analysis, **DARIS:** Diversity adjusted required information size

GRADE Working Group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

[a] We downgraded the evidence one level due to risk of bias in the included studies (indication of incomplete outcome data in the included studies) (rated by HEC and OJS)
[b] We downgraded the evidence one level due to imprecision (wide CI around the pooled effect estimate suggest both an appreciable effect and no effect) (rated by HEC and OJS)
[c] We downgraded the evidence one level due to inconsistency (a high I^2 score of 55%) (rated by HEC and OJS)
[d] We downgraded the evidence one level due to risk of bias (indication of selective outcome reporting in the included study) (rated by HEC and OJS)

[e]We downgraded the evidence two levels due to imprecision (wide CI around the pooled effect estimate suggest both an appreciable effect and no effects; results based on 1 study or few participants) (rated by HEC and OJS)
[f]We downgraded the evidence one level due to inconsistency (a high I^2 score of 81%) (rated by HEC and OJS)
[g]We downgraded the evidence one level due to inconsistency (a high I^2 score of 73%) (rated by HEC and OJS)
[h]We downgraded the evidence one level due to risk of bias (indication of incomplete outcome data and vested interests)
[i]We downgraded the evidence one level due to imprecision (wide CI around the pooled effect estimate suggest both an appreciable effect and no effects; TSA not reaching required information size (RIS)) (rated by HEC and OJS)

BACKGROUND

Description of the condition

According to current diagnostic criteria, borderline personality disorder (BPD) is characterised by a pervasive pattern of instability in affect regulation, impulse control, interpersonal relationships, and self-image (APA 2013; WHO 1993). Clinical hallmarks include emotional dysregulation, impulsive aggression, repeated self-injury, and chronic suicidal tendencies (Bohus 2021; Fonagy 2009; Lieb 2004). BPD is being widely researched in order to better understand and treat the disorder-specific symptoms. Its importance stems from the large amount of suffering of the persons concerned (Bohus 2021; Stiglmayr 2005; Zanarini 1998), debilitating functional impairments (Gunderson 2011a; Gunderson 2011b; Niesten 2016; Skodol 2002; Soetmann 2008b), and from the significant impact it has on mental health services (Cailhol 2015; Hörz 2010; Soetmann 2008a; Tyrer 2015; Zanarini 2004a; Zanarini 2012). The problem of deliberate self-harm is also a particular issue within this group (Ayodeji 2015; Kongerslev 2015; Linehan 1997; Ose 2021; Rossouw 2012). In medical settings, people with BPD often present after self-harming behaviour or in suicidal crisis and are treated in emergency settings, often involving repeated psychiatric hospitalisations (Bender 2006; Cailhol 2015). It is estimated that about 60% to 78% of people with BPD attempt suicide (Links 2009), though the rate of completed suicides is far less (Bohus 2021). Zanarini and colleagues found suicide rates of 4.5% during 16 years of follow-up (Zanarini 2015), whereas Stone 1993 reported a suicide rate of 8.5% after 16.5 years. Study estimates of the lifetime risk of suicide among people with BPD range from 3% to 10% (Links 2009). Suicidal behaviour (e.g. behaviour that could cause death such as medication overdosing and purposely crashing in traffic) is reported to occur in up to 84% of people with BPD (Goodman 2012; Soloff 2002). Common risk factors associated with completed suicide are low socioeconomic status, poor psychosocial adjustment, family history of suicide, previous psychiatric hospitalisation, and absence of any outpatient treatment before the attempt (Soloff 2012).

The definition of BPD in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) Fifth Edition (DSM-5; APA 2013), Fourth Edition Text Revision (DMS-IV-TR; APA 2000) and Fourth Edition (DSM-IV; APA 1994) comprises nine criteria that cover the features mentioned above. At least five criteria should be met for a definite categorical BPD diagnosis to be made, and four criteria for probable diagnosis (see Appendix 1). In the alternative diagnostic classification system of the World Health Organization (WHO), the *International Classification of Diseases*, which is currently in its tenth edition (ICD-10; WHO 1993), the relating condition is referred to as "Emotionally unstable personality disorder (F60.3)", of which there is an impulsive type (F60.30) and a borderline type (F60.31: see Appendix 2). The latter essentially overlaps with the DSM-IV definition. There are 10 possible criteria in the ICD-10 diagnosis for BPD that very closely resembles the DSM-IV/5 criteria (Ottosson 2002), with the exception of one criterion which is not included in the DSM ("4. Difficulty in maintaining any course of action that offers no immediate reward"; WHO 1993). Out of the 10 ICD-10 criteria, at least five must be met, one of which must be "a marked tendency to quarrelsome behaviour and to conflicts with others, especially when impulsive acts are thwarted or criticised". Currently, the successive version of the ICD (ICD-11) is being finalised (WHO 2021). It will abolish any personality disorder categories for the sake of a general description of personality disorder in terms of severity (mild, moderate, severe) and five personality trait domains (negative affectivity, dissociality, anankastia, detachment, and disinhibition). In addition, it will include a "borderline specifier" (6D11.5), which can additionally be diagnosed and which will essentially consist of all nine BPD criteria defined in DSM-5 (Mulder 2021; WHO 2021; see Appendix 2).

Overall, the prevalence of BPD in the general population is estimated to be about 1.5% (Torgersen 2012), with findings of single epidemiological studies ranging between 0.6% (Coid 2006) and 2.7% (Trull 2010). In clinical populations, BPD occurs frequently (Munk-Jørgensen 2010), with studies reporting a prevalence ranging from 9.3% to 46.3% and a mean point prevalence across studies of 28.5% (Torgersen 2012). Though BPD is predominantly diagnosed in women (75%; APA 2000, APA 2013, Widiger 1993), it is estimated to be equally prevalent in men by representative community studies (Coid 2006; Grant 2008; Lenzenweger 2007; Ten Have 2016; Tomko 2014; Torgersen 2001; Torgersen 2012). Reasons for this obvious gender bias are discussed as: bias in the diagnostic criteria, bias in the application of the diagnostic criteria by clinicians, bias in diagnostic thresholds across disorders more prevalent in one gender or another, biased population sampling, bias in the assessment instruments, and bias in the diagnostic construct itself (Widiger 1998).

BPD commonly co-occurs with mood disorders, substance misuse, eating disorders, post-traumatic stress disorder (PTSD), attention-deficit hyperactivity disorder (ADHD), and is also associated with other personality disorders (Coid 2006; Lenzenweger 2007; Stepp 2012; Storebø 2014; Tomko 2014).

Although the short- to medium-term outcome of BPD is poor, symptomatic remission rates of about 85% to 88% have been reported within 10 years (Gunderson 2011b; Zanarini 2007). Another, smaller prospective longitudinal study reported a diagnostic remission rate of 55% after 10 years (Alvarez-Tomas 2017). However, remission only means that diagnostic criteria are no longer fulfilled; it does not indicate the absence of any symptoms. Indeed, whereas acute symptoms — such as self-mutilation, help-seeking suicide threats or attempts and impulsivity — in most cases decrease with time, affective symptoms reflecting areas of chronic dysphoria, such as chronic feelings of emptiness, intense anger or a profound sense abandonment, largely remain (Zanarini 2007). Therefore, the majority of people with BPD still have significant levels of symptoms and experience severe and persistent impairment in social functioning, high unemployment rates, physical ill-health, and a substantially reduced life expectancy (Bohus 2021; Kongerslev 2015; Ng 2016; Schneider 2019). 'Good recovery', defined as being in remission of BPD for a minimum of two years, good social functioning in terms of having at least one emotionally sustaining relationship, and good vocational functioning (working or attending school consistently on a full-time basis) was only achieved by 50% of individuals with BPD after 10 years of prospective follow-up, and 59% after 20 years of follow-up (Zanarini 2012; Zanarini 2018). Younger age seems to be associated with a higher probability of diagnostic remission in the long term (Alvarez-Tomas 2019), indicating the importance of early diagnosis and intervention (Chanen 2017).

BPD onsets happen in young people, i.e. between puberty and emerging adulthood (Chanen 2013). Today, the diagnosis is regarded reliable and valid also in adolescents, as a similarity in

prevalence, phenomenology, and stability has been observed, as well as a markedly different course and outcome as compared to other disorders (Chanen 2017) or ordinary problems. For a long time, clinicians were reluctant to diagnose BPD (not only, but specifically) in adolescents due to the assumed stigma, and wanting to avoid giving young people a diagnosis believed to be an 'uncurable' disorder. However, due to emerging evidence, there is now consensus among the scientific community that the disorder should be detected and diagnosed as early as possible, given that helpful treatments do exist, and that later interventions tend to reinforce functional impairment, disability and therapeutic nihilism (Chanen 2013; Chanen 2017).

Risk factors for a poorer long-term outcome are comorbid substance use disorders, PTSD, and anxiety cluster disorders (Zanarini 2005; Zanarini 2007), a family history of psychiatric disorder (especially mood disorders and substance use disorders), as well as individual factors such as older age, longer treatment history, pathological childhood experiences, and adult psychosocial functioning (Bohus 2021; Chanen 2012; Kongerslev 2015; Zanarini 2007).

People with BPD often have difficulties achieving and maintaining vocational and social functioning over time (Hastrup 2019b; Zanarini 2010). Furthermore, treatment-seeking people with personality disorders, such as BPD, pose a high economic burden on society due to a frequent and often long-term utilisation of both psychiatric and emergency services as well as loss of occupational function and income (Hastrup 2019a; Van Asselt 2007). Effective treatments could potentially decrease the high costs associated with the condition (Soetmann 2008a).

In summary, BPD is a condition that has been extensively studied and has a major impact on health services (Bode 2017; Jacobi 2021; Meuldijk 2017). The recovery from symptoms or functional impairment (or both) was previously considered likely for only a low percentage of people diagnosed with BPD. However, the long-term course is better than what was previously assumed, due to more favourable symptomatic recoveries (Zanarini 2012). Nonetheless, people with BPD continue to have considerable interpersonal and functional problems, and sustainable recovery appears difficult to attain (Biskin 2015; Kongerslev 2015; Rossouw 2012).

Description of the intervention

To date, all major treatment guidelines consider psychotherapy as the treatment of choice for BPD and assign medications an adjunctive role (e.g. APA 2001; Bateman 2015; Cristea 2017; DGPPN 2009; Herpertz 2007; NHMRC 2013; NICE 2009; Simonsen 2019; Storebø 2020). However, the large majority of people with BPD are prescribed psychotropic medications during the course of their illness. This may be the case in times of crisis, when people with BPD present to mental health services with raised suicidality or parasuicidality, impulsivity-associated outbreaks, psychotic-like exacerbations, severe dissociations or aggravations of comorbid conditions (e.g. mood disorders), and so medications are used to achieve short-term stabilisation (NHMRC 2013; NICE 2009; Riffer 2019). Such crisis interventions will not be considered in this review, but are subject to another Cochrane Review, which is currently being updated (Borschmann 2012).

In contrast to short-term crisis medication, up to 84.1% of people with BPD who are engaged in treatment have been reported to use standing (i.e. long-term) psychotropic medications (Bender 2001; Zanarini 2015), and as many as 92% have been reported to use any psychotropic medication for a non-specified period of time (Paton 2015). Indeed, it is a common finding that people with BPD are more likely to use psychotropic medications than people with other psychiatric conditions such as major depressive disorder (Bender 2001; Bender 2006), mood or anxiety disorders in general (Ansell 2007), or other personality disorders (Zanarini 2004a).

Studies across different countries show that antidepressants are the class of medication most often prescribed to people with BPD (Bender 2001; Knappich 2014; Makela 2006; Paton 2015; Sansone 2003; Zanarini 2015). Zanarini and colleagues found that 79.7% of people with BPD were taking antidepressant medication, followed by anxiolytics (46.6%), neuroleptics (38.6%), and mood stabilisers (35.9%) (Zanarini 2015). They also found that about 71% of people with BPD were using medications at six-year follow-up (Zanarini 2004a; Zanarini 2004b), and that they were still more likely to be using antidepressants, mood stabilisers, antipsychotics or anxiolytics than Axis-II comparison participants at 16-year follow-up (Zanarini 2015). Additionally, polypharmacy is common, with reports of people with BPD taking, on average, 2.02 psychotropic medications at a time (Ansell 2007), and up to 28.6% taking four or more medications (Zanarini 2004a; Zanarini 2004b).

There is no stringent or binding classification of psychotropic medications. In routine clinical care, the most commonly used classification is likely to be that which builds on the Anatomical Therapeutic Chemical (ATC) classification (WHO Collaborating Center for Drug Statistics.), where medications are grouped primarily by indication, such as antidepressants, antipsychotics, antidementive drugs, etc. This classification has been criticised for various reasons, including: not considering the fact that many psychotropic medications are not only used for one, but several indications, which may confuse consumers and lower adherence; the grouping of too heterogeneous kinds of medications into the same group; and having too close connection to marketing claims of the pharmaceutical industry (names may be mistaken to imply that the drugs definitely are effective as regards the respective outcomes; Brühl 2017). In order to target these shortcomings, the Neuroscience-based Nomenclature has been developed (Brühl 2017; NbN3 2021), with the aim of moving from a disease-based classification system to one that is pharmacologically driven, focusing on modes of actions rather than symptoms. This review use traditional categories, such as antipsychotics, antidepressants, mood stabilisers, antidementive medications, etc., as these might be most familiar to consumers and clinicians in the field as well as healthcare professionals (who might not have a background in psychiatry or psychology). A translation of these terms into the Neuroscience-based Nomenclature (NBN) (NbN3 2021) can be found in Appendix 3.

In summary, prescription rates of psychotropic medications are high among people with BPD and these medications are often administered for sustained periods of time, even though medication is only advised as an adjunctive to psychotherapy (Bateman 2015; Bohus 2021; NHMRC 2013; NICE 2018). Different classes of medication are used, with antidepressants being the most frequent, but there is no standard medication treatment. Currently, any medication use in BPD is off-label (if not used to target associated psychopathology, such as depression or anxiety, for which there is evidence for use), but up to 82% of people

with BPD without comorbid conditions still receive medications to directly target BPD symptoms (Paton 2015).

How the intervention might work

The most important pharmacological domains and modes of action of each included medication are presented in Appendix 3. Essentially, the psychotropic medications included in this review are thought to work - at least partially - in ways described below:

The **serotonergic system** has been associated with mood (depressive mood, anxiety), impulsiveness and aggressiveness (Herpertz 2007). Antidepressants effectuate a higher concentration and longer availability of serotonin in the synaptic cleft by preventing its reuptake (e.g. selective serotonin reuptake inhibitors (SSRIs)), or degradation (e.g. monoamin oxidase inhibitors (MAOIs)). As an inverse relationship between serotonin levels in the brain and low mood, as well as increased impulsive behaviour, has been demonstrated, substances increasing serotonin availability might improve mood and lower impulsive behaviour.

The monoamines norepinephrine and dopamine have also been implicated in emotion and reward. **Norepinephrine** is related to stress as it helps the brain and body to prepare for immediate action ('fight-flight-response'). It increases arousal, alertness and attention, but is also related to restlessness and anxiety. **Dopamine** is a neurotransmitter which not only plays a major role in schizophrenia but is also related to executive functions and arousal, along with reward and motivation. Substances which increase the level of these monoamines might therefore have an impact on perception and behavioural choices.

GABA (gamma-aminobutyric acid) is an inhibitory neurotransmitter that reduces neural excitability in the central nervous system. Heightened GABA levels have been shown to be associated with relaxing, anti-anxiety, and anti-convulsive effects.

Glutamate is an excitatory neurotransmitter in the central nervous system which is involved in e.g. motor-executive functions, as well as learning and memory.

Opioid peptides bind as agonists to opioid receptors and act as endogenous analgesics. They have modulating effects on mood and have a role in the aetiology and maintenance of substance use disorders. Opioid antagonists are used in the treatment of opioid and alcohol use disorders, and opioid substances in the treatment of substance withdrawal.

Psychotropic medications may target one or several of these pharmacology domains and comprise one or more modes of action. However, it is unlikely that direct and immediate effects at the synapses can explain changes in mood, anxiety etc., since such changes only occur after weeks of treatment. Much more likely modes of actions are secondary effects on plastic brain adaptation processes, which are not well understood yet, especially in BPD.

Why it is important to do this review

BPD poses a major burden, both personal (Soetmann 2008b) and financial (Soetmann 2008a) on those directly affected, their relatives, as well as for society at large. Despite the frequent use of pharmacological interventions in clinical practice, and in research over the last three decades, any medication used in the treatment of BPD is off-label. Given the absence of reliable evidence being supportive of medication use, prescription is often undertaken based upon known effects on symptom clusters in other disorders, out of habit, ignorance, passed-on clinical rules of thumb or desperation (Aguglia 2019; Paris 2015; Pascual 2021; Riffer 2019; Zanarini 2004a). Clinicians and consumers, however, must be able to make informed decisions on the basis of up-to-date evidence (Ingenhoven 2015; Paris 2015; Silk 2015), allowing them to weigh up potential benefits and harms. This Cochrane Review aims to systematically identify, investigate, and present the current state of evidence on the topic of medications in BPD, and make suggestions about the directions for future trials.

This review supersedes a previous Cochrane Review on pharmacological interventions for BPD (Stoffers 2010). In addition to updating the former Cochrane Review, our study also seeks to address some of the methodological limitations of the preceding two reviews (Binks 2006; Stoffers 2010) by using updated methods, and including a more comprehensive search strategy. In order to do this transparently, we developed and published a new protocol prior to conducting this review (Stoffers-Winterling 2018). The Stoffers 2010 review came to the conclusion that the evidence available at that time indicated beneficial effects for some medications (i.e. second-generation antipsychotics, mood stabilisers and omega-3 fatty acids), but that the overall quality of the evidence was not robust enough to draw any reliable conclusions. In the proceeding 11 years, research has continued in the field, and new findings may change conclusions of the previous review. Therefore, an update of this review seems both appropriate and timely (Garner 2016).

OBJECTIVES

To assess the effects of pharmacological treatment for people with BPD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Individuals of all ages, in any setting, with a formal diagnosis of BPD according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) Third Edition (DSM-III; APA 1980), Third Edition Revised (DSM-III R; APA 1987), Fourth Edition (DSM-IV; APA 1994), Fourth Edition Text Revision (DSM-IV-TR; APA 2000), and Fifth Edition (DSM-5; APA 2013)), with or without comorbid conditions.

We required at least 70% of trial participants to have a formal diagnosis of BPD. We also included trials involving subsamples of people with BPD if data on these were available separately. We did not include trials that focused on people with mental impairment, organic brain disorder, dementia, or other severe neurologic diseases.

Types of interventions

Any medication or defined combination of medications administered at any dosage, prescribed to treat the disorder or its symptoms, compared to a placebo or active comparator medication(s) was eligible. We included trials that paired

medications with an adjunctive intervention (e.g. psychological therapies), providing this was given to participants in both the intervention and control arm, and the pharmacological intervention was unique to the treatment group.

Medication should have been prescribed continuously for a minimum duration of two weeks for the trial to be eligible for our review. In addition, we judged the actual duration required for inclusion in light of the specific mode of action of the medical agent. Medication should have been used to treat the disorder or symptoms thereof.

Types of outcome measures

Outcomes could either be self-rated or observer-rated by clinicians. We included only adequately validated measures (plus spontaneous reporting of adverse events).

Primary outcomes

1. BPD severity, as assessed by, for example, the Zanarini Rating Scale for Borderline Personality Disorder (Zan-BPD; Zanarini 2003), the Borderline Personality Disorder Severity Index (BPDSI-IV; Arntz 2003), or the Clinical Global Impression Scale for Borderline Personality Disorder Patients (CGI-BPD; Perez 2007).
2. Self-harm, in terms of the proportion of participants with self-harming behaviour, or as assessed by, for example, the Deliberate Self-harm Inventory (DSHI; Gratz 2001) or the Self-harm Behavior Questionnaire (SHBQ; Guttierez 2001).
3. Suicide-related outcomes, as assessed by, for example, the Suicidal Behaviours Questionnaire (SBQ; Osman 2001) or the Beck Scale for Suicidal Ideation (BSSI; Beck 1979) or in terms of the proportion of people with BPD with suicidal acts.
4. Functioning, as assessed by, for example, the Global Assessment Scale (GAS; Endicott 1976), the Global Assessment of Functioning Scale (GAF; APA 1987) or the Social Functioning Questionnaire (SFQ; Tyrer 2005).

Secondary outcomes

1. Anger, as assessed by, for example, the 'Hostility' subscale of the Symptom Checklist-90-Revised (SCL-90-R; Derogatis 1994), or the State-Trait Anger Expression Inventory (STAXI; Spielberger 1988).
2. Affective instability, as assessed by, for example, the relevant item or subscale on the Zan-BPD (Zanarini 2003), CGI-BPD (Perez 2007) or BPDSI-IV (Arntz 2003).
3. Chronic feelings of emptiness, as assessed by, for example, the relevant item or subscale on the Zan-BPD (Zanarini 2003), CGI-BPD (Perez 2007) or BPDSI-IV (Arntz 2003).
4. Impulsivity, as assessed by, for example, the Barrett Impulsiveness Scale (BIS; Barrett 1995), or the Anger, Irritability and Assault Questionnaire (AIAQ; Coccaro 1991).
5. Interpersonal problems, as assessed by, for example, the Inventory of Interpersonal Problems (IIP; Horowitz 1988), or the relevant item or subscale of the Zan-BPD (Zanarini 2003), CGI-BPD (Perez 2007), BPDSI-IV (Arntz 2003), or SCL-90-R (Derogatis 1994).
6. Abandonment, as assessed by, for example, the relevant item or subscale on the Zan-BPD (Zanarini 2003), CGI-BPD (Perez 2007) or BPDSI-IV (Arntz 2003).
7. Identity disturbance, as assessed by, for example, the relevant item or subscale on the Zan-BPD (Zanarini 2003), CGI-BPD (Perez 2007) or BPDSI-IV (Arntz 2003).
8. Dissociation and psychotic-like symptoms, as assessed by, for example, the Dissociative Experience Scale (DES; Bernstein 1986), or the Brief Psychiatric Rating Scale (BPRS; Overall 1962).
9. Depression, as assessed by, for example, the Beck Depression Inventory (BDI; Beck 1961), or the Montgomery Åsberg Depression Rating Scale (MADRS; Montgomery 1979).
10. Attrition, in terms of participants lost after randomisation in each group.
11. Adverse effects, as measured by use of standardised psychometric rating scales such as the Systematic Assessment for Treatment Emergent Events (SAFTEE; Levine 1986), laboratory values or spontaneous reporting.

Search methods for identification of studies

This current review is part of a series of reviews on interventions for BPD (Stoffers-Winterling 2018; Storebø 2018; Storebø 2020; Stoffers 2010). Therefore, the search strategy is very comprehensive and covers all psychotherapeutic or pharmacological treatment (or both) of BPD. The search has been run four times in all databases over the years. A full search in all databases was carried out in 2017 and then additional top-up searches were used to update search hits until the most recent search on 21 February 2022. Trial registries were handsearched several times during the work with this update, most recently on individual dates as close to the submission date of this manuscript as possible.

Electronic searches

We searched the electronic databases and trials registers listed below to identify relevant trials.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2022, Issue 2), in the Cochrane Library, which includes the Cochrane Developmental, Psychosocial and Learning Problems Specialised Register (searched 21 February 2022).
2. MEDLINE Ovid (1948 to 21 February 2022).
3. Embase Ovid (1974 to 21 February 2022).
4. CINAHL EBSCOhost (Cumulative Index to Nursing and Allied Health Literature; 1980 to 21 February 2022).
5. PsycINFO Ovid (1806 to 21 February 2022).
6. ERIC EBSCOhost (Education Resources Information Center; 1966 to 21 February 2022).
7. BIOSIS Previews Web of Science Clarivate Analytics (1969 to 29 June 2022).
8. Web of Science Clarivate Analytics (Science Citation Index Expanded and Social Sciences Citation Index 2002 to 21 February 2022).
9. Sociological Abstracts ProQuest (1952 to 21 February 2022).
10. LILACS (Latin American and Caribbean Health Science Information database (lilacs.bvsalud.org/en; searched 21 February 2022)).
11. Library Hub Discover (previously Copac National, Academic and Specialist Library Catalogue; copac.jisc.ac.uk, searched 21 February 2022).
12. ProQuest Dissertations and Theses A&I (1973 to 21 February 2022).

13. OpenGrey; searched 28 December 2020 (OpenGrey was shut down before top-up searches).
14. DART Europe E-Theses Portal (www.dart-europe.eu/basic-search.php, searched 27 June 2022).
15. Networked Digital Library of Theses and Dissertations (NDLTD; ndltd.org, searched 27 June 2022).
16. Australian New Zealand Clinical Trials Registry (ANZCTR; anzctr.org.au/TrialSearch.aspx, searched 25 February 2022).
17. ClinicalTrials.gov (clinicaltrials.gov/, searched 21 February 2022).
18. EU Clinical Trials Register (www.clinicaltrialsregister.eu/ctr-search/search, searched 25 February 2022).
19. ISRCTN Registry (www.isrctn.com/, searched 23 June 2022).
20. WHO International Clinical Trials Registry Platform (ICTRP; trialsearch.who.int/, searched 22 June 2022).

The search strategies for each source are available in Appendix 4. We did not limit our searches by language, year of publication, or type of publication. We sought translation of the relevant sections of non-English language articles.

Searching other resources

On 10 and 11 March 2022, we searched for unpublished data on the websites of the United States Food and Drug Administration (FDA; www.fda.gov) and the European Medicines Agency (EMA; www.ema.europa.eu/ema) (see Appendix 4). We also handsearched relevant journals: the Journal of Personality Disorders; the American Journal of Psychiatry; JAMA Psychiatry; British Journal of Psychiatry; ACTA Psychiatrica Scandinavica; Journal of the American Academy of Child and Adolescent Psychiatry; Personality Disorders: Theory, Research and Treatment; and the Journal of Clinical Psychiatry. Additionally, we contacted researchers working in the field by email, to ask for unpublished data,and traced cross-references from relevant literature.

Data collection and analysis

We conducted this review according to guidelines set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022), and performed the analyses using the latest version of Review Manager Web (RevMan Web), Cochrane's statistical software (RevMan Web 2020).

We were not able to use all of our methods as planned (Stoffers-Winterling 2018). We report the unused methods in Table 1.

Selection of studies

Thirteen reviewers (JMSW, OJS, AT, EF, BAV, MLK, MTK, CPS, JTM, JPR, HEC, SSN, JPS) worked in pairs and independently screened titles and abstracts of all records retrieved by the searches; we resolved uncertainty or disagreement by consensus. For records that could be eligible RCTs, we obtained the full-text reports and assessed them for eligibility based on the inclusion criteria (Criteria for considering studies for this review). Review authors discussed disagreements and, if they could not reach an agreement, they consulted a third review author (ES or KL). We listed potentially relevant RCTs that did not fulfil the inclusion criteria with reasons for exclusion in the 'Characteristics of excluded studies' tables. We used Covidence software to keep track of appraised trials and decisions. To ensure transparency of study selection, we provided a flow chart in accordance with the PRISMA statement (Moher 1999), to show how many records had been excluded and for what reason (Figure 1).

Figure 1. PRISMA flow diagram of study selection

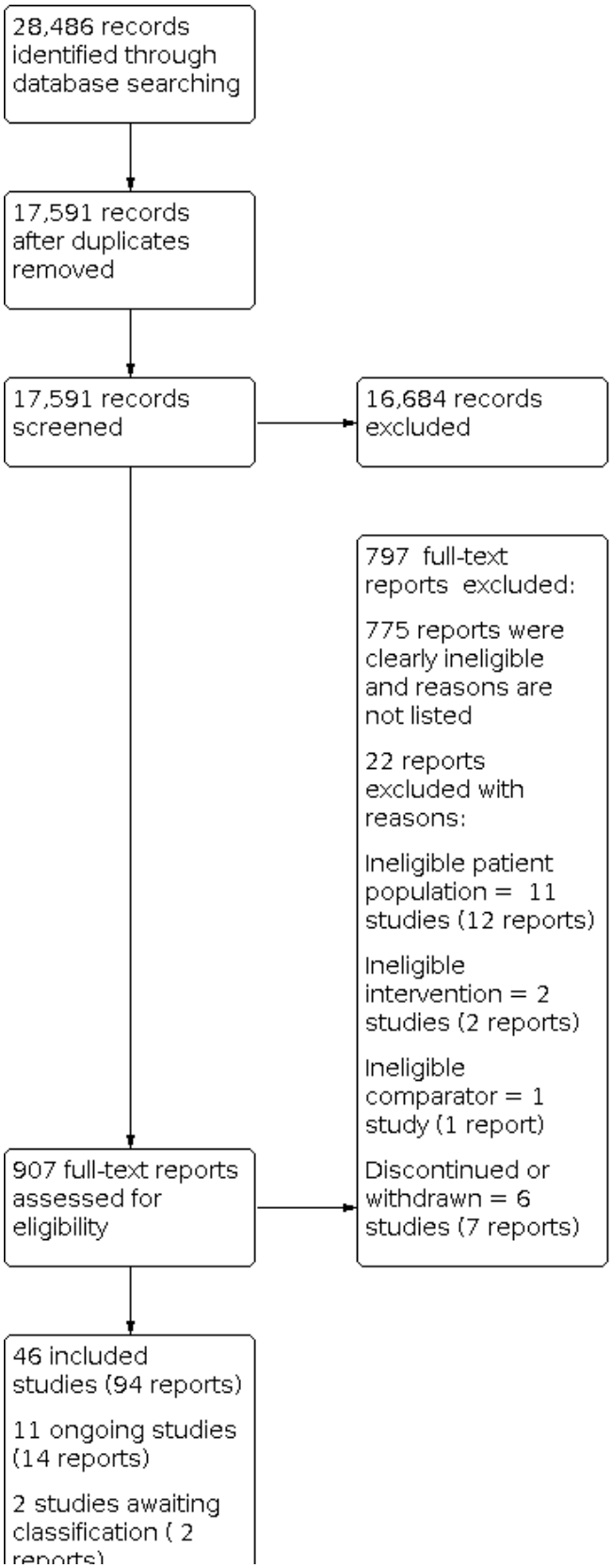
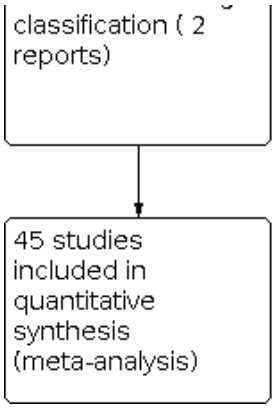


Figure 1. (Continued)



Data extraction and management

We developed data extraction forms to facilitate standardisation of data extraction. All review authors extracted data. Review authors worked in pairs and completed the data collection form independently to ensure accuracy. We resolved disagreements by discussion or used an arbiter (ES) if required. JMSW, JRP, and OJS entered the data into RevMan 5 (RevMan Web 2020). In those cases where there were not enough data or data were unclear in the published trial reports, we contacted the trial authors, requesting them to supply the missing information.

Assessment of risk of bias in included studies

Using the Cochrane tool for assessing risk of bias (Higgins 2017), all review authors assessed the risk of bias in each included study across the following domains: random sequence generation, allocation concealment, performance bias, detection bias, attrition bias, reporting bias and other potential sources of bias. We included vested interest in this last domain. Andreas Lundh and colleagues have illustrated the many subtle mechanisms through which sponsorship and conflict of interest may influence intervention effects on outcomes. For more information, please see editorials by Bero 2013 and Sterne 2013, and the commentary by Gøtzsche 2015.

For each included trial, data extractors independently evaluated each risk of bias domain as being at low, unclear (uncertain) or high risk of bias, resolving disagreements by discussion. We categorised trials that had a low risk of bias in all domains as being at low risk of bias overall, and we considered trials with one or more unclear or high risk of bias domains as trials at high risk of bias overall. Given the risk of overestimation of beneficial intervention effects and underestimation of harmful intervention effects in RCTs with unclear or inadequate methodological quality (Kjaergard 2001; Lundh 2017; Moher 1998; Savović 2012a; Savović 2012b; Schulz 1995; Wood 2008), we assessed the influence of risk of bias on our results (see Sensitivity analysis).

Measures of treatment effect

Dichotomous data

We summarised dichotomous data as risk ratios (RRs) with 95% CIs. The RR is the ratio of the risk of an event in the two groups. We decided to use the RR as it may be easier to interpret than odds ratios (ORs).

Continuous data

For continuous data, we compared the mean score between the two groups to give a mean difference (MD) and presented this with 95% CIs. We used the overall MD, where possible, to compare the outcome measures from trials. We estimated the standardised MD (SMD) where different outcome measures were used to measure the same construct in the trials. We calculated SMDs using end-scores at post-treatment results. Where the direction of a scale was opposite to most of the other scales, we multiplied the corresponding mean values by −1 to ensure adjusted values. If the trials did not report means and standard deviations but reported other values like t-tests and P values, we tried to transform these into standard deviations.

Our first choice was to calculate effect sizes on the basis of intention-to-treat (ITT) data. If means and standard deviations from an ITT analysis and missing values that were replaced were available, we used these data. In other cases, we conducted the analysis using only the available data.

We performed all calculations using the latest release of RevMan 5 software (RevMan Web 2020).

To identify the minimum relevant clinical difference (MIREDIF), we transformed the SMD to MD, using the scale with the best validity and reliability for the given outcome. For the analyses of the primary outcome, BPD symptom severity, in the comparison of psychotherapy versus treatment-as-usual (TAU), we transformed SMDs into MDs on the following scale, to assess whether results exceeded the MIREDIF: ZAN-BPD Scale, We identified a MIREDIF of −3.0 points on the ZAN-BPD, ranging from 0 to 36 points, based on a trial by Zanarini 2007. We used a MIREDIF of 0.61 in the interpersonal problems outcome, which corresponds to ½ SD based on a trial by Schulz 2007. For attrition, we used a relative risk reduction of 40%, and for non-serious adverse events, we used a relative risk reduction of 20%.

Unit of analysis issues

Repeated observations

We calculated study estimates on the basis of post-treatment group results. We did not use interim observations.

Cross-over trials

We included data from four randomised cross-over trials (Cowdry 1988; Schmahl 2012a; Schmahl 2012b; Ziegenhorn 2009). We were not able to obtain first-period data from these cross-over trials (by writing to the study authors) and therefore used end of period data (Curtin 2002; Elbourne 2002) because the data were unavailable. Cross-over trials are more prone to bias from carryover effects, period effects and unit of analysis errors, but it is still possible to use the end of period data when first-period data are not available (Curtin 2002; Elbourne 2002). This approach might however introduce a risk of a unit of analyses error, the confidence intervals will probably be too wide, and also the trial will receive too little weight. There is also a possibility of overlooking important heterogeneity. The Cochrane Handbook states, however, that this approach is conservative as the studies are under-weighted instead of over-weighted (Higgins 2019). Some argue that the unit of analyses errors introduced by doing this might be regarded as less serious than other types of unit of analysis error. The trial by Cowdry (Cowdry 1988) was the only one pooled with parallel-group trials. Cowdry and colleagues reported a washout period of one week before cross-over. When excluding the Cowdry study from the parallel-group trials, we found no differences in the result of the analyses. The other cross-over trials (Schmahl 2012a; Schmahl 2012b; Ziegenhorn 2009) were reported separately in the analyses.

Studies with multiple treatment groups

If a trial compared more than two intervention groups, we included all pairwise comparisons as long as they were not subject to the same meta-analysis. If a trial included two arms at different doses of a certain medication that were tested against placebo, we combined the experimental groups into a single group, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, making a single, pairwise comparison (Higgins 2022). We hereby avoided including the same group of participants twice in the same meta-analysis.

Adjustment for multiplicity

Multiplicity reflects the concern that performing multiple comparisons increases the risk of falsely rejecting the null hypothesis. Multiplicity, therefore, may affect the results found within a systematic review and, as a result, needs to be adjusted for. We adjusted the P values and CIs of the primary outcomes (BPD severity) and secondary outcomes (interpersonal problems, non-serious adverse events and attrition) for multiplicity using the method described by Jakobsen 2014. We have made a conservative estimation of the anticipated intervention effect to control the risk of type 1 error (Jakobsen 2014). We have four primary outcomes, and therefore we considered a P value of 0.02 or less as the threshold for evidence of a difference for the primary outcomes. We have 11 secondary outcomes, and therefore we considered a P value of 0.008 or less as the threshold for evidence of a difference for the secondary outcomes (Jakobsen 2014).

Dealing with missing data

We tried to obtain any missing data, including incomplete outcome data, by contacting trial authors. We reported this information in the risk of bias tables.

We evaluated the methods used to handle the missing data in the publications and to what extent it was likely that the missing data influenced the results of outcomes of interest. For preference, we calculated effect sizes on the basis of ITT data. If only available data were reported, we calculated effect sizes on this basis. Where dichotomous data were not presented on the basis of ITT data, we added the number of participants lost in each group to the participants with unfavourable results, acting on the assumption that most people with BPD did not get lost at random. For continuous outcomes, we discussed each trial's methodology for dealing with missing continuous data (e.g. last-observation-carried-forward or modified ITT approach). We used per protocol analysis, as available from the trial reports (that is, results were based on the number of participants at follow-up).

If data were not reported in an immediately usable way, we consulted a statistician.

We assessed results derived from statistically processed data in sensitivity analyses (see Sensitivity analysis).

Assessment of heterogeneity

We assessed trials for clinical homogeneity with respect to type of pharmacological interventions, setting and control groups. We took into account the number of trials and trial characteristics, such as duration, dose and participants, to judge if heterogeneity was more probable due to clinical (i.e. explainable factors) or unknown factors. In case of substantial heterogeneity, we divided analyses into subgroups according to trial characteristics, such as trial size, duration, dose or participants, and discussed the most apparent sources of heterogeneity. We evaluated methodological heterogeneity by comparing the design of trials (see Subgroup analysis and investigation of heterogeneity).

We investigated statistical heterogeneity within a certain comparison by visual inspection of the graphs and the I^2 statistic (Higgins 2003). We judged I^2 values between 0% and 40% to indicate little heterogeneity, between 30% and 60% to indicate moderate heterogeneity, between 50% and 90% to indicate substantial heterogeneity, and between 75% and 100% to indicate considerable heterogeneity (Deeks 2021). We also assessed statistical heterogeneity by the Chi^2 test ($P < 0.10$) and tau^2 – an estimate of between-trial variability.

Assessment of reporting biases

We produced funnel plots for comparisons with sufficient primary studies i.e. 10 or more trials and we performed Egger's statistical test for small-trial effects (Egger 1997). We did not use a visual inspection of the funnel plot if there were fewer than 10 trials in the meta-analysis, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2017).

Data synthesis

We performed statistical analyses according to recommendations in the latest version of the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2021). In carrying out the meta-analysis, we used the inverse-variance method for continuous data, in order to give more weight to more precise estimates from trials with less variance (mostly larger trials). For dichotomous data we used the Mantel-Haenszel analysis method. We used the random-effects model for meta-analysis when there were two or more trials, since we expected some degree of clinical heterogeneity to be present in most cases, though not so substantial as to

prevent pooling in principle. Where only one trial was included in an analysis, we used the fixed-effect model, and where different models led to different results, we reported the results of both models (Sensitivity analysis). For trials with a high level of statistical heterogeneity, and where the amount of clinical heterogeneity made it inappropriate to use these trials in meta-analyses, we provided a narrative description of the trial results. If we considered data pooling to be feasible, we pooled the primary trials effects and calculated their 95% CIs. If a trial provided more than one measure for the same outcome construct (e.g. several questionnaires for the assessment of depression), we selected the one used most often in the whole pool of included trials for effect size calculation, in order to minimise heterogeneity of outcomes in form and content. If a trial reported data of two assessment instruments that were equally frequently used, two review authors discussed the issue and chose the one which was, in its content, most appropriate for assessing people with BPD. We preferred observer-rated measures as the primary analysis measure.

Subgroup analysis and investigation of heterogeneity

We conducted subgroup analyses to investigate the subgroups mentioned below.

1. Types of medication (comparing pharmacological classes as well as active medications)
2. Setting (outpatient compared to inpatient)

We attempted to undergo subgroup analyses for all primary outcomes; however, data were not available for all subgroups and so we investigated subgroups for the primary outcomes of BPD symptom severity, psychosocial functioning, suicide-related outcome, and the secondary outcome anger (as this was the only outcome where it was possible to perform subgroup analyses).

We added the following subgroup analyses post hoc.

1. Funding (funded or partially funded by pharmaceutical industry compared to no funding received compared to funded by universities or research foundations)
2. Psychosocial functioning at baseline as measured by GAS, GAF or SFQ15 (comparing groups of participants with low, moderate and high impairment)
3. Trial size (trial size ≤ 50 compared to trial size ≤ 100 compared to trial size ≥ 100)
4. Type of screening (referrals compared to advertisements)

Heterogeneity-adjusted required information size and Trial Sequential Analysis

Sequential methods like Trial Sequential Analysis (TSA) are not in general recommended to be used in Cochrane reviews. They can be used as a secondary analyses, to give an additional interpretation of the data from a specific perspective. We have used the TSA in this review as a secondary analysis testing the imprecision of some of the most important outcomes (Thomas 2021). We only performed a TSA for BPD symptom severity, interpersonal problems, non-serious adverse events and attrition as these were the outcomes in the SoF tables where we needed to test our GRADE assessment of imprecision.

TSA is a methodology that combines a required information size (RIS) calculation for a meta-analysis with the threshold for statistical significance (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008). TSA is a tool for quantifying the statistical reliability of the data in cumulative meta-analysis, adjusting P values for sparse data and for repetitive testing on accumulating data (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008).

Comparable to the *a priori* sample size estimation in a single randomised trial, a meta-analysis should include a RIS calculation at least as large as the sample size of an adequately powered single trial to reduce the risk of random error. TSA calculates the RIS in a meta-analysis and provides an alpha-spending boundary to adjust the significance level for sparse data and repetitive testing on accumulating data (CTU 2011; Wetterslev 2008), and consequently the risk of random error can be assessed. Multiple analysis of accumulating data when new trials emerge leads to repeated significant testing and hence introduces multiplicity, thus use of a conventional P value is prone to exacerbate the risk of random error (Berkey 1996; Lau 1995). Meta-analyses not reaching the RIS are analysed with trial sequential alpha-spending monitoring boundaries analogous to interim monitoring boundaries in a single trial (Wetterslev 2008). This approach will be crucial in future updates of the review.

If a TSA does not reveal significant findings (no crossing of the alpha-spending boundary and no crossing of the conventional boundary of P = 0.05) before the RIS has been reached, then the conclusion should either be that more trials are needed to reject or accept an intervention effect that was used for calculation of the required sample size or — in case the cumulated Z-curve enters the futility area — the anticipated effect can be rejected.

We used a minimally relevant clinical difference (MIREDIF) from trials defining this or, where we could not find this, we used an assumption that the minimal relevant clinical intervention effect was approximately ½ SD on the used scale, which can be used as a MIREDIF (Norman 2003).

We calculated the diversity-adjusted required information size (DARIS; that is, the number of participants required to detect or reject a specific intervention effect in a meta-analysis), and performed a TSA for the primary outcome, BPD symptom severity, at the end of treatment for the main comparison versus placebo, based on the following *a priori* assumptions:

1. the SD of the primary outcome;
2. an anticipated MIREDIF defined in a trial reporting on this or we used a ½ SD on the used scale;
3. a maximum type I error of 2.0% (due to four primary outcomes; Jakobsen 2014);
4. a maximum type II error of 10% (minimum 90% power; Castellini 2018); and
5. the diversity observed in the meta-analysis.

We furthermore performed a TSA for the secondary outcome, interpersonal problems (for the main comparison versus placebo), based on the following priori assumptions:

1. the SD of the secondary outcome;
2. an anticipated MIREDIF defined in a trial reporting on this or we used a ½ SD on the used scale;
3. a maximum type I error of 0.8% (due to 11 secondary outcomes; Jakobsen 2014);

4. a maximum type II error of 10% (minimum 90% power; Castellini 2018); and
5. the diversity observed in the meta-analysis.

For the secondary outcomes, 'attrition', and 'non-serious adverse events', we calculated the *a priori* diversity-adjusted required information size (DARIS; i.e. number of participants in the meta-analysis required to detect or reject a specific intervention effect) and performed a Trial Sequential Analysis for these outcomes based on the following assumptions (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008; Wetterslev 2009):

1. Proportion of participants in the control group with adverse events;
2. Relative risk reduction of 40% (20% on 'non-serious adverse events');
3. Type I error of 0.8% (due to 11 secondary outcomes; Jakobsen 2014);
4. Type II error of 10%;
5. Observed diversity of the meta-analysis.

Sensitivity analysis

We assessed the impact of heterogeneity on the overall pooled effect estimate. First, we visually inspected the forest plot for 'outliers' that might contribute to heterogeneity and then removed them one-by-one to assess their impact on the overall outcome. Overall results were reported in the main analysis with outliers excluded, while we also conducted sensitivity analyses including these outliers.

We conducted sensitivity analyses to determine whether findings were sensitive to the following.

1. Imprecision, as assessed by GRADE, by conducting TSAs on the primary outcomes and for the secondary outcomes (for the main comparison versus placebo) where we were uncertain about the assessment of imprecision.
2. Differences when adding data from end-of-period data from cross-over trials to the analyses.
3. Decisions made during the review process in relation to the:
   a. choice of data (differences between data from trial registers and data from peer reviewed sources);
   b. exclusion of outliers; and
   c. type of model used for analysis (repeating the analysis using the fixed-effect model to test the robustness of the results).

Summary of findings and assessment of the certainty of the evidence

We used Gradepro (GRADEpro 2021) to construct summary of findings tables. We reported the four primary outcomes (BPD severity, self-harm, suicide-related outcomes, and psychosocial functioning) and three secondary outcomes (interpersonal problems, attrition, and adverse events). We produced three summary of findings tables; one focusing on the comparison between antipsychotics and placebo at end of treatment, one on antidepressants compared with placebo at end of treatment, and one on mood stabilisers compared with placebo at end of treatment.

We used the GRADE approach to assess the quality of the body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Two authors independently assessed the certainty of the evidence according to study limitations (risk of bias), indirectness of evidence, inconsistency of results, imprecision and publication bias (Atkins 2004; Andrews 2013a; Andrews 2013b; Balshem 2011; Brunetti 2013; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Mustafa 2013). Any differences of opinion were resolved by consulting a third author. When possible, we used the MD or the RR, and we used TSA to rate the imprecision (Jakobsen 2014). Two authors (HEC and OJS) downgraded imprecision in GRADE by two levels if the accumulated number of participants was below 50% of the DARIS, and one level if between 50 and 100% of DARIS. We did not downgrade when the cumulative Z-curve crossed the monitoring boundaries for benefit, harm, or futility, or DARIS was reached. We justified all decisions to downgrade the quality of evidence in footnotes (Korang 2020).

RESULTS

Description of studies

For a full description of trials, see Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification and Characteristics of ongoing studies tables.

Results of the search

Combined, all searches generated 28,486 records, of which 10,895 were duplicates, leaving 17,591 records for title and abstract screening. Of these, 16,684 records were deemed irrelevant based on title and abstract screening, leaving 907 records for full-text inspection. Of the full-text reports, 797 were excluded as they clearly did not match the inclusion criteria. Reasons for exclusion at this stage included not being a clinical trial or a pharmacological intervention (due to the comprehensive search) or similar. The remaining reports were examined closely to determine their eligibility. Of these, 22 reports (20 trials) were excluded for the reasons reported in Characteristics of excluded studies. We also identified 11 ongoing studies (14 reports) and two studies (2 reports) are awaiting classification (see Characteristics of studies awaiting classification and Characteristics of ongoing studies). This left 46 studies (from 94 reports) which were eligible for inclusion in the review. Data were unavailable for effect size calculations in one of these trials, leaving 93 reports from 45 trials to be included in the quantitative synthesis. This is 18 more studies than in the 2010 review (Stoffers 2010). The 46 trials are thoroughly described in Characteristics of included studies.

Included studies

Design

We included 46 randomised controlled trials. Four of these were cross-over trials (Cowdry 1988; Schmahl 2012a; Schmahl 2012b; Ziegenhorn 2009); six were multi-armed (Black 2014; Cowdry 1988: Soloff 1989; Soloff 1993; Zanarini 2004; Zanarini 2007), and three had a randomised open-label design (Bellino 2014; Bozzatello 2017; Shafti 2014).

Sample size

The total number of participants with BPD in the included trials varied considerably from 13 in the smallest trial (Schmahl 2012a) to 451 in the largest (Zanarini 2007). There were four trials with more than 100 participants (Jariani 2010; Schulz 2007; Soloff 1993; Zanarini 2001).

Setting

Thirty-two of the included trials took place in an outpatient setting, while nine trials took place in an inpatient setting (De la Fuente 1994; Markovitz 1995a; Moen 2012; NCT00533117; Schmahl 2012a; Shafti 2010; Shafti 2014; Simpson 2004; Ziegenhorn 2009). Four trials included both inpatients and outpatients or allowed inpatients to complete as outpatients if discharged from the hospital (Crawford 2018; Schmahl 2012b; Soloff 1989; Soloff 1993), and one trial did not state whether it took place in an in- or outpatient setting (AstraZeneca 2007).

Country

Twenty trials were from Europe. Of these, eight were from Germany (Loew 2006; Nickel 2004; Nickel 2005; Nickel 2006; Schmahl 2012a; Schmahl 2012b; Tritt 2005; Ziegenhorn 2009), one was from Austria (Amminger 2013), one was from Belgium (De la Fuente 1994), two were from the Netherlands (AstraZeneca 2007; Rinne 2002), two were from Italy (Bellino 2014; Bozzatello 2017), two were from Spain (Pascual 2008; Soler 2005), three were from the UK (Crawford 2018; Montgomery 1982a; Montgomery 1982b), and one was from Ireland (Hallahan 2007). Three trials were from Southwest Asia (Middle East); all of them from Iran: Jariani 2010; Shafti 2010; Shafti 2014. One trial was from Australia: Kulkarni 2018. Two trials were multi-country and were carried out in nine countries each: Schulz 2007 (Belgium, France, Germany, Norway, Portugal, Spain, Sweden, UK and US), and Zanarini 2007 (US, Italy Poland, Romania, Turkey, Chile, Peru, Argentina and Venezuela). The remaining 20 trials were from the US (Black 2014; Bogenschutz 2004; Cowdry 1988; Frankenburg 2002; Goldberg 1986; Grant 2022; Hollander 2001; Leone 1982; Linehan 2008; Markovitz 1995a; Moen 2012; NCT00533117; Reich 2009; Salzman 1995; Simpson 2004; Soloff 1989; Soloff 1993; Zanarini 2001; Zanarini 2003; Zanarini 2004).

Funding

Seventeen trials were funded or partially funded by the pharmaceutical industry (AstraZeneca 2007; Black 2014; Bogenschutz 2004; Frankenburg 2002; Grant 2022; Hollander 2001; Leone 1982; Linehan 2008; Moen 2012; Pascual 2008; Reich 2009; Schulz 2007; Simpson 2004; Soler 2005; Zanarini 2001; Zanarini 2004; Zanarini 2007), 10 where funded by universities or research foundations (Amminger 2013; Crawford 2018; Hallahan 2007; Kulkarni 2018; NCT00533117; Rinne 2002; Shafti 2014; Soloff 1989; Soloff 1993; Zanarini 2003), eight received no funding (Bellino 2014; Bozzatello 2017; Loew 2006; Nickel 2005; Nickel 2006; Shafti 2010; Tritt 2005; Ziegenhorn 2009), and 11 had unclear funding (Cowdry 1988; De la Fuente 1994; Goldberg 1986; Jariani 2010; Markovitz 1995a; Montgomery 1982a; Montgomery 1982b; Nickel 2004; Salzman 1995; Schmahl 2012a; Schmahl 2012b).

Participants

The 46 trials included a total of 2769 participants with BPD. One trial, Markovitz 1995a, was not included in the quantitative analysis due to insufficient reporting for effect size calculations, leaving a total of 45 trials (2752 participants) in the quantitative analysis. Two trials reported on completers only (Montgomery 1982b; Salzman 1995), and thus the number of participants was probably higher. The mean age ranged from 16.2 (Amminger 2013) to 39.7 years (Grant 2022). One trial did not report on demographics at baseline, leaving sex and mean age unknown (Markovitz 1995a). Fifteen trials included only females (Cowdry 1988; Frankenburg 2002; Linehan 2008; Loew 2006; Nickel 2004; Rinne 2002; Schmahl 2012a; Schmahl 2012b; Shafti 2010; Shafti 2014; Simpson 2004; Tritt 2005; Zanarini 2001; Zanarini 2003; Zanarini 2004); and one trial included only males (Nickel 2005). All remaining trials included both sexes, though predominantly females.

Diagnostic criteria

Participants were diagnosed with BPD according to criteria from DSM III, DSM III R, DSM IV, DSM IV R or ICD-10. BPD diagnoses were confirmed by one or more standardised means of assessment. Four trials used the Diagnostic Interview for Borderline personality disorder (DIB) (Cowdry 1988; De la Fuente 1994; Soloff 1989; Soloff 1993), while four used the revised version (DIB-R) (Reich 2009; Zanarini 2001; Zanarini 2003; Zanarini 2004). Two of the included trials used the International Personality Disorder Examination scale (IPDE) (Schmahl 2012a; Schmahl 2012b) while one used IPDE in addition to SCID-I (Crawford 2018). One trial used the Scales of independent behaviour (SIB) (Goldberg 1986), and two trials used the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) (Grant 2022; Kulkarni 2018). One trial used the DIPD-IV scale (Frankenburg 2002) while two used both DIPD-IV and ZAN-BPD (Schulz 2007; Zanarini 2007). Three trials used an unspecified clinical interview (Jariani 2010; Montgomery 1982a; Montgomery 1982b). One trial did not use a structured instrument but confirmed BPD diagnosis through consensus (Amminger 2013). Four trials stated that BPD was diagnosed according to the formal DSM criteria but did not specify if a standardised assessment instrument was used to confirm the diagnosis (Leone 1982; NCT00533117; Shafti 2010; Shafti 2014). Eleven of the trials used the Structured Clinical Interview for DSM-IV axis II disorders (SCID II): AstraZeneca 2007; Bogenschutz 2004; Hallahan 2007; Hollander 2001; Linehan 2008; Loew 2006; Nickel 2004; Nickel 2005; Nickel 2006; Simpson 2004; Tritt 2005. In addition to SCID-II, nine trials used one or more additional means of assessment (Bellino 2014; Bozzatello 2017; Markovitz 1995a; Moen 2012; Pascual 2008; Rinne 2002; Salzman 1995; Soler 2005; Ziegenhorn 2009). One trial used SCID but did not specify which version (Black 2014). An overview of assessment instruments used by the individual trials is found in Table 1 and Characteristics of included studies.

Participant exclusion criteria

Most trials had several exclusion criteria, with the most common one used in 38 trials, the exclusion of participants with current major depression, bipolar affective disorder or psychotic disorder. Thirty of the trials also excluded participants with alcohol or substance abuse or dependence. Other common exclusion criteria were organic illness, mental retardation, cognitive disorder or impairment, severe somatic illness, chronic medical conditions, and pregnancy or breastfeeding. For exclusion criteria in all trials, see Table 1 and Characteristics of included studies.

Interventions

Duration of interventions

Trial duration lasted from four weeks (Ziegenhorn 2009) to 52 weeks (Crawford 2018; NCT00533117). Thirty-five of the trials had a duration of three months or less, leaving only 11 trials with a duration between three months and one year.

Format of intervention

The majority of trial interventions tested one type of medication to alleviate borderline symptoms. Two trials had more than one treatment arm investigating the effect of various doses or treatment durations of the same medication (Black 2014; Zanarini 2007). Two trials compared a medication in addition to treatment-as-usual with a placebo intervention in addition to treatment-as-usual (Crawford 2018; Kulkarni 2018), and one trial intervention specifically combined Dialectic Behaviour Therapy (DBT) with the selective serotonin reuptake inhibitor fluoxetine (NCT00533117). Ten trials were head-to-head trials comparing active medications to each other (Cowdry 1988; Bellino 2014; Bozzatello 2017; Jariani 2010: Leone 1982; Shafti 2010; Shafti 2014; Soloff 1989; Soloff 1993; Zanarini 2004); four of which were multiple-arm trials, with an additional placebo comparator (Cowdry 1988; Soloff 1989; Soloff 1993; Zanarini 2004).

Type of intervention

The trials included in this review investigated the following 27 medications:

1. Amitriptyline
2. Alprazolam
3. Aripiprazole
4. Asenapine
5. Brexpiprazole
6. Carbamazepine
7. Clonidine
8. Fluoxetine
9. Flupenthixol
10. Fluvoxamine
11. Haloperidol
12. Lamotrigine
13. Loxapine
14. Memantine hydrochloride
15. Mianserin
16. Naltrexone
17. Olanzapine
18. Omega-3 fatty acids
19. Phenelzine
20. Quetiapine
21. Sertraline
22. Thiothixene
23. Topiramate
24. Tranylcypromine
25. Trifluoperazine
26. Valporate semi sodium
27. Ziprasidone

Antipsychotics

First-generation antipsychotics were used in six trials, two of which had haloperidol interventions (Soloff 1993; Shafti 2010). The other four had a thiothixene intervention (Goldberg 1986), a loxapine intervention (Leone 1982), a flupenthixol intervention (Montgomery 1982a) and a trifluoperazine hydrochloride intervention (Cowdry 1988).

Second-generation antipsychotics were used in 16 trials, of which ten had an olanzapine intervention (Bogenschutz 2004; Bozzatello 2017; Jariani 2010; Linehan 2008; Schulz 2007; Shafti 2010; Shafti 2014; Soler 2005; Zanarini 2001; Zanarini 2007). Two trials had an aripiprazole intervention (Nickel 2006; Shafti 2014), and one trial each had a quetiapine (Black 2014), asenapine (Bozzatello 2017) ziprasidone (Pascual 2008) and brexpiprazole (Grant 2022) intervention.

Antidepressants

Seven trials had selective serotonin reuptake inhibitor (SSRI) interventions. Of these, five had a fluoxetine intervention (Markovitz 1995a; NCT00533117; Salzman 1995; Simpson 2004; Zanarini 2004). one had a fluvoxamine intervention (Rinne 2002), and one head-to-head trial had a sertraline intervention (Jariani 2010).

One multiple-arm cross-over trial had a monoamine oxidase inhibitor (MAO-I) intervention of tranylcypromine sulfate (Cowdry 1988).

One trial had an intervention with the noradrenergic and specific serotonergic antidepressant (NaSSA) mianserin (Montgomery 1982b).

One trial had an intervention with the tricyclic antidepressant (TCA) amitriptyline (Soloff 1989).

Mood stabilisers

Eleven trials had interventions with anticonvulsants. Three trials had a lamotrigine intervention (Crawford 2018; Reich 2009; Tritt 2005) while another three used topiramate (Loew 2006; Nickel 2004; Nickel 2005). Two trials had an intervention of valproate semi sodium (Frankenburg 2002; Hollander 2001), while two others had a carbamazepine intervention and a valproate intervention (De la Fuente 1994; Moen 2012, respectively). One trial, Cowdry 1988, had a carbamazepine intervention.

Miscellaneous medications

The antidementia drug, memantine hydrochloride, was used in one trial (Kulkarni 2018). The opioid antagonist naltrexone was used in two trials (Schmahl 2012a; Schmahl 2012b). Omega-3 fatty acids were used in four trials (Amminger 2013; Bellino 2014; Hallahan 2007; Zanarini 2003). An antihypertensive/α2-adrenoceptor agonist was used in one trial with a clonidine intervention (Ziegenhorn 2009), and the benzodiazepine alprazolam was used in one trial (Cowdry 1988).

Concomitant medication

Eight trials did not allow concomitant medication (Bellino 2014; Bozzatello 2017; Moen 2012; Nickel 2004; Nickel 2006; Salzman 1995; Shafti 2014; Soloff 1993). Another seven trials gave specific information that psychotropics were not allowed (Frankenburg

2002; Loew 2006, Nickel 2005; Rinne 2002; Shafti 2010; Tritt 2005; Zanarini 2001). Thirteen trials did not allow for psychotropic co-medication with the exception of benzodiazepines, SSRIs or both (Amminger 2013; AstraZeneca 2007; Black 2014; Kulkarni 2018; Leone 1982; NCT00533117; Pascual 2008; Reich 2009; Schulz 2007; Simpson 2004; Soler 2005; Soloff 1989; Ziegenhorn 2009). However, many of these had restrictions and limitations regarding dosage, stability and drug initiation of concomitant medication prior to and during the trial. One trial allowed for patients to continue with standard psychiatric care and have changes to their psychotropic medication as prescribed, which 53.1% of participants did (Hallahan 2007). In another trial, 100% of participants used methadone, but there was no further mention of co-medication (Jariani 2010). One trial allowed antidepressants, mood stabilisers, and stimulants, but the use of any new psychotropic medication was an exclusion criterion (Grant 2022). Lastly, one trial specifically allowed medication for stable, chronic medical conditions such as hypertension but gave no further mention of other admissible concomitant medications (Bogenschutz 2004). Twelve trials did not give any information on concomitant medication (Cowdry 1988; Goldberg 1986; Hollander 2001; Linehan 2008; Markovitz 1995a; Montgomery 1982a; Montgomery 1982b; Schmahl 2012a; Schmahl 2012b; Zanarini 2003, Zanarini 2004; Zanarini 2007). Further, two trials similarly gave no details on permissible medications in the full report; however, Crawford 2018 excluded patients that were already prescribed a mood stabiliser within the past four weeks. Additionally, both arms received usual care. Another had a psychotropic medication washout for at least 10 days, a 15-day washout for antidepressants (TCAs and MAOIs), and no patient had taken neuroleptics two months prior to the trial (De la Fuente 1994).

Concomitant treatment

Twelve trials did not allow for concomitant psychotherapeutic treatment or treatment-as-usual (Black 2014; Bozzatello 2017; Frankenburg 2002; Hallahan 2007; Loew 2006; Nickel 2004; Nickel 2005; Nickel 2006; Reich 2009; Rinne 2002; Shafti 2010; Tritt 2005). Five trials offered or allowed for Dialectic Behavioural therapy (DBT) (Linehan 2008; Moen 2012; NCT00533117; Simpson 2004; Soler 2005) and another eight trials allowed or provided unspecified psychotherapy, psychological and psychosocial interventions concomitant with trial intervention or supportive atheoretical psychotherapy: Amminger 2013; De la Fuente 1994; Kulkarni 2018; Montgomery 1982a; Montgomery 1982b; Pascual 2008; Schmahl 2012a; Schmahl 2012b. One trial allowed psychotherapy if initiated a minimum of three months prior to randomisation (Bogenschutz 2004). The remaining 20 trials, did not state whether any type of concomitant treatment was offered or allowed.

Comparators

The review included 22 different comparators. Nine had a placebo control intervention, and 13 were head-to-head trials with an active comparison intervention that was either another single medication or a combination of medications.

Control intervention

The control intervention was a placebo.

Active medication versus placebo

1. *Antidepressants SSRIs, NaSSAs, TCAs and MAOIs versus placebo*: tranylcypromine sulfate (Cowdry 1988), fluoxetine (Markovitz 1995a; NCT00533117; Salzman 1995; Simpson 2004), mianserin (Montgomery 1982b), fluvoxamine (Rinne 2002), amitriptyline (Soloff 1989), phenelzine sulfate (Soloff 1993);
2. *First-generation antipsychotics versus placebo:* trifluoperazine hydrochloride (Cowdry 1988), thiothixene (Goldberg 1986), loxapine (Leone 1982), flupenthixole (Montgomery 1982a), haloperidol (Soloff 1989; Soloff 1993);
3. *Second generation antipsychotics versus placebo*: olanzapine (Bogenschutz 2004; Linehan 2008; Schulz 2007; Soler 2005; Zanarini 2001; Zanarini 2007), aripiprazole (Nickel 2006), ziprasidone (Pascual 2008), quetiapine (Black 2014), brexpiprazole (Grant 2022);
4. *Anticonvulsants versus placebo:* lamotrigine (Crawford 2018; Reich 2009; Tritt 2005), topiramate (Loew 2006; Nickel 2004; Nickel 2005), valproate semi sodium (Frankenburg 2002; Hollander 2001; Moen 2012), carbamazepine (Cowdry 1988; De la Fuente 1994), divalproex (Moen 2012);
5. *Omega-3 fatty acids versus placebo:* (Amminger 2013; Hallahan 2007; Zanarini 2003);
6. *Antidementia drug versus placebo:* memantine hydrochloride (Kulkarni 2018);
7. *Opiod antagonist versus placebo*: naltrexone (Schmahl 2012a; Schmahl 2012b);
8. *Antihypertensives/alpha-2 adrenoceptor agonist versus placebo:* clonidine (Ziegenhorn 2009);
9. *Benzodiazepine versus placebo:* alprazolam (Cowdry 1988).

Active medication versus active comparator medication

1. *First-generation antipsychotic versus first-generation antipsychotic:* loxapine versus chlorpromazine (Leone 1982);
2. *Second-generation antipsychotic versus second-generation antipsychotic:* olanzapine versus aripiprazole (Shafti 2014), and olanzapine versus asenapine (Bozzatello 2017);
3. *Second-generation antipsychotic versus first-generation antipsychotic*: olanzapine versus haloperidol (Shafti 2010);
4. *First-generation antipsychotic versus antidepressant:* trifluoperazine hydrochloride versus tranylcypromine sulfate (Cowdry 1988), haloperidol versus amitriptyline (Soloff 1989), and haloperidol versus phenelzine sulfate (Soloff 1993);
5. *Second-generation antipsychotic versus antidepressant:* olanzapine versus sertraline (Jariani 2010), and olanzapine versus fluoxetine (Zanarini 2004);
6. *Benzodiazepine versus mood stabiliser:* alprazolam versus carbamazepine (Cowdry 1988);
7. *Benzodiazepine versus first-generation antipsychotic*: alprazolam versus trifluoperazine hydrochloride (Cowdry 1988);
8. *Benzodiazepine versus antidepressant:* alprazolam versus tranylcypromine sulfate (Cowdry 1988);
9. *Mood stabiliser versus first-generation antipsychotic:* carbamazepine versus trifluoperazine hydrochloride (Cowdry 1988);
10. *Mood stabiliser versus antidepressant:* carbamazepine versus tranylcypromine sulfate (Cowdry 1988).

Active medication versus combination of medications

1. *Second generation antipsychotic versus second generation antipsychotic plus antidepressant:* olanzapine versus olanzapine plus fluoxetine (Zanarini 2004);

2. *Antidepressant versus antidepressant plus second-generation antipsychotic*: fluoxetine versus fluoxetine plus olanzapine (Zanarini 2004);
3. *Mood stabiliser versus mood stabiliser plus miscellaneous (omega-3 fatty acid):* valproic acid versus valproic acid plus eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) (Bellino 2014).

Outcomes

See Appendix 5 for information on outcome measurements in each trial.

Adverse effects

Adverse effects were registered in all but seven trials. Adverse effects were, in most cases, measured spontaneously, but some trials also used anthropometric and laboratory values as measurement. Five trials used the Abnormal Involuntary Movement Scale (AIMS) and the Simpson-Angus Scale (SAS), and a few used the Side Effect Rating Scale for extrapyramidal side effects. See Appendix 5 for specifications on scales used in each trial.

Excluded studies

We excluded a total of 20 trials (from 22 reports) from this review (see Figure 1). We excluded 11 due to an ineligible population; two included people with PD but none had BPD and in nine < 70% had a BPD diagnosis. For these nine, we tried to retrieve subsample data, but the subsample data were unavailable. We also excluded two studies due to an ineligible intervention (intervention was less than two weeks and not continuous) and one included an ineligible comparator. The remaining six trials were withdrawn or discontinued. For further information, see the table of Characteristics of excluded studies.

Studies awaiting classification

We assessed two trials as awaiting classification. One trial used an omega-3 fatty acids intervention, comparing omacor to placebo (NCT00437099), while the other investigated the antidepressant selegiline and compared it to placebo (NCT01912391). Both trials included a study population of adults with BPD and were registered, with start dates in 2009 (NCT00437099) and 2012 (NCT01912391). See Characteristics of studies awaiting classification tables for further information.

Despite rigorous searches, we were unable to find any corresponding publications or reports of trial results for either of these. Contact information was provided for the omacor trial (NCT00437099); however, we were unable to get in contact with the principal investigator, despite multiple attempts. No contact information was provided for the selegiline trial (NCT01912391), and we were unable to obtain this information. Judging from the trial registrations, both trials seem eligible for inclusion in this review. However, we are unaware of what has happened to the trials and if their results can be obtained. For this reason, we have categorised them as awaiting classification.

Ongoing studies

We included 11 ongoing trials that are assessing different pharmacological interventions for the treatment of BPD, and for which the outcome data are not yet available (see Characteristics of ongoing studies tables). All ongoing trials have a parallel design with a placebo or inert control intervention. Four of these are investigating antipsychotics, of which one has a brexpiprazole intervention (NCT04100096), one has a clozapine intervention (EudraCT 2018-002471-18-GB), one has a lumateperone intervention (NCT05356013) and another is using aripiprazole (Chanen 2019). The remaining ongoing trials are investigating miscellaneous medications; one trial is investigating the female hormone, estradiol (ACTRN12617001317381), one has a vafidemstat intervention (inhibitor of Lysine Demethylase 1) (EUCTR2020-003469-20-ES), one has a memantine intervention (NMDA-receptor antagonist) (IRCT20210106049948N1), one is investigating omega-3 fatty acids (IRCT20210531051453N1), one is a phase two trial from Boehringer Ingelheim with a medication labelled BI 1358894 (NCT04566601),one is investigating the effects of a stellate ganglion block (DRKS00015817) and one has a randomised, open-label design and is investigating a probiotic intervention (Arteaga-Henríquez 2020).

One trial, Chanen 2019, has a patient population of adolescents and young adults (15 to 25 years old), with auditory verbal hallucinations and BPD or ADHD. Another has a minimum age of 16 and, therefore, also include adolescents (IRCT20210106049948N1). All remaining trials are examining adults with BPD. One trial is investigating females only (ACTRN12617001317381), while the rest are including both men and women. Five trials have a duration of 12 weeks (ACTRN12617001317381; Chanen 2019; IRCT20210106049948N1; NCT04100096; NCT04566601). The duration in the remaining six trials are six months (EudraCT 2018-002471-18-GB), 14 weeks (EUCTR2020-003469-20-ES), 10 weeks (Arteaga-Henríquez 2020), eight weeks (DRKS00015817; NCT05356013) and six weeks (IRCT20210531051453N1).

Risk of bias in included studies

Figure 2 and Figure 3 portray the review authors' judgements on the risk of bias across the included trials and for each trial. Extended information about the individual trials can be found in the Characteristics of included studies tables.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

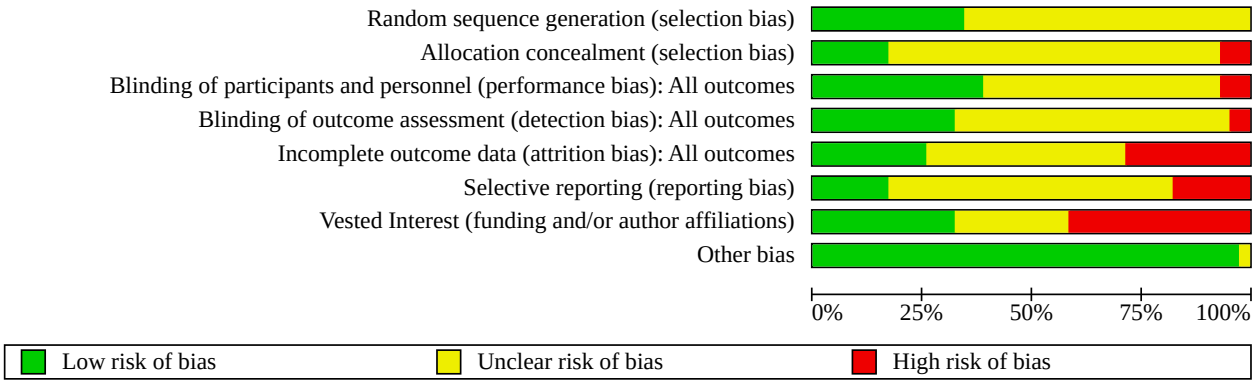


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial

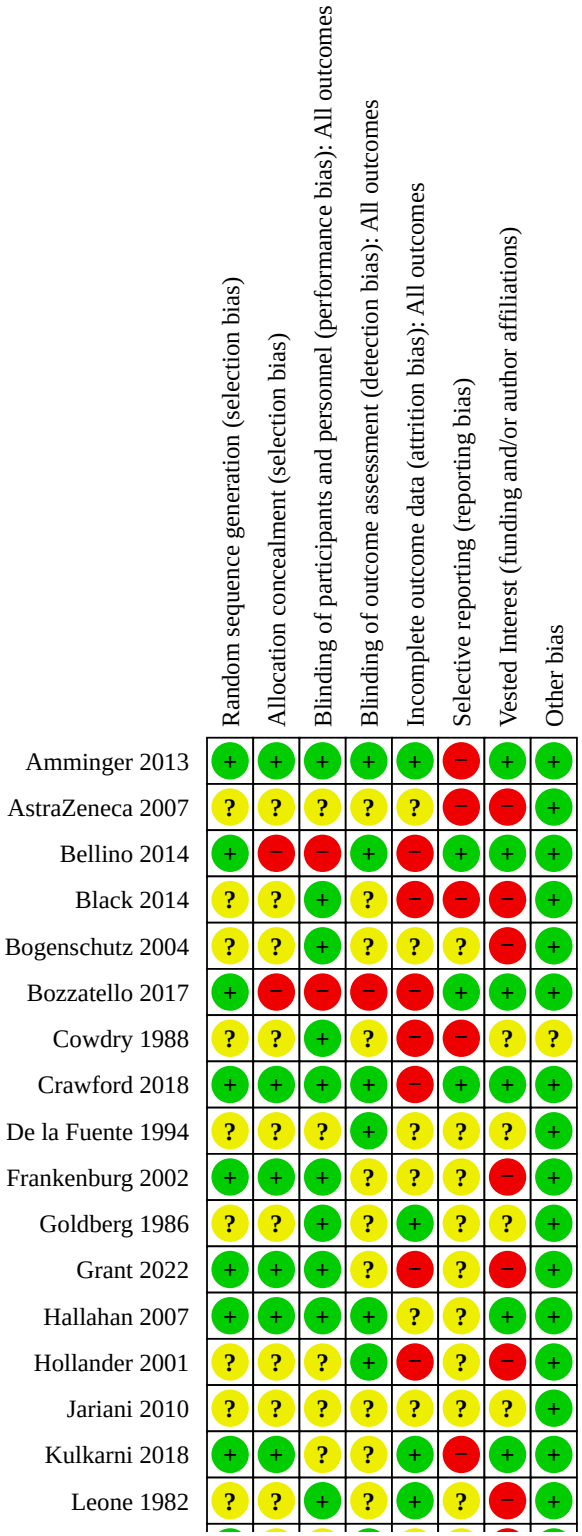
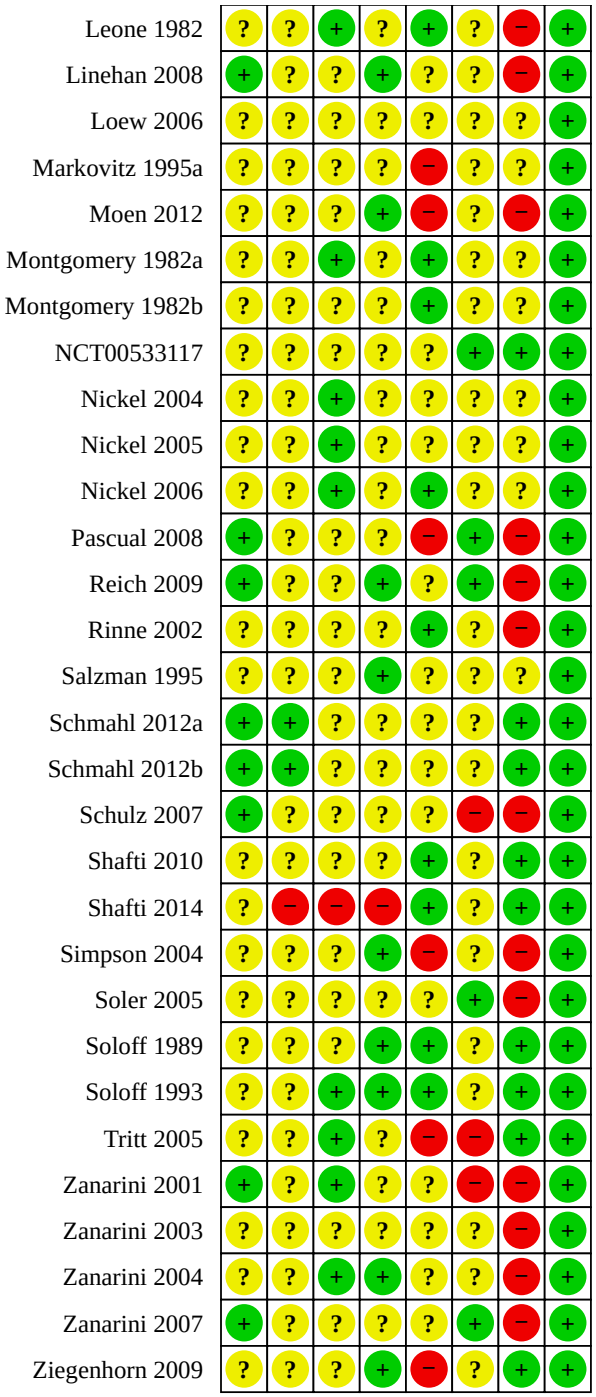


Figure 3. (Continued)



Allocation

Sequence generation

We judged 16 trials as having a low risk of bias, where the randomisation method was described and adequate (e.g. using computer-generated random numbers) (Amminger 2013; Bellino 2014; Bozzatello 2017; Crawford 2018; Frankenburg 2002; Grant 2022; Hallahan 2007; Kulkarni 2018; Linehan 2008; Pascual 2008; Reich 2009; Schmahl 2012a; Schmahl 2012b; Schulz 2007; Zanarini 2001; Zanarini 2007). The remaining 30 trials did not contain an exact description of how treatment allocation had been conducted, so we rated these trials as having unclear risk of bias.

Allocation concealment

We assessed eight trials as having a low risk of bias (e.g. central third party randomisation) (Amminger 2013; Crawford 2018; Frankenburg 2002; Grant 2022; Hallahan 2007; Kulkarni 2018; Schmahl 2012a; Schmahl 2012b). Three trials were rated as having a high risk of bias due to inadequate (e.g. based on day of admission

or case record number) or no allocation concealment (Bellino 2014; Bozzatello 2017; Shafti 2014). The remaining 35 of the trials did not have adequate information to enable a judgement about the allocation concealment, thus they were rated as having an unclear risk of bias.

Blinding

Blinding of participants and personnel

We rated 18 trials as having a low risk of bias as they reported how the participants and personnel were kept blind to the treatment allocation (Amminger 2013; Black 2014; Bogenschutz 2004; Cowdry 1988; Crawford 2018; Frankenburg 2002; Goldberg 1986; Grant 2022; Hallahan 2007; Leone 1982; Montgomery 1982a; Nickel 2004; Nickel 2005; Soloff 1993; Tritt 2005; Zanarini 2001; Zanarini 2004). We rated three trials as having a high risk of bias due to no blinding of participants and personnel (Bellino 2014; Bozzatello 2017; Shafti 2014). The remaining 25 trials were judged as having an unclear risk of bias due to inadequate description of the blinding of participants and personnel.

Blinding of outcome assessors

We judged 15 trials as having a low risk of bias due to adequate blinding of outcome assessors (i.e. described efforts to ensure the blinding of outcome assessment and due to these efforts blinding was deemed unlikely to be broken) (Amminger 2013; Bellino 2014; Crawford 2018; De la Fuente 1994; Hallahan 2007; Hollander 2001; Linehan 2008; Moen 2012; Reich 2009; Salzman 1995; Simpson 2004; Soloff 1989; Soloff 1993; Zanarini 2004; Ziegenhorn 2009). Two trials were rated as having a high risk of bias due to no blinding of outcome assessors (Bozzatello 2017; Shafti 2014). The remaining 29 trials were rated as having an unclear risk of bias due to inadequate description (e.g. insufficient information to permit judgement of low or high risk) of the blinding of outcome assessors.

Incomplete outcome data

We judged 12 trials as having a low risk of bias due to no indication of incomplete outcome reporting (e.g. due to no missing outcome data or appropriate methods to handle missing data were described) (Amminger 2013; Goldberg 1986; Kulkarni 2018; Leone 1982; Montgomery 1982a; Montgomery 1982b; Nickel 2006; Rinne 2002; Shafti 2010; Shafti 2014; Soloff 1989; Soloff 1993). Thirteen trials were considered to be at high risk of bias due to the inadequate descriptions of possible reasons for missing data (e.g. by inappropriate application of simple imputation or the likelihood of missing data being related to the true outcome) (Bellino 2014; Black 2014; Bozzatello 2017; Cowdry 1988; Crawford 2018; Grant 2022; Hollander 2001; Markovitz 1995a; Moen 2012; Pascual 2008; Simpson 2004; Tritt 2005; Ziegenhorn 2009). The remaining 21 trials did not provide descriptions of possible reasons for missing data, so we rated these trials as having an unclear risk of bias.

Selective reporting

We considered eight trials to be at low risk of bias, as all prespecified outcomes were reported according to the published protocol or the registration of the trial, which was registered prior to conducting the trial (Bellino 2014; Bozzatello 2017; Crawford 2018; NCT00533117; Pascual 2008; Reich 2009; Soler 2005; Zanarini 2007). We rated eight trials to be at high risk of bias due to the trials not explicitly reporting data for the prespecified outcomes, even when they had initially planned to report them (Amminger 2013; AstraZeneca 2007; Black 2014; Cowdry 1988; Kulkarni 2018; Schulz 2007; Tritt 2005; Zanarini 2001). We rated the remaining 30 trials as having an unclear risk of bias due to either not having a published protocol prior to initiating the trial or not providing sufficient information in the report to assess the extent of reporting bias.

Other potential sources of bias

Vested interest

Fifteen trials were rated as having a low risk of bias in terms of funding or author affiliations (Amminger 2013; Bellino 2014; Bozzatello 2017; Crawford 2018; Hallahan 2007; Kulkarni 2018; NCT00533117; Schmahl 2012a; Schmahl 2012b; Shafti 2010; Shafti 2014; Soloff 1989; Soloff 1993; Tritt 2005; Ziegenhorn 2009). We rated 19 trials to be at high risk of bias due to author affiliations with or funding from pharmaceutical companies: AstraZeneca 2007; Black 2014; Bogenschutz 2004; Frankenburg 2002; Grant 2022; Hollander 2001; Leone 1982; Linehan 2008; Moen 2012; Pascual 2008; Reich 2009; Rinne 2002; Schulz 2007; Simpson 2004; Soler 2005; Zanarini 2001; Zanarini 2003; Zanarini 2004; Zanarini 2007. Twelve trials did not provide sufficient information about funding or affiliations to permit a judgement of low or high risk, so these trials have been rated as having an unclear risk of bias (Cowdry 1988; De la Fuente 1994; Goldberg 1986; Jariani 2010; Loew 2006; Markovitz 1995a; Montgomery 1982a; Montgomery 1982b; Nickel 2004; Nickel 2005; Nickel 2006; Salzman 1995).

Other risk of bias

We had intended to use this domain as a default category of bias that might not have been covered by the remaining categories, and could potentially be a threat to validity. Only one of the included trials, Cowdry 1988, was rated as having unclear risk of bias in this domain due to an obvious carry-over effect between medication phases. The remaining trials had no apparent other sources of bias and were rated as low risk.

Overall risk of bias

All trials were assessed as being at high risk of bias because at least one domain was rated as being at high or unclear risk of bias.

Effects of interventions

See: **Summary of findings 1** Antipsychotics compared with placebo for people with borderline personality disorder; **Summary of findings 2** Antidepressants compared with placebo for people with borderline personality disorder; **Summary of findings 3** Mood stabilisers compared with placebo for people with borderline personality disorder

We present the results for each of the primary and secondary outcomes connected to the three comparisons.

1. *Medications compared to placebo*, which covers analyses of medications and a placebo comparator. All medications have been divided into the four drug classifications: antipsychotics, antidepressants, mood stabilisers, and miscellaneous medications that have been reported by name (omega-3 fatty acids, naltrexone, clonidine, memantine hydrochloride and alprazolam).
2. *Medication compared to another medication,* which covers head-to-head analyses (where the comparator is an active medication instead of a placebo).

3. *Medication compared to a combination of medications,* which covers analyses of a medication compared to the combination of the same medication and another active medication.

Where a meta-analysis involved two or more different instruments to measure the same construct, we reported effect sizes as SMD, otherwise we reported the MD. To identify the MIREDIF, we transformed the SMD to MD for the scale with best validity and reliability for that outcome. Where we could not find this, we used an assumption that the minimal relevant clinical intervention effect was approximately ½ SD on the used scale, which can be used as a MIREDIF (Norman 2004). An overview of the specific instruments used to measure each outcome by the individual trials can be found in Appendix 5.

We contacted authors of 25 trials with unclear or missing data and requested the necessary information. Authors of seven trials replied that their registered trials had never been started or had to be discontinued early due to recruiting problems, personal changes, or no funding. We retrieved additional information by email from five authors of included trials (Bellino 2014; Black 2014; Crawford 2018; Kulkarni 2018; Schmahl 2012a; Schmahl 2012b). We received no reply from authors of 17 trials (Amminger 2013; AstraZeneca 2007; Bogenschutz 2004; Coccaro 1997; Cowdry 1988; De la Fuente 1994; Jariani 2010; Koenigsberg 2003; La Malfa 2003; Markovitz 1995a; NCT00437099; NCT00533117; Shafti 2010; Shafti 2014; Serban 1984; Verkes 1998; Ziegenhorn 2009).

We performed TSA on relevant primary outcomes and the relevant secondary outcomes, interpersonal problems, attrition, and adverse events at end of treatment for the three comparisons in our summary of findings tables, adjusting for multiplicity and sparse data. We used the TSA for our rating of imprecision where we were uncertain about our ratings. We considered all trials as being at high risk of bias overall. However, we used all eligible trials in the meta-analyses, as the *Cochrane Handbook for Systematic Reviews of Interventions* recommends doing when all trials are assigned the same risk of bias. We took account of our risk of bias assessment when considering the quality of the evidence using the GRADE approach, to ensure that judgements about risk of bias and other factors affecting the quality of the evidence were taken into account when interpreting the results of the review (Higgins 2022).

Negative effect estimates indicate beneficial effects by the active medication, in terms of a reduction of burden. If scales were used by the primary studies where higher scores were the preferable outcome, e.g. in terms of a better level of psychosocial functioning, scores were multiplied by (-1) before entering them for effect size calculation, to ensure that a negative direction of effect indicated a beneficial effect throughout the whole review.

Comparison 1: Medication compared with placebo

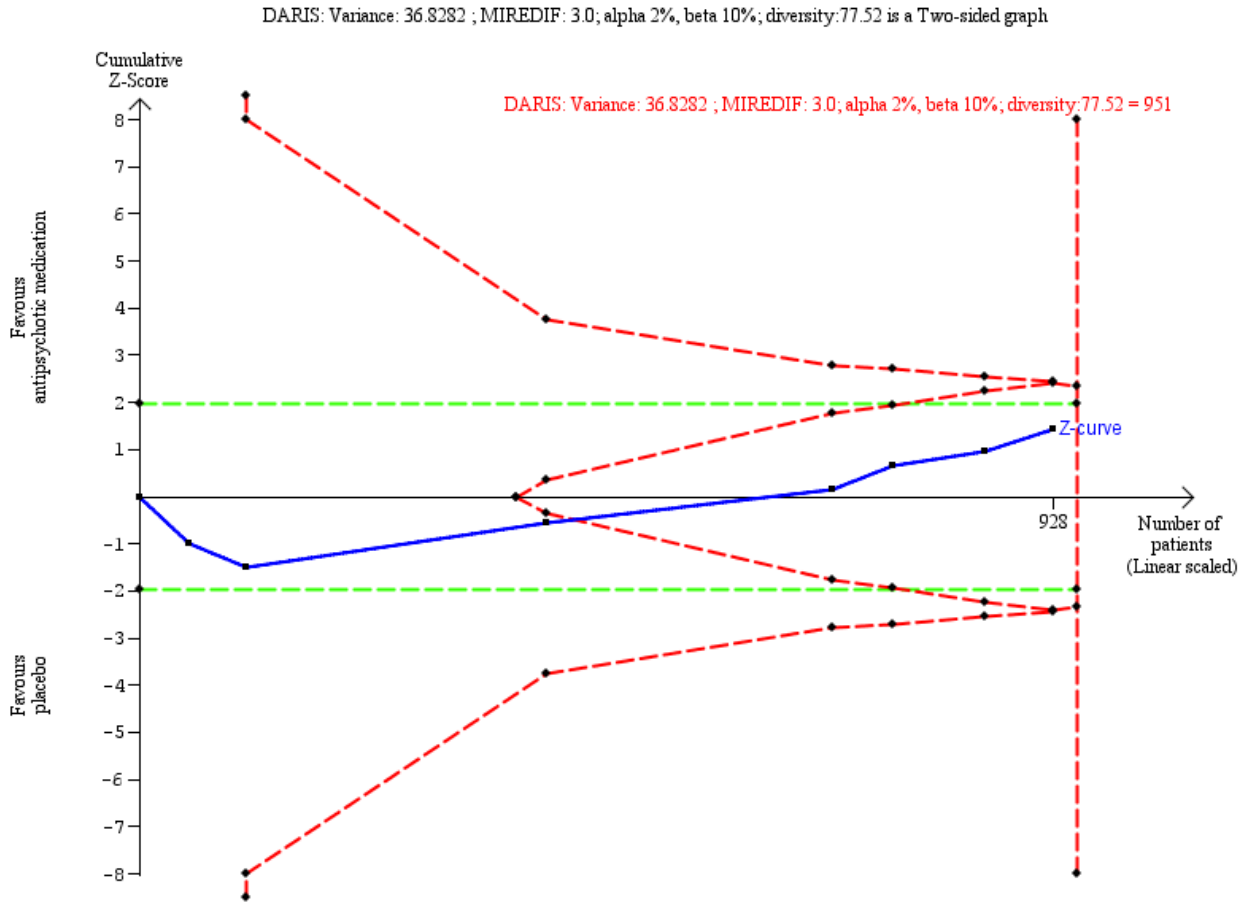
Primary outcomes

1.1 BPD symptom severity

A total of 16 trials comparing medication with placebo reported data for BPD symptom severity.

Eight trials compared antipsychotics to placebo (Black 2014; Cowdry 1988; Goldberg 1986; Grant 2022; Pascual 2008; Schulz 2007; Soloff 1993; Zanarini 2007). The evidence indicates little to no difference but is very uncertain about the effect of antipsychotics compared with placebo on BPD symptom severity at the end of treatment (SMD -0.18, 95% CI -0.45 to 0.08; P = 0.18; I^2 = 70%; 8 trials, 951 participants; very low-certainty evidence; Analysis 1.1). The TSA showed that the z-curve ended in the futility area, which means that the anticipated effect can be rejected. See Figure 4 in Appendix 6.

Figure 4. TSA borderline severity: antipsychotics DARIS: Diversity-adjusted required information size; MIREDIF: Minimal relevant difference; TSA: Trial Sequential Analysis



Two trials compared antidepressants to placebo post-treatment (Cowdry 1988; Soloff 1993). The evidence indicates little to no difference but is very uncertain about the effect of antidepressants compared with placebo regarding BPD symptom severity (SMD 0.27, 95% CI −0.65 to 1.18; P = 0.57, I^2 = 73%; 2 trials, 87 participants; very low-certainty evidence; Analysis 1.1).

Four trials compared mood stabilisers to placebo (Cowdry 1988; Crawford 2018; Moen 2012; Reich 2009). The evidence indicates little to no difference but is very uncertain about the effect of mood stabilisers compared with placebo at end of treatment (SMD 0.07, 95% CI −0.43 to 0.57; P = 0.78, I^2 = 55%; 4 trials, 256 participants; very low-certainty evidence; Analysis 1.1).

Four trials compared miscellaneous pharmacological therapies to placebo: Cowdry 1988 compared alprazolam to placebo; Kulkarni 2018 compared memantin-hydrochloride to placebo; Schmahl 2012b compared naltrexone to placebo; and Ziegenhorn 2009 compared clonidine to placebo. There was no evidence that any of these miscellaneous medications had an effect on BPD symptom severity at the end of treatment compared to placebo; Cowdry 1988: MD −0.58, 95% CI −1.63 to 0.47; P = 0.28; 1 trial, 25 participants; Analysis 1.2; Kulkarni 2018: MD 2.00, 95% CI −1.62 to 5.62; P = 0.28; 1 trial, 33 participants; Analysis 1.2; Schmahl 2012b: MD 0.10, 95% CI −0.29 to 0.49; P = 0.62; 1 trial, 32 participants; Analysis 1.2; and Ziegenhorn 2009: MD −13.11, 95% CI −65.36 to 39.14; P = 0.62; 1 trial, 34 participants; Analysis 1.2.

1.2 Self-harm

Five trials comparing medications with placebo reported data for self-harm.

Two trials compared antipsychotics to placebo (Linehan 2008; Nickel 2006). The evidence is very uncertain about the effect of antipsychotics compared with placebo at end of treatment (RR 0.66, 95% CI 0.15 to 2.84; P = 0.57, I^2 = 67%; 2 trials, 76 participants; very low-certainty evidence; Analysis 1.4).

One trial compared an antidepressant to placebo (Simpson 2004). It may have little to no effect but the evidence is very uncertain about the effect of the antidepressant compared with placebo at the end of treatment (MD 0.45, 95% CI −10.55 to 11.45; P = 0.94; 1 trial, 20 participants; very low-certainty evidence; Analysis 1.3).

One trial compared a mood stabiliser to placebo (Crawford 2018). The evidence is very uncertain about the effect of mood stabiliser lamotrigine compared with placebo at the end of treatment (RR 1.08, 95% CI 0.79 to 1.48; P = 0.64; 1 trial, 276 participants; very low-certainty evidence; Analysis 1.4).

One trial compared omega-3 fatty acids to placebo (Hallahan 2007). There was no clear evidence of a difference between omega-3 fatty acids and placebo regarding self-harm at the end of treatment (RR 1.23, 95% CI 0.51 to 2.97; P = 0.65; 1 trial, 49 participants; Analysis 1.4).

1.3 Suicide-related outcomes

Thirteen trials comparing medications with placebo reported data for suicide-related outcomes.

Eight trials compared antipsychotics to placebo (Bogenschutz 2004; Cowdry 1988; Grant 2022; Linehan 2008; Montgomery 1982a; Pascual 2008; Soler 2005; Schulz 2007; Zanarini 2007). The evidence indicates little to no effect but is very uncertain about the effect of antipsychotics compared with placebo at the end of treatment either with continuous outcome data (SMD 0.05, 95% CI -0.18 to 0.29; P = 0.67; I^2 = 55%; 7 trials, 854 participants; very low-certainty evidence; Analysis 1.5) or with dichotomous outcome data (RR 0.73, 95% CI 0.31 to 1.73; P = 0.47, I^2 = 62%; 2 trials, 61 participants; very low-certainty evidence; Analysis 1.7).

Three trials compared antidepressants to placebo (Cowdry 1988; Montgomery 1982b; Simpson 2004). The evidence indicates little to no effect but is very uncertain about the effect of antidepressants at end of treatment compared with placebo either with continuous data (SMD −0.26, 95% CI −1.62 to 1.09; P = 0.70, I^2 = 80%; 2 trials, 45 participants; very low-certainty evidence; Analysis 1.5), or with dichotomous data (RR 1.00, 95% CI 0.71 to 1.41; P = 1.00; 1 trial, 58 participants; very low-certainty evidence; Analysis 1.7).

Two trials compared mood stabilisers to placebo (Cowdry 1988; Hollander 2001). The evidence indicates little to no effect but is very uncertain about the effect of mood stabilisers compared with placebo at the end of treatment (SMD -0.36, 95% CI -1.96 to 1.25; P = 0.66, I^2 = 81%; 2 trials, 44 participants; very low-certainty evidence; Analysis 1.5).

One trial compared omega-3 fatty acids to placebo (Hallahan 2007). There was evidence that omega-3 fatty acids may reduce suicide-related outcomes more than placebo at the end of treatment (RR 0.52, 95% CI 0.28 to 0.95; P = 0.03; 1 trial, 49 participants; Analysis 1.7).

One trial also compared the benzodiazepine alprazolam to placebo (Cowdry 1988). There was no clear evidence of a difference between alprazolam and placebo on suicide-related outcomes at end of treatment (MD 0.75, 95% CI -0.18 to 1.68; P = 0.11; 1 trial, 25 participants; Analysis 1.6).

1.4 Psychosocial functioning

Seventeen trials comparing medications to placebo reported data for psychosocial functioning. For consistency, negative values indicate favourable results for the active medication as for the remaining outcomes.

Seven trials compared antipsychotics to placebo (Black 2014; Goldberg 1986; Schulz 2007; Soler 2005; Soloff 1989; Soloff 1993; Zanarini 2007). The evidence indicates little to no difference in outcome but is very uncertain about the effect of antipsychotics compared with placebo on psychosocial functioning at end of treatment (SMD −0.16, 95% CI −0.33 to 0.00; P = 0.05, I^2 = 23%; 7 trials, 904 participants; very low-certainty evidence; Analysis 1.8).

Four trials compared antidepressants to placebo (Salzman 1995; Simpson 2004; Soloff 1989; Soloff 1993). The evidence indicates little to no difference between antidepressants and placebo regarding psychosocial functioning at end of treatment, but the evidence is very uncertain (SMD -0.25, 95% CI −0.57 to 0.06; P = 0.11, I^2 = 0%; 4 trials, 161 participants; very low-certainty evidence; Analysis 1.8).

Two trials compared mood stabilisers to placebo (Crawford 2018; De la Fuente 1994) with little to no difference in psychosocial functioning at the end of treatment as compared to placebo (SMD −0.01, 95% CI −0.28 to 0.26; P = 0.94, I^2 = 0%; 2 trials, 214 participants; very low-certainty evidence; Analysis 1.8). Hollander 2001 obtained a similar result (RR 0.64, 95% CI 0.37 to 1.11; P = 0.11; 1 trial, 16 participants; very low-certainty evidence; Analysis 1.10).

One trial compared omega-3 fatty acids to placebo (Amminger 2013). There was evidence of a difference between mood stabilisers and placebo regarding psychosocial function at the end of treatment favouring placebo (MD 19.90, 95% CI 7.11 to 32.69; P = 0.002; 1 trial, 15 participants; Analysis 1.9).

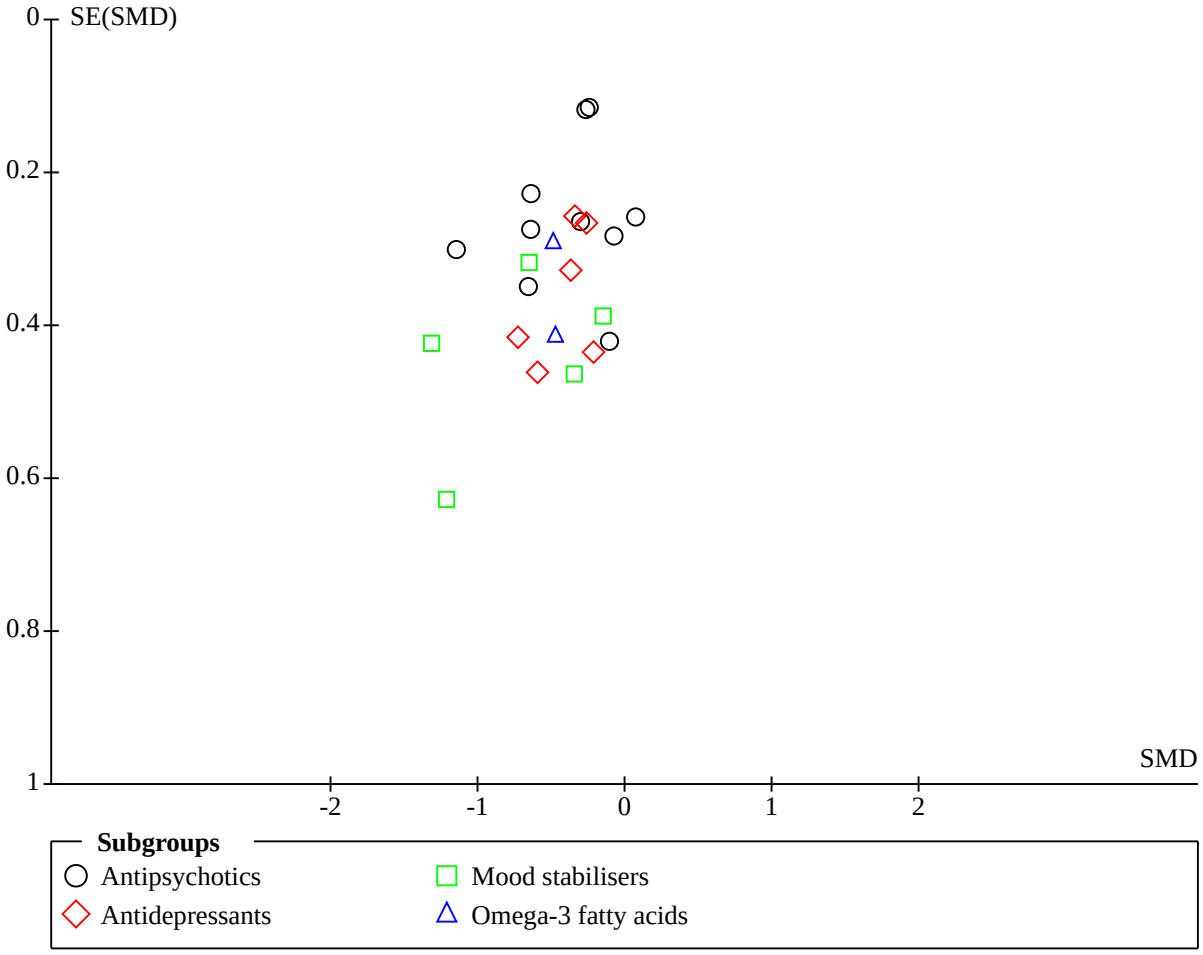
Secondary outcomes

1.5 Anger

Twenty trials comparing medications with placebo reported data for anger at the end of treatment.

Ten trials compared antipsychotics to placebo (Black 2014; Bogenschutz 2004; Cowdry 1988; Goldberg 1986; Nickel 2006; Pascual 2008; Schulz 2007; Soloff 1989; Soloff 1993; Zanarini 2007). There was evidence of a difference between treatments regarding anger at the end of treatment favouring antipsychotics (SMD −0.37, 95% CI −0.55 to −0.18; P = 0.0001, I^2 = 48%; 10 trials, 1025 participants; Analysis 1.11). Inspection of the funnel plot suggested potential bias (small asymmetry; see Figure 5; Appendix 6), but we found no evidence of possible significant publication bias: Egger's regression intercept (bias) 2.10 (two tailed, P = 0.069).

Figure 5. Funnel plot of comparison: 1 Medications compared with placebo, outcome: 1.11 Secondary: Anger at end of treatment (continuous outcomes, SMDs)



Six trials compared antidepressants to placebo (Cowdry 1988; Rinne 2002; Salzman 1995; Soloff 1989; Soloff 1993). There was evidence of a difference between treatments regarding anger at the end of treatment favouring antidepressants (SMD −0.37, 95% CI −0.64 to −0.11; P = 0.006, I^2 = 0%; 6 trials, 224 participants; Analysis 1.11).

Eight trials compared mood stabilisers to placebo (Cowdry 1988; De la Fuente 1994; Frankenburg 2002; Hollander 2001; Loew 2006; Nickel 2004; Nickel 2005; Tritt 2005). Three of these trials reported extraordinarily large SMDs (Tritt 2005: SMD −1.69, 95% CI −2.62 to −0.75; Loew 2006: SMD −3.10, 95% CI −3.89 to −2.30; Nickel 2004: SMD −2.80, 95% CI −3.89 to −1.71). We decided to exclude the outliers one by one from the primary analyses, until low heterogeneity was reached (see Analysis 26.1 for sensitivity analysis). After excluding outliers, there was evidence of a difference between treatments regarding anger at the end of treatment favouring mood stabilisers (SMD −0.67, 95% CI −1.10 to −0.24; P = 0.002, I^2 = 26%; 5 trials, 135 participants; Analysis 1.11).

Two trials compared omega-3 fatty acids to placebo (Hallahan 2007; Zanarini 2003). There was a difference between treatments regarding anger at the end of treatment favouring omega-3 fatty acids (SMD −0.48, 95% CI −0.95 to −0.01; P = 0.04, I^2 = 0%; 2 trials, 76 participants; Analysis 1.11).

One cross-over trial compared naltrexone to placebo (Schmahl 2012b). There was no evidence of a difference between treatments regarding anger at the end of treatment (MD 1.65, 95% CI −4.54 to 7.84; P = 0.60; 1 trial, 32 participants; Analysis 1.12).

Another cross-over trial compared alprazolam to placebo (Cowdry 1988). There was no evidence of a difference between treatments regarding anger at the end of treatment (MD −0.57, 95% CI −1.48 to 0.34; P = 0.22; 1 trial, 25 participants; Analysis 1.12).

1.6 Affective instability

Seven trials comparing pharmacological treatments to placebo reported data for affective instability.

Four trials compared antipsychotics to placebo (Bogenschutz 2004; Pascual 2008; Schulz 2007; Zanarini 2007). There was a small difference between treatments regarding affective instability at the end of treatment favouring antipsychotics (SMD -0.16, 95% CI -0.31 to -0.01; P = 0.04; I^2 = 0%; 4 trials, 691 participants; Analysis 1.13).

One trial (Rinne 2002) compared an antidepressant to placebo. There was a small difference between treatments regarding affective instability at the end of treatment favouring the antidepressant (MD -1.66, 95% CI -3.26 to -0.06; P = 0.04; 1 trial, 38 participants; Analysis 1.14).

Two trials (Reich 2009 and Crawford 2018) compared mood stabilisers to placebo. There was no difference between treatments regarding affective instability at the end of treatment (SMD −0.21, 95% CI −0.68 to 0.26; P = 0.38, I^2 = 39%; 2 trials, 222 participants; Analysis 1.13).

1.7 Chronic feelings of emptiness

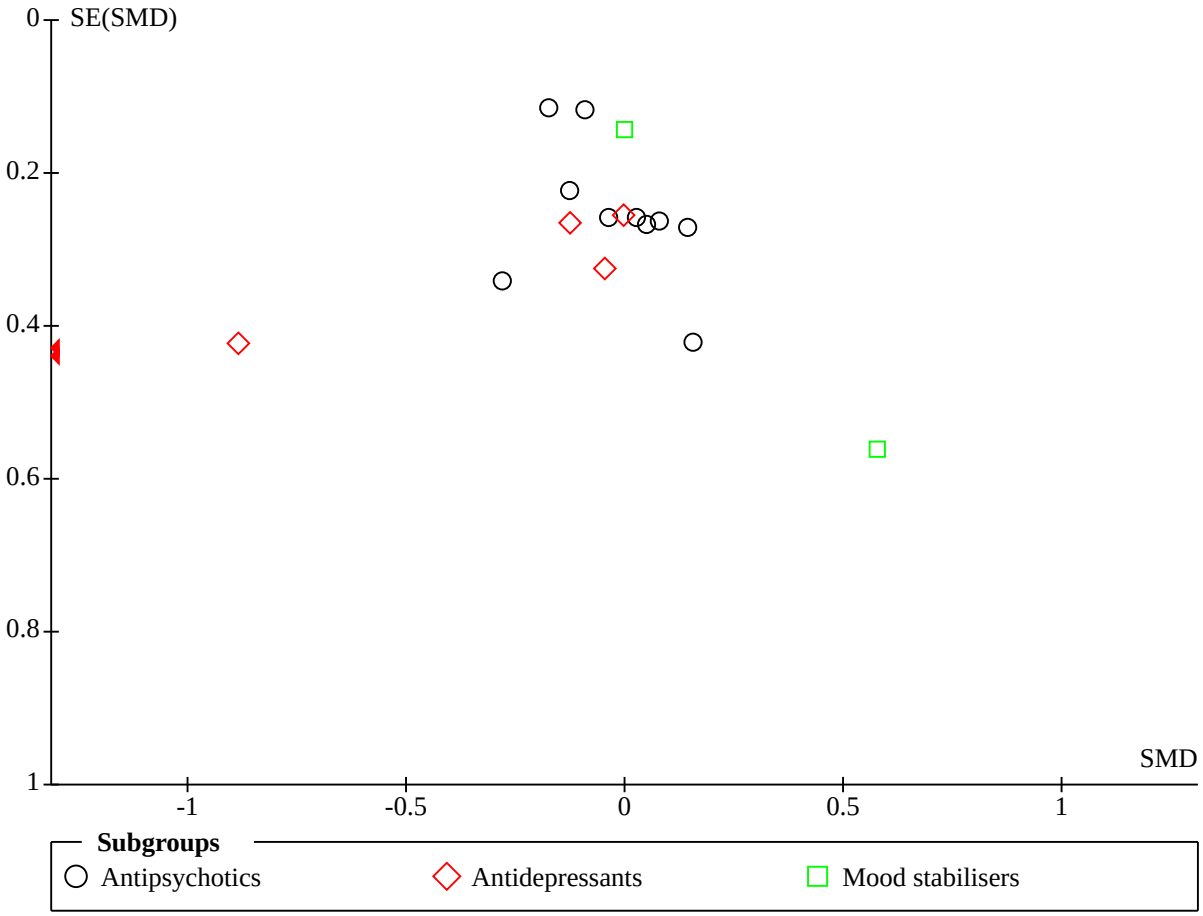
Four trials comparing pharmacological treatments to placebo reported data for chronic feelings of emptiness. All four trials compared antipsychotics to placebo (Bogenschutz 2004; Pascual 2008; Schulz 2007; Zanarini 2007). There was no difference between treatments regarding chronic feelings of emptiness at the end of treatment (SMD −0.00, 95% CI −0.16 to 0.15; P = 0.96, I^2 = 6%; 4 trials, 691 participants; Analysis 1.15).

1.8 Impulsivity

Sixteen trials comparing pharmacological treatments to placebo reported data for impulsivity.

Ten trials compared antipsychotics to placebo (Black 2014; Bogenschutz 2004; Cowdry 1988; Grant 2022; Pascual 2008; Schulz 2007; Soler 2005; Soloff 1989; Soloff 1993; Zanarini 2007). There was no difference between treatments regarding impulsivity at end of treatment (SMD -0.08, 95% CI -0.20 to 0.04; P = 0.21; I^2 = 0%: 10 trials, 1038 participants; Analysis 1.16). Inspection of the funnel plot suggested potential bias (small asymmetry; see Figure 6; Appendix 6), but we found no evidence of possible significant publication bias: Egger's regression intercept (bias) 2.10 (two tailed, P = 0.069).

Figure 6. Funnel plot of comparison: 1 Medications compared with placebo, outcome: 1.16 Secondary: Impulsivity at end of treatment (continuous outcomes, SMDs)



Four trials compared antidepressants to placebo (Cowdry 1988; Rinne 2002; Soloff 1989; Soloff 1993). There was no clear difference between treatments regarding impulsivity at end of treatment (SMD -0.17, 95% CI -0.49 to 0.15; P = 0.29; I^2 = 13%; 4 trials, 182 participants; Analysis 1.16).

Five trials compared mood stabilisers to placebo (Cowdry 1988; Crawford 2018; De la Fuente 1994; Moen 2012; Reich 2009). In the analysis using dichotomous data, there was no difference between treatments regarding impulsivity at the end of treatment (RR 0.88, 95% CI 0.53 to 1.46; P = 0.61; 1 trial, 20 participants; Analysis 1.18). In the analysis using continuous data, there was little to no difference

between treatments regarding impulsivity at the end of treatment favouring mood stabilisers (SMD -0.56, 95% CI -1.46 to 0.35; P = 0.23; I^2 = 84%; 4 trials, 265 participants; Analysis 1.16).

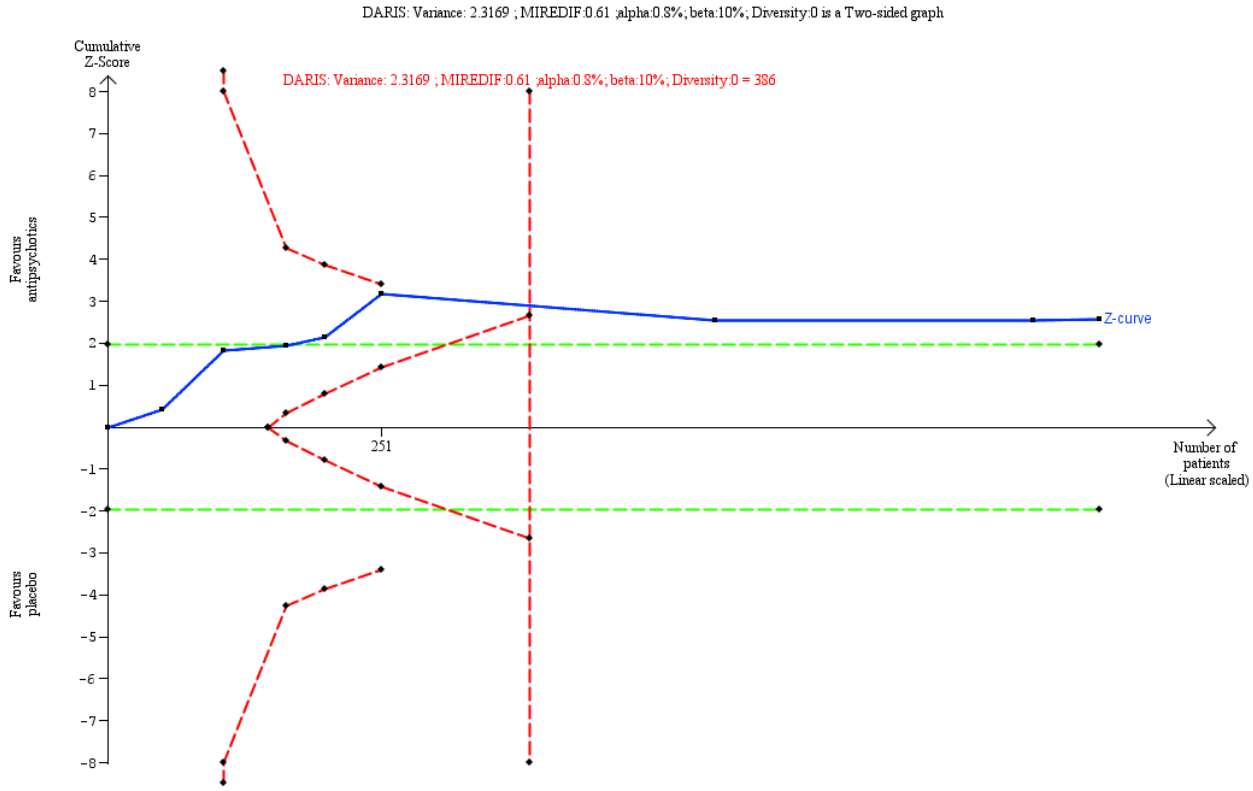
One trial also compared the benzodiazepine alprazolam to placebo (Cowdry 1988). There was no difference between treatments regarding impulsivity at the end of treatment (MD 0.67, 95% CI −0.36 to 1.70; P = 0.20; 1 trial, 25 participants; Analysis 1.17).

1.9 Interpersonal problems

Fourteen trials comparing pharmacological treatments to placebo reported data for interpersonal problems.

Eight trials compared antipsychotics to placebo (Bogenschutz 2004; Goldberg 1986; Nickel 2006; Pascual 2008; Schulz 2007; Soloff 1989; Soloff 1993; Zanarini 2007). Low-certainty evidence suggests that antipsychotics may slightly reduce interpersonal problems (SMD −0.21, 95% CI −0.34 to −0.08; P = 0.002, I^2 = 0%; 8 trials, 907 participants; low-certainty evidence; Analysis 1.19). The TSA analysis showed that the DARIS was reached (n = 386), and that there was no risk of type 1 error (TSA adjusted CI −0.60 to 0.08). See Figure 7; Appendix 6.

Figure 7. TSA interpersonal problems: antipsychotics DARIS: Diversity-adjusted required information size; MIREDIF: Minimal relevant difference; TSA: Trial Sequential Analysis



Two trials compared antidepressants to placebo (Soloff 1989; Soloff 1993). There was little to no difference between treatments regarding interpersonal problems at the end of treatment (SMD −0.07, 95% CI −0.69 to 0.55; P = 0.82, I^2 = 66%; 2 trials, 119 participants; low-certainty evidence; Analysis 1.19).

Four trials compared mood stabilisers with placebo (Crawford 2018; De la Fuente 1994; Frankenburg 2002; Loew 2006). This low-certainty evidence suggested that mood stabilisers may result in a reduction of interpersonal problems, compared with placebo at end of treatment on interpersonal (SMD −0.58, 95% CI −1.14 to −0.02; P = 0.04, I^2 = 73%; 4 trials, 300 participants; low-certainty evidence; Analysis 1.19).

1.10 Abandonment

Four trials comparing pharmacological treatments to placebo reported continuous data for fear of abandonment. All four trials compared antipsychotics to placebo (Bogenschutz 2004; Pascual 2008; Schulz 2007; Zanarini 2007). There was no difference between treatments regarding fear of abandonment at the end of treatment (SMD −0.01, 95% CI −0.17 to 0.14; P = 0.88, I^2 = 5%; 4 trials, 691 participants; Analysis 1.20).

1.11 Identity disturbance

Four trials comparing pharmacological treatments to placebo reported continuous data for identity disturbance. All four trials compared antipsychotics to placebo (Bogenschutz 2004; Pascual 2008; Schulz 2007; Zanarini 2007). There was no difference between treatments regarding identity disturbance at the end of treatment (SMD −0.09, 95% CI −0.25 to 0.07; P = 0.28, I^2 = 7%; 4 trials, 691 participants; Analysis 1.21).

1.12 Dissociation and psychotic-like symptoms

Thirteen trials comparing pharmacological treatments to placebo reported data for dissociation and psychotic-like symptoms.

Eight trials compared antipsychotics to placebo (Bogenschutz 2004; Goldberg 1986; Nickel 2006; Pascual 2008; Schulz 2007; Soloff 1989; Soloff 1993; Zanarini 2007). There was a small difference between treatments regarding dissociation and psychotic-like symptoms at the end of treatment favouring antipsychotics (SMD −0.28, 95% CI −0.50 to −0.06; P = 0.01, I^2 = 55%; 8 trials, 907 participants; Analysis 1.22).

Three trials compared antidepressants to placebo (Simpson 2004; Soloff 1989; Soloff 1993). There was no difference between treatments regarding dissociation and psychotic-like symptoms at the end of treatment (SMD −0.22, 95% CI −0.62 to 0.18; P = 0.29, I^2 = 25%; 3 trials, 139 participants; Analysis 1.22).

Three trials compared mood stabilisers to placebo (Crawford 2018; De la Fuente 1994; Loew 2006). There was no difference between treatments regarding dissociation and psychotic-like symptoms at the end of treatment (SMD −0.23, 95% CI −0.66 to 0.20; P = 0.30; I^2 = 51%; 3 trials, 270 participants; Analysis 1.22).

One trial compared omega-3 fatty acids to placebo (Amminger 2013). There was no difference between treatments regarding dissociation and psychotic-like symptoms at the end of treatment (MD −2.80, 95% CI −5.70 to 0.10; P = 0.09; 1 trial, 15 participants; Analysis 1.23).

1.13 Depression

Twenty-six trials comparing pharmacological treatments to placebo reported data for depression.

Twelve trials compared antipsychotics to placebo (Black 2014; Cowdry 1988; Goldberg 1986; Grant 2022; Linehan 2008; Nickel 2006; Pascual 2008; Schulz 2007; Soler 2005; Soloff 1989; Soloff 1993; Zanarini 2007). There was a difference between treatments regarding depression at end of treatment favouring antipsychotics (SMD -0.22, 95% CI -0.42 to -0.01; P = 0.04; I^2 = 59; 12 trials, 1138 participants; Analysis 1.24).

Five trials compared antidepressants to placebo (Cowdry 1988; Salzman 1995; Simpson 2004; Soloff 1989; Soloff 1993). There was no clear difference between treatments regarding depression at end of treatment (SMD −0.37, 95% CI −0.82 to 0.08; P = 0.11, I^2 = 52%; 5 trials, 187 participants; Analysis 1.24).

Six trials compared mood stabilisers to placebo (Cowdry 1988; Crawford 2018; De la Fuente 1994; Frankenburg 2002; Hollander 2001; Loew 2006). There was a difference between treatments regarding depression at the end of treatment favouring mood stabilisers (SMD −0.44, 95% CI −0.80 to −0.08; P = 0.02, I^2 = 46%; 6 trials, 344 participants: Analysis 1.24).

Six trials compared miscellaneous pharmacological treatments to placebo.

Three of these trials used a parallel design and compared omega-3 fatty acids to placebo (Amminger 2013; Hallahan 2007; Zanarini 2003). The analysis with dichotomous data showed that there was a difference between omega-3 fatty acids and placebo regarding depression at the end of treatment favouring omega-3 fatty acids (RR 0.48, 95% CI 0.28 to 0.81; P = 0.006; 1 trial, 49 participants; Analysis 1.26), while in the analysis with continuous data there was no difference between treatments regarding depression at end of treatment (SMD −0.54, 95% CI −1.18 to 0.11; P = 0.10, I^2 = 0%; 2 trials, 42 participants; Analysis 1.24).

The other three trials used cross-over designs. The first trial compared clonidine to placebo (Ziegenhorn 2009), and found no difference between clonidine and placebo regarding depression at the end of treatment (MD −2.54, 95% CI −10.27 to 5.19; P = 0.52; 1 trial, 34 participants; Analysis 1.25). The second trial compared naltrexone to placebo (Schmahl 2012b), and found no difference between naltrexone and placebo regarding depression at the end of treatment (MD 2.50, 95% CI −4.22 to 9.22; P = 0.47; 1 trial, 32 participants; Analysis 1.25). The third trial compared the benzodiazepine alprazolam to placebo (Cowdry 1988), and found no difference between alprazolam and placebo on depression at the end of treatment (MD 0.27, 95% CI −0.73 to 1.27; P = 0.60; 1 trial, 25 participants; Analysis 1.25).

1.14 Attrition

Thirty-two trials comparing medications to placebo reported data on attrition.

Thirteen trials compared antipsychotics to placebo (Black 2014: Bogenschutz 2004; Goldberg 1986; Grant 2022; Linehan 2008; Montgomery 1982a; Pascual 2008; Schulz 2007; Soler 2005; Soloff 1989; Soloff 1993; Zanarini 2001; Zanarini 2007). There was no clear difference between treatments regarding attrition at the end of treatment (RR 1.11, 95% CI 0.89 to 1.38; P = 0.34; I^2 = 35%; 13 trials, 1216 participants; low-certainty evidence ; Analysis 1.27). However, the TSA showed that the DARIS was not reached (n = 2008), and that there was a potential risk of type 1 error (TSA-adjusted CI 0.74 to 2.13). See Figure 8 in Appendix 6. Inspection of the funnel plot suggested potential bias (small asymmetry; see in Figure 9 in Appendix 6), but we found no evidence of possible significant publication bias: Egger's regression intercept (bias) 1.89 (two tailed, P = 0.089).

Figure 8. TSA attrition: antipsychotics DARIS: Diversity-adjusted required information size; Pc: proportion with an outcome in the control group; RRR: Relative risk ratio; TSA: Trial Sequential Analysis

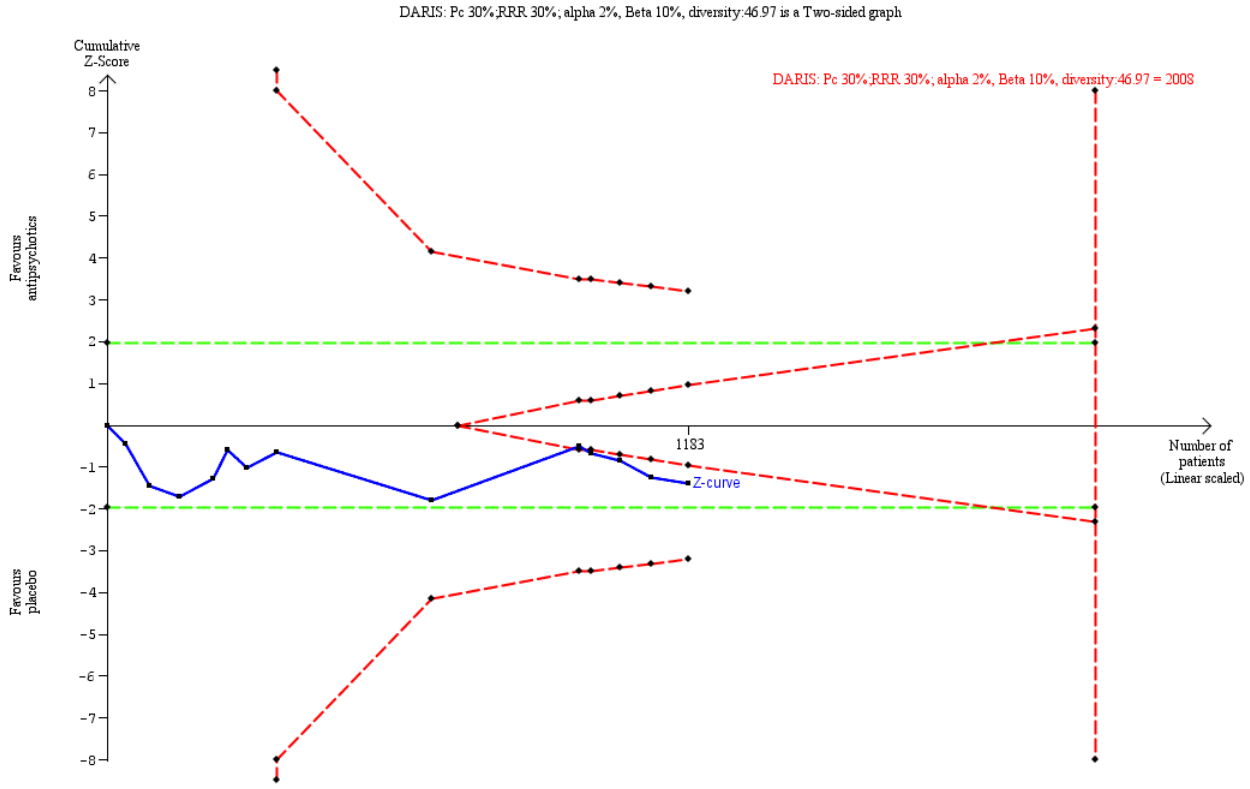
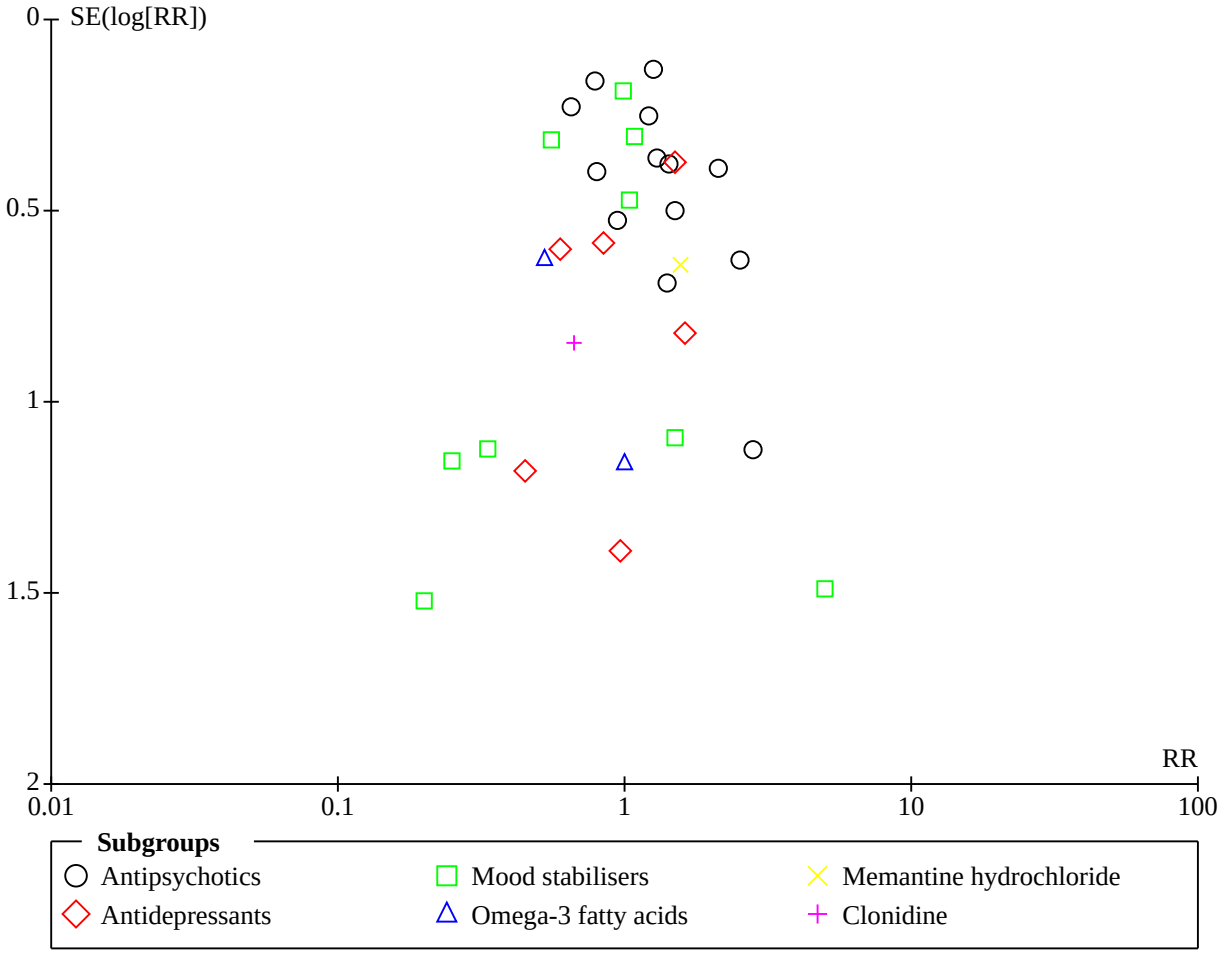
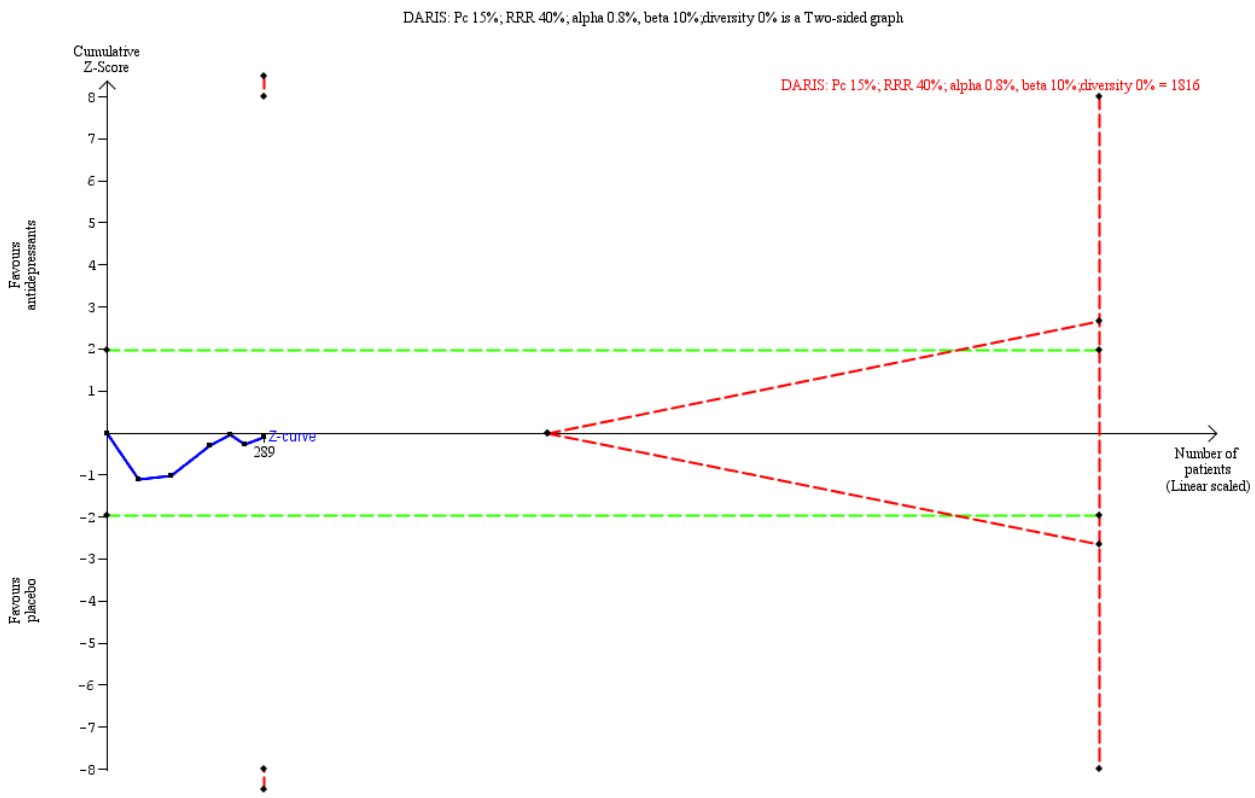


Figure 9. Funnel plot of comparison: 1 Pharmacotherapies compared with placebo, outcome: 1.19 Secondary: Attrition at end of treatment RR: Relative Risk; SE(log[RR]): Standard Error of the logarithmic Risk Ratio



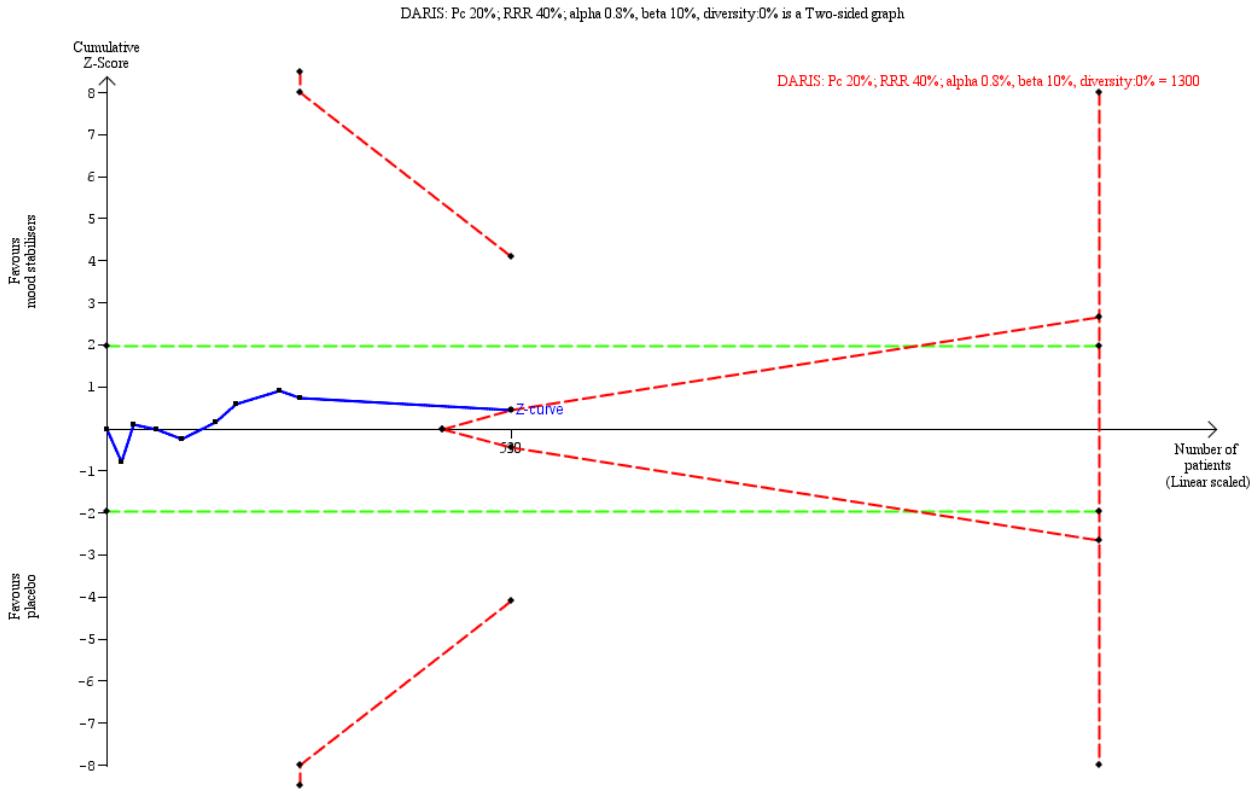
Six trials compared antidepressants to placebo (Montgomery 1982b; NCT00533117; Rinne 2002; Simpson 2004; Soloff 1989; Soloff 1993). There was no difference between treatments regarding attrition at the end of treatment (RR 1.07, 95% CI 0.65 to 1.76; P = 0.78, I^2 = 0%; 6 trials, 289 participants; low-certainty evidence; Analysis 1.27). The TSA, however, showed that the DARIS was not reached (n = 1816), and that there was a potential risk of type 1 error (TSA-adjusted CI 0.07 to 14.98). See Figure 10 in Appendix 6.

Figure 10. TSA attrition: antidepressants DARIS: Diversity-adjusted required information size;Pc: proportion with an outcome in the control group; RRR: Relative risk ratio; TSA: Trial Sequential Analysis



Nine trials compared mood stabilisers to placebo (Crawford 2018; De la Fuente 1994; Frankenburg 2002; Hollander 2001; Loew 2006; Nickel 2004; Nickel 2005; Reich 2009; Tritt 2005). The evidence is very uncertain about the effect of mood stabilisers compared with placebo on attrition at the end of treatment (RR 0.89, 95% CI 0.69 to 1.15; P = 0.37, I^2 = 0%; 9 trials, 530 participants; very low-certainty evidence; Analysis 1.27). The TSA showed that the DARIS was not reached (n = 1300), and that there was a potential risk of type 1 error (TSA-adjusted CI 0.37 to 2.23). See Figure 11 in Appendix 6.

Figure 11. TSA attrition: mood stabilisers DARIS: Diversity-adjusted required information size; Pc: proportion with an outcome in the control group; RRR: Relative risk ratio; TSA: Trial Sequential Analysis

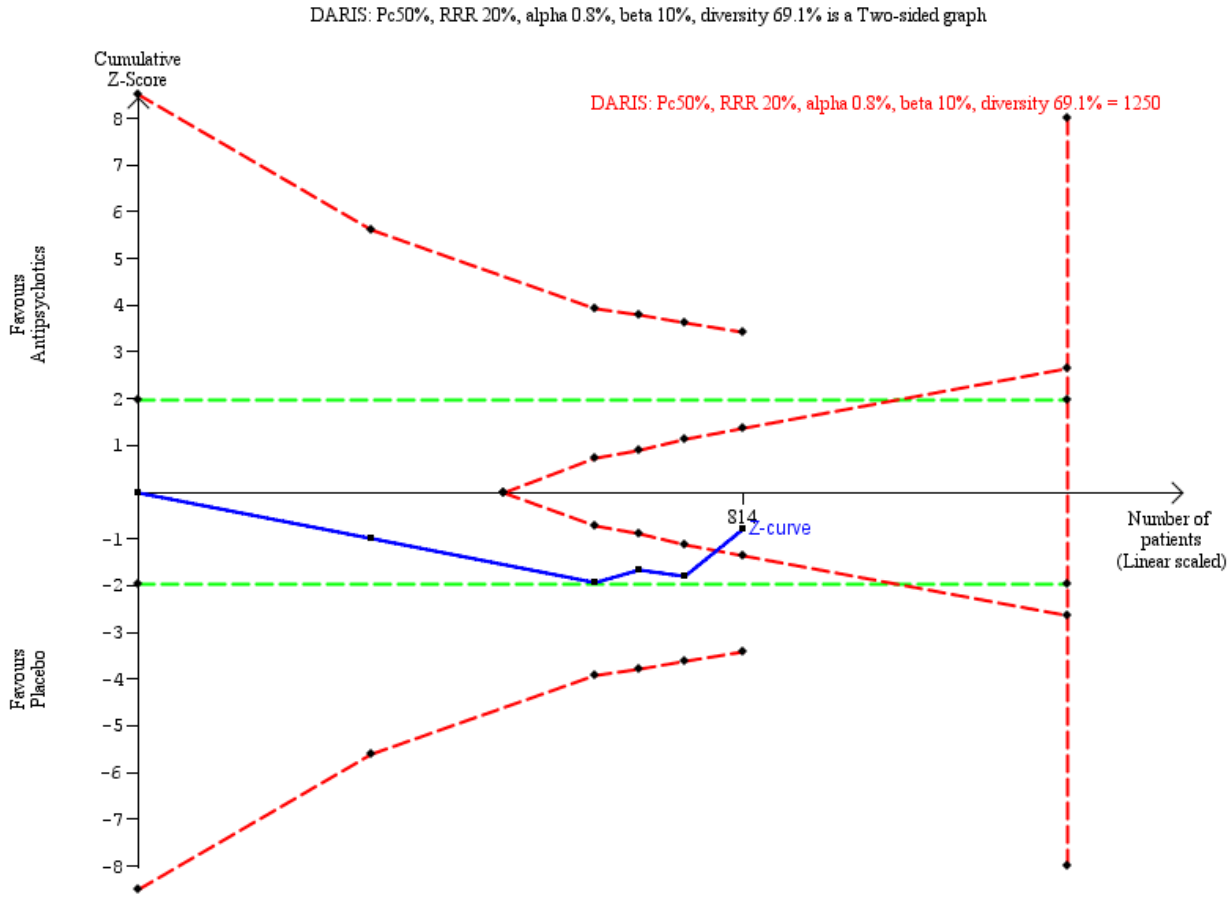


Four trials compared miscellaneous medications to placebo. Of these, two trials compared omega-3 fatty acids to placebo (Hallahan 2007; Zanarini 2003). There was no difference between omega-3 fatty acids and placebo regarding omega attrition at end of treatment (RR 0.61, 95% CI 0.21 to 1.79; P = 0.37, I^2 = 0%; 2 trials, 79 participants; Analysis 1.27). One trial compared memantine hydrochloride to placebo (Kulkarni 2018). There was no difference between memantine hydrochloride and placebo regarding attrition at end of treatment (RR 1.57, 95% CI 0.45 to 5.52; P = 0.48; 1 trial, 33 participants; Analysis 1.27). Another trial compared clonidine to placebo (Ziegenhorn 2009). There was no difference between clonidine and placebo regarding attrition at end of treatment (RR 0.67, 95% CI 0.13 to 3.50; P = 0.63; 1 trial, 34 participants; Analysis 1.27).

1.15 Adverse events

Seven trials comparing medications to placebo reported dichotomous data on total non-serious adverse events at end of treatment. Five trials compared antipsychotics to placebo (Black 2014; Grant 2022; Pascual 2008; Schulz 2007; Zanarini 2007). There was no clear difference in the presence of adverse events between the two groups receiving antipsychotics and placebo (RR 1.07, 95% CI 0.90 to 1.29; P = 0.43; I^2 = 57%; 5 trials, 814 participants; very low-certainty evidence; Analysis 1.28). The TSA showed that the z-curve ended in the fidelity area. See Figure 12 in Appendix 6.

Figure 12. TSA non-serious adverse events: antipsychotics DARIS: Diversity-adjusted required information size; Pc: proportion with an outcome in the control group; RRR: Relative risk ratio; TSA: Trial Sequential Analysis



One trial compared a mood stabiliser to placebo (Crawford 2018). There was no difference in the presence of adverse events between the two groups (RR 0.84, 95% CI 0.70 to 1.01; P = 0.07; 1 trial, 276 participants; very low-certainty evidence; Analysis 1.28).

Another trial compared memantine hydrochloride to placebo (Kulkarni 2018). There was no difference in any adverse events between the two groups (RR 1.41, 95% CI 0.79 to 2.52; P = 0.24; 1 trial, 33 participants; Analysis 1.28).

Two trials compared pharmacological treatment to placebo and reported dichotomous data on total serious adverse events. Kulkarni 2018 compared memantine hydrochloride to placebo and reported no serious adverse events in either the experimental or the placebo group (Analysis 1.29). Grant 2022 compared brexpiprazole to placebo. One serious adverse event (mild suicidal ideation without a plan, considered serious as it necessitated hospitalisation) occurred in the placebo group. There was no statistical difference in the occurrence of serious adverse events between the two groups (RR 3.00, 95% CI 0.13 to 71.51; 1 trial, 80 participants; Analysis 1.29). No other trials specifically reported data on serious adverse events.

Please refer to Table 2 for an overview of adverse events.

Central nervous system

Headache

Six trials comparing pharmacological treatment to placebo reported data on headache as a non-serious adverse event.

Four trials compared antipsychotics to placebo (Black 2014; Grant 2022; Schulz 2007; Zanarini 2007). There was no difference in the presence of headache between the two groups (RR 1.01, 95% CI 0.63 to 1.62; P = 0.97; I^2 = 32%; 4 trials, 754 participants; Analysis 2.1).

One trial compared a mood stabiliser to placebo (Loew 2006). There was no difference in the presence of headache between the two groups (RR 1.00, 95% CI 0.15 to 6.61; P = 1.00; 1 trial, 56 participants; Analysis 2.2).

One trial compared memantine hydrochloride to placebo (Kulkarni 2018). There was no difference in the presence of headache between the two groups (RR 1.29, 95% CI 0.71 to 2.36; P = 0.40; 1 trial, 33 participants; Analysis 2.3)

Dizziness

Four trials comparing pharmacological treatment to placebo reported data on dizziness as a non-serious adverse event.

Two trials compared antipsychotics to placebo (Black 2014; Pascual 2008). There was no difference in the presence of dizziness between

the two groups (RR 3.07, 95% CI 0.40 to 23.45; P = 0.28, I^2 = 9%; 2 trials, 68 participants; Analysis 2.1).

One trial compared a mood stabiliser to placebo (Loew 2006). There was no difference in the presence of dizziness between the two groups (RR 1.50, 95% CI 0.27 to 8.30; P = 0.64; 1 trial, 56 participants; Analysis 2.2).

One trial compared memantine hydrochloride to placebo (Kulkarni 2018). There was no difference in the presence of dizziness between the two groups (RR 1.69, 95% CI 0.72 to 3.98; P = 0.23; 1 trial, 33 participants; Analysis 2.3).

Fatigue

Five trials comparing pharmacological treatment to placebo reported data on fatigue as a non-serious adverse event.

Three trials compared antipsychotics to placebo (Grant 2022; Schulz 2007; Zanarini 2007). There was no difference in the presence of fatigue between the two groups (RR 1.50, 95% CI 0.58 to 3.89; P = 0.40; I^2 = 56%; 3 trials, 692 participants; Analysis 2.1).

One trial compared a mood stabiliser to placebo (Loew 2006). There was no difference in the presence of fatigue between the two groups (RR 2.00, 95% CI 0.40 to 10.05; P = 0.40; 1 trial, 56 participants; Analysis 2.2).

One trial compared memantine hydrochloride to placebo (Kulkarni 2018). There was no difference in the presence of fatigue between the two groups (RR 1.32, 95% CI 0.52 to 3.31; P = 0.56; 1 trial, 33 participants; Analysis 2.3).

Somnolence

Three trials comparing pharmacological treatment to placebo reported data on somnolence as a non-serious adverse event.

Two trials compared antipsychotics to placebo (Schulz 2007; Zanarini 2007). There was a difference between the groups on somnolence, with an increased risk of somnolence using antipsychotics (RR 2.97, 95% CI 1.75 to 5.03; P < 0.0001, I^2 = 0%; 2 trials, 615 participants; Analysis 2.1).

One trial compared memantine hydrochloride to placebo (Kulkarni 2018). There was no difference in the presence of somnolence between the two groups (RR 1.65, 95% CI 0.59 to 4.57; P = 0.34; 1 trial, 33 participants; Analysis 2.3).

Sedation

Four trials comparing pharmacological treatment to placebo reported continuous data on sedation as a non-serious adverse event. All four trials compared antipsychotics to placebo (Black 2014; Pascual 2008; Schulz 2007; Zanarini 2001). There was a very slight difference in sedation between the two groups in favour of placebo (RR 2.66, 95% CI 0.99 to 7.12; P = 0.05, I^2 = 67%; 4 trials, 445 participants; Analysis 2.1).

Anxiety

One trial comparing pharmacological treatment to placebo reported data on anxiety as a non-serious adverse event. Schulz 2007 compared an antipsychotic to placebo. There was no difference in anxiety between the two groups (RR 0.90, 95% CI 0.33 to 2.42; P = 0.83; 1 trial, 314 participants; Analysis 2.1).

Insomnia

Two trials comparing pharmacological treatment to placebo reported data on insomnia as a non-serious adverse event. Both trials compared antipsychotics to placebo (Schulz 2007; Zanarini 2007). There was no difference in effects on insomnia between the two groups (RR 0.68, 95% CI 0.33 to 1.37; P = 0.28, I^2 = 15%; 2 trials, 615 participants; Analysis 2.1).

Hyperinsomnia

One trial comparing pharmacological treatment to placebo reported data on hyperinsomnia as a non-serious adverse event. Black 2014 compared an antipsychotic to placebo. There was no difference in hyperinsomnia between the two groups (RR 2.34, 95% CI 0.69 to 8.01; P = 0.17; 1 trial, 62 participants; Analysis 2.1).

Increased appetite

Three trials comparing pharmacological treatment to placebo reported data on increased appetite as a non-serious adverse event. Grant 2022, Schulz 2007 and Zanarini 2007 compared antipsychotics to placebo. There was an effect on increased appetite in favour of placebo, (RR 2.68, 95% CI 1.71 to 4.19; P < 0.0001; I^2 = 0%, 3 trials, 692 participants; Analysis 2.1).

Change in appetite

One trial comparing pharmacological treatment to placebo reported dichotomous data on changes in appetite as a non-serious adverse event. Black 2014 compared an antipsychotic to placebo. There was no difference in changes in appetite between the two groups (RR 0.65, 95% CI 0.10 to 4.06; P = 0.64; 1 trial, 17 participants; Analysis 2.1).

Forgetfulness or confusion

One trial comparing pharmacological treatment to placebo reported data on forgetfulness/confusion as a non-serious adverse event. Black 2014 compared an antipsychotic to placebo. There was no difference in forgetfulness/confusion between the two groups (RR 1.46, 95% CI 0.38 to 5.60; P = 0.58; 1 trial, 62 participants; Analysis 2.1).

Disturbances in attention

One trial comparing pharmacological treatment to placebo reported data on disturbances in attention as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was no difference in disturbances in attention between the two groups (RR 11.37, 95% CI 0.63 to 203.81; P = 0.10; 1 trial, 301 participants; Analysis 2.1).

Restlessness

One trial comparing pharmacological treatment to placebo reported data on restlessness as a non-serious adverse event. Grant 2022 compared an antipsychotic to placebo. There was no difference in restlessness between the two groups (RR 0.93, 95% CI 0.20 to 4.30; P = 0.92; 1 trial, 77 participants; Analysis 2.1).

Hallucinations

One trial comparing pharmacological treatment to placebo reported data on hallucinations as a non-serious adverse event. Grant 2022 compared an antipsychotic to placebo. There was no difference in hallucinations between the two groups (RR 0.19, 95% CI 0.01 to 3.74; P = 0.27; 1 trial, 77 participants; Analysis 2.1).

Sleep problems

One trial comparing pharmacological treatment to placebo reported data on sleep problems as a non-serious adverse event. Grant 2022 compared an antipsychotic to placebo. There was no difference in sleep problems between the two groups (RR 0.19, 95% CI 0.01 to 3.74; P = 0.27; 1 trial, 77 participants; Analysis 2.1).

Tremor

One trial comparing pharmacological treatment to placebo reported data on tremor as a non-serious adverse event. Grant 2022 compared an antipsychotic to placebo. There was no difference in tremor between the two groups (RR 0.31, 95% CI 0.01 to 7.36; P = 0.47; 1 trial, 77 participants; Analysis 2.1).

Memory problems

One trial comparing pharmacological treatment to placebo reported dichotomous data on memory problems as a non-serious adverse event. Loew 2006 compared a mood stabiliser to placebo. There was no difference in memory problems between the two groups (RR 2.00, 95% CI 0.55 to 7.22; P = 0.29; 1 trial, 56 participants; Analysis 2.2).

Paraesthesia

One trial comparing pharmacological treatment to placebo reported dichotomous data on paraesthesia as a non-serious adverse event. Loew 2006 compared a mood stabiliser to placebo. There was no difference in paraesthesia between the two groups (RR 3.00, 95% CI 0.33 to 27.12; P = 0.33; 1 trial, 56 participants; Analysis 2.2).

Gait/balance disturbances

One trial comparing pharmacological treatment to placebo reported dichotomous data on gait/balance disturbances. Kulkarni 2018 compared memantine hydrochloride to placebo. There was no difference in gait/balance disturbances between the two groups (RR 2.35, 95% CI 0.53 to 10.45; P = 0.26; 1 trial, 33 participants; Analysis 2.3).

Nervous system disorders

One trial comparing pharmacological treatment to placebo reported dichotomous data on nervous system disorders as a non-serious adverse event. Crawford 2018 compared a mood stabiliser to placebo. There was no difference in the appearance of nervous system disorders between the two groups (RR 1.05, 95% CI 0.68 to 1.62; P = 0.83; 1 trial, 276 participants; Analysis 2.2).

Psychiatric disorders

One trial comparing pharmacological treatment to placebo reported data on psychiatric disorders as a non-serious adverse event. Crawford 2018 compared a mood stabiliser to placebo. There was no difference in the appearance of psychiatric disorders between the two groups (RR 0.94, 95% CI 0.64 to 1.37; P = 0.74; 1 trial, 276 participants; Analysis 2.2).

Cardiovascular and respiratory system

Cold/flu symptoms

One trial comparing pharmacological treatment to placebo reported dichotomous data on cold/flu symptoms as a non-serious adverse event. Black 2014 compared an antipsychotic to placebo. There was no difference in cold/flu symptoms between the two groups (RR 1.54, 95% CI 0.50 to 4.73; P = 0.45; 1 trial, 62 participants; Analysis 3.1).

Nasopharyngitis

One trial comparing pharmacological treatment to placebo reported dichotomous data on nasopharyngitis as a non-serious adverse event. Schulz 2007 compared an antipsychotic to placebo. There was no difference in nasopharyngitis between the two groups (RR 0.62, 95% CI 0.23 to 1.66; P = 0.34; 1 trial, 301 participants; Analysis 3.1).

Sweating

One trial comparing pharmacological treatment to placebo reported dichotomous data on sweating as a non-serious adverse event. Grant 2022 compared an antipsychotic to placebo. There was no difference in sweating between the two groups (RR 0.31, 95% CI 0.01 to 7.36; P = 0.47; 1 trial, 77 participants; Analysis 3.1).

Blood and lymphatic system disorders

One trial comparing pharmacological treatment to placebo reported dichotomous data on blood and lymphatic system disorders as a non-serious adverse event. Crawford 2018 compared a mood stabiliser to placebo. There was no difference in blood and lymphatic system disorders between the two groups (RR 0.68, 95% CI 0.11 to 3.99; P = 0.67; 1 trial, 276 participants; Analysis 3.3).

Cardiac disorders

One trial comparing pharmacological treatment to placebo reported dichotomous data on cardiac disorders as a non-serious adverse event. Crawford 2018 compared a mood stabiliser to placebo. There was no difference in cardiac disorders between the two groups (RR 0.34, 95% CI 0.01 to 8.23; P = 0.51; 1 trial, 276 participants; Analysis 3.3).

Endocrine disorders

One trial comparing pharmacological treatment to placebo reported dichotomous data on endocrine disorders as a non-serious adverse event. Crawford 2018 compared a mood stabiliser to placebo. There was no difference in endocrine disorders between the two groups (RR 0.34, 95% CI 0.01 to 8.23; P = 0.51; 1 trial, 276 participants; Analysis 3.3).

Respiratory, thoracic and mediastinal disorders

One trial comparing pharmacological treatment to placebo reported dichotomous data on respiratory, thoracic and mediastinal disorders as a non-serious adverse event. Crawford 2018 compared a mood stabiliser to placebo. There was no difference in respiratory, thoracic and mediastinal disorders

between the two groups (RR 1.80, 95% CI 0.83 to 3.94; P = 0.14; 1 trial, 276 participants; Analysis 3.3).

Diastolic blood pressure in standing position (mean change from baseline to endpoint)

One trial comparing pharmacological treatment to placebo reported continuous data on diastolic blood pressure in standing position (mean change from baseline to endpoint) as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was no difference in mean change between the two groups (MD −0.28, 95% CI −2.29 to 1.73; P = 0.78; 1 trial, 290 participants; Analysis 3.2).

Diastolic blood pressure in supine position (mean change from baseline to endpoint)

One trial comparing pharmacological treatment to placebo reported continuous data on diastolic blood pressure in supine position (mean change from baseline to endpoint) as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was no difference in mean change between the two groups (MD −0.11, 95% CI −2.28 to 2.06; P = 0.92; 1 trial, 290 participants; Analysis 3.2).

Systolic blood pressure in standing position (mean change from baseline to endpoint)

One trial comparing pharmacological treatment to placebo reported continuous data on systolic blood pressure in standing position (mean change from baseline to endpoint) as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was no difference in mean change between the two groups (MD 0.35, 95% CI −2.39 to 3.09; P = 0.80; 1 trial, 290 participants; Analysis 3.2).

Systolic blood pressure in supine position (mean change from baseline to endpoint)

One trial comparing pharmacological treatment to placebo reported continuous data on systolic blood pressure in supine position (mean change from baseline to endpoint) as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was no difference in mean change between the two groups (MD −1.31, 95% CI −4.00 to 1.38; P = 0.34; 1 trial, 290 participants; Analysis 3.2).

Pulse in standing position (mean change from baseline to endpoint)

One trial comparing pharmacological treatment to placebo reported continuous data on pulse in standing position (mean change from baseline to endpoint) as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was no difference in mean change between the two groups (MD 0.85, 95% CI −1.65 to 3.35; P = 0.50; 1 trial, 290 participants; Analysis 3.2).

Pulse in supine position (mean change from baseline to endpoint)

One trial comparing pharmacological treatment to placebo reported continuous data on pulse in supine position (mean change from baseline to endpoint) as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was no difference in mean change between the two groups (MD −0.11, 95% CI −2.28 to 2.06; P = 0.92; 1 trial, 290 participants; Analysis 3.2).

Gastrointestinal system

Nausea

Five trials comparing pharmacological treatment to placebo reported dichotomous data on nausea and vomiting as a non-serious adverse event.

Four trials compared antipsychotics to placebo (Black 2014; Grant 2022; Schulz 2007; Zanarini 2007). There was no difference in nausea and vomiting between the two groups ((RR 0.80, 95% CI 0.49 to 1.29; P = 0.36; I^2 = 0%; 4 trials, 754 participants; Analysis 4.1).

One trial compared memantine hydrochloride to placebo (Kulkarni 2018). There was no difference in nausea and vomiting between the two groups (RR 1.00, 95% CI 0.45 to 2.23; P = 1.00; 1 trial, 34 participants; Analysis 4.4).

Uneasy feeling

One trial comparing pharmacological treatment to placebo reported dichotomous data on feelings of uneasiness as a non-serious adverse event. Pascual 2008 compared an antipsychotic to placebo. There was no difference in the feeling of uneasiness between the two groups (RR 7.00, 95% CI 0.38 to 129.93; P = 0.19; 1 trial, 60 participants; Analysis 4.1).

Constipation

Two trials comparing pharmacological treatment to placebo reported dichotomous data on constipation as a non-serious adverse event. One trial compared an antipsychotic to placebo (Zanarini 2001). There was no difference in constipation between the two groups (RR 6.50, 95% CI 0.41 to 104.20; P = 0.19; 1 trial, 28 participants; Analysis 4.1). Another trial compared memantine hydrochloride to placebo (Kulkarni 2018). There was no difference in constipation between the two groups (RR 1.65, 95% CI 0.59 to 4.57; P = 0.34; 1 trial, 33 participants; Analysis 4.4).

Dry mouth

Four trials comparing pharmacological treatment to placebo reported dichotomous data on dry mouth as a non-serious adverse event. They all compared antipsychotics to placebo (Black 2014; Grant 2022; Schulz 2007; Zanarini 2007). There was a difference between the two groups, with an increased risk of dry mouth for antipsychotics (RR 2.60, 95% CI 1.46 to 4.64; P = 0.001; I^2 = 0%; 4 trials, 754 participants; Analysis 4.1).

Gastrointestinal disorders

One trial comparing pharmacological treatment to placebo reported dichotomous data on gastrointestinal disorders as a non-serious adverse event. Crawford 2018 compared a mood stabiliser to placebo. There was a slight difference between the two groups, with an increased risk of gastrointestinal disorders for placebo (RR 0.70, 95% CI 0.50 to 0.98; P = 0.04; 1 trial, 276 participants; Analysis 4.3).

General disorders and administration site conditions

One trial comparing pharmacological treatment to placebo reported dichotomous data on general disorders and administration site conditions as a non-serious adverse event. Crawford 2018 compared a mood stabiliser to placebo. There was no difference in general disorders and administration site conditions between the two groups (RR 1.01, 95% CI 0.50 to 2.05; P = 0.97; 1 trial, 276 participants; Analysis 4.3).

Hepatobiliary disorders

One trial comparing pharmacological treatment to placebo reported dichotomous data on hepatobiliary disorders as a non-serious adverse event. Crawford 2018 compared a mood stabiliser to placebo. There was no difference in hepatobiliary disorders between the two groups (RR 3.04, 95% CI 0.13 to 74.07; P = 0.49; 1 trial, 276 participants; Analysis 4.3).

Metabolism and nutrition disorders

One trial that compared a pharmacological treatment to placebo reported dichotomous data on metabolism and nutrition disorders as a non-serious adverse event. Crawford 2018 compared a mood stabiliser to placebo. There was no difference in metabolism and nutrition disorders between the two groups (RR 2.03, 95% CI 0.19 to 22.12; P = 0.56; 1 trial, 276 participants; Analysis 4.3).

Liver function: alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) baseline to endpoint mean change (u/L)

Two trials that compared a pharmacological treatment to placebo reported continuous data on mean change in ALT/SGPT as a non-serious adverse event. Schulz 2007 and Zanarini 2007 compared antipsychotics to placebo. There was a difference between the two groups regarding mean change in ALT/SGPT favouring placebo (SMD 0.46, 95% CI 0.29 to 0.63; P < 0.001, I^2 = 0%; 2 trials, 530 participants; Analysis 4.2).

Liver function: aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) baseline to endpoint mean change (u/L)

Two trials that compared a pharmacological treatment to placebo reported continuous data on mean change in AST/SGOT as a non-serious adverse event. Schulz 2007 and Zanarini 2007 compared antipsychotics to placebo. There was a difference between the two groups regarding mean change in AST/SGOT favouring placebo (SMD 0.35, 95% CI 0.18 to 0.52; P < 0.001, I^2 = 0%; 2 trials, 526 participants; Analysis 4.2).

Liver function: total bilirubin baseline to endpoint mean change (µmol/L)

One trial that compared a pharmacological treatment to placebo reported continuous data on mean change in total bilirubin as a non-serious adverse event. Schulz 2007 compared an antipsychotic to placebo. There was a difference between the two groups regarding mean change in total bilirubin favouring the antipsychotic (MD −0.98, 95% CI −1.80 to −0.16; P = 0.02; 1 trial, 264 participants; Analysis 4.2).

Liver function: direct bilirubin baseline to endpoint mean change (µmol/L)

One trial that compared a pharmacological treatment to placebo reported continuous data on mean change in direct bilirubin as a non-serious adverse event. Schulz 2007 compared an antipsychotic to placebo. There was a difference between the two groups regarding mean change in direct bilirubin favouring the antipsychotic (MD −0.30, 95% CI −0.51 to −0.09; P = 0.004; 1 trial, 258 participants; Analysis 4.2).

Liver function: gamma-glutamyl transferase (GGT) baseline to endpoint mean change

One trial comparing a pharmacological treatment to placebo reported continuous data on mean change in GGT as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was a difference between the two groups regarding mean change in GGT favouring placebo (MD 2.96, 95% CI 0.22 to 5.70; P = 0.03; 1 trial, 268 participants; Analysis 4.2).

Lipids: total cholesterol baseline to endpoint change (mmol/L)

Two trials comparing pharmacological treatment to placebo reported continuous data on mean change in total cholesterol as a non-serious adverse event. Both trials compared antipsychotics to placebo (Schulz 2007; Soler 2005). There was a difference between the two groups regarding mean change in total cholesterol favouring placebo (SMD 0.42, 95% CI 0.20 to 0.64; P = 0.0002, I^2 = 0%; 2 trials, 327 participants; Analysis 4.2).

Lipids: low-density lipoprotein (LDL) cholesterol baseline to endpoint mean change (mmol/L)

One trial comparing a pharmacological treatment to placebo reported continuous data on mean change in LDL cholesterol as a non-serious adverse event. Schulz 2007 compared an antipsychotic to placebo. There was a difference between the two groups regarding mean change in LDL cholesterol favouring placebo (MD 0.21, 95% CI 0.06 to 0.36; P = 0.005; 1 trial, 259 participants; Analysis 4.2).

Lipids: high-density lipoprotein (HDL) cholesterol (dextran precip.) baseline to endpoint mean change (mmol/L)

One trial comparing a pharmacological treatment to placebo reported continuous data on mean change in HDL cholesterol as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was a difference between the two groups regarding mean change in HDL cholesterol favouring the antipsychotic (MD −0.06, 95% CI −0.11 to −0.01; P = 0.02; 1 trial, 269 participants; Analysis 4.2).

Lipids: triglycerides, fasting, baseline to endpoint mean change (mmol/L)

One trial compared a pharmacological treatment to placebo reported continuous data on mean change in triglycerides as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was a difference between the two groups regarding mean change in triglycerides favouring placebo (MD 0.27, 95% CI 0.07 to 0.47; P = 0.009; 1 trial, 203 participants; Analysis 4.2).

Prolactin: baseline to endpoint mean change (µg/L)

One trial comparing a pharmacological treatment to placebo reported continuous data on mean change in prolactin as a non-

serious adverse event. Schulz 2007 compared an antipsychotic to placebo. There was a difference between the two groups regarding mean change in prolactin favouring placebo (MD 7.10, 95% CI 1.64 to 12.56; P = 0.01; 1 trial, 259 participants; Analysis 4.2).

Platelet count baseline to endpoint mean change (GI/L)

Two trials comparing a pharmacological treatment to placebo reported continuous data on mean change in platelet count as a non-serious adverse event. Both trials compared antipsychotics to placebo (Schulz 2007; Zanarini 2007). There was no difference in platelet count between the two groups (SMD 0.03, 95% CI −0.53 to 0.59; P = 0.91, I^2 = 90%; 2 trials, 517 participants; Analysis 4.2).

Erythrocyte count baseline to endpoint mean change (TI/L)

One trial comparing a pharmacological treatment to placebo reported continuous data on mean change in erythrocyte count as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was no difference in erythrocyte count between the two groups (MD −0.05, 95% CI −0.12 to 0.02; P = 0.14; 1 trial, 262 participants; Analysis 4.2).

Leukocyte count baseline to endpoint mean change (GI/L)

One trial comparing a pharmacological treatment to placebo reported continuous data on mean change in leukocyte count as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was a difference between the two groups regarding mean change in leukocyte count favouring the antipsychotic (MD −0.70, 95% CI −1.12 to −0.28; P = 0.001; 1 trial, 262 participants; Analysis 4.2).

Neutrophils, segmented, baseline to endpoint mean change (GI/L)

One trial comparing a pharmacological treatment to placebo reported continuous data on mean change in neutrophils as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was a difference between the two groups regarding mean change in neutrophils favouring the antipsychotic (MD −0.60, 95% CI −0.97 to −0.23; P = 0.002; 1 trial, 262 participants; Analysis 4.2).

Basophils baseline to endpoint mean change (GI/L)

One trial comparing a pharmacological treatment to placebo reported continuous data on mean change in basophils as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was a difference between the two groups regarding mean change in basophils favouring the antipsychotic (MD −0.01, 95% CI −0.02 to −0.00; P = 0.02; 1 trial, 262 participants; Analysis 4.2).

Monocytes baseline to endpoint mean change (GI/L)

One trial comparing a pharmacological treatment to placebo reported continuous data on mean change in monocytes as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was a difference between the two groups regarding mean change in monocytes favouring the antipsychotic (MD −0.04, 95% CI −0.07 to −0.01; P = 0.02; 1 trial, 262 participants; Analysis 4.2).

Haemoglobin baseline to endpoint mean change (mml/L-F)

One trial comparing a pharmacological treatment to placebo reported continuous data on mean change in haemoglobin as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was no difference between the two groups regarding mean change in haemoglobin (MD −0.11, 95% CI −0.24 to 0.02; P = 0.09; 1 trial, 262 participants; Analysis 4.2).

Mean cell haemoglobin concentration (MCHC) baseline to endpoint mean change (mml/L-F)

One trial comparing a pharmacological treatment to placebo reported continuous data on mean change in MCHC as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was no difference between the two groups regarding MCHC (MD 0.02, 95% CI −0.17 to 0.21; P = 0.84; 1 trial, 260 participants; Analysis 4.2).

Calcium baseline to endpoint mean change (mmol/L)

One trial comparing a pharmacological treatment to placebo reported continuous data on mean change in calcium as a non-serious adverse event. Schulz 2007 compared an antipsychotic to placebo. There was a difference between the two groups regarding mean change in calcium favouring the antipsychotic (MD −0.03, 95% CI −0.05 to −0.01; P = 0.006; 1 trial, 268 participants; Analysis 4.2).

Albumin baseline to endpoint mean change (g/L)

One trial comparing a pharmacological treatment to placebo reported continuous data on mean change in albumin as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was no difference between the two groups regarding mean change in albumin (MD −0.67, 95% CI −1.42 to 0.08; P = 0.08; 1 trial, 269 participants; Analysis 4.2).

Creatine phosphokinase baseline to endpoint mean change (u/L)

One trial comparing a pharmacological treatment to placebo reported continuous data on mean change in creatine phosphokinase as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was no difference between the two groups regarding mean change in creatine phosphokinase (MD −44.81, 95% CI −95.39 to 5.77; P = 0.08; 1 trial, 268 participants; Analysis 4.2).

Urea nitrogen baseline to endpoint mean change (mmol/L)

One trial comparing a pharmacological treatment to placebo reported continuous data on mean change in urea nitrogen as a non-serious adverse event. Zanarini 2007 compared an antipsychotic to placebo. There was no difference between the two groups regarding mean change in urea nitrogen (MD −0.17, 95% CI −0.46 to 0.12; P = 0.25; 1 trial, 269 participants Analysis 4.2).

Musculoskeletal system

Bodily pain

One trial comparing a pharmacological treatment to placebo reported dichotomous data on bodily pain as a non-serious adverse event. Black 2014 compared an antipsychotic to placebo. There was no difference in bodily pain between the two groups (RR 0.88, 95% CI 0.47 to 1.64; P = 0.69; 1 trial, 62 participants; Analysis 5.1).

Musculoskeletal and connective tissue disorders

One trial comparing a pharmacological treatment to placebo reported dichotomous data on musculoskeletal and connective tissue disorders as a non-serious adverse event. Crawford 2018 compared a mood stabiliser to placebo. There was no difference in musculoskeletal and connective tissue disorders between the two groups (RR 1.16, 95% CI 0.43 to 3.11; P = 0.77; 1 trial; 276 participants; Analysis 5.4).

Body weight change

Twelve trials comparing a pharmacological treatment to placebo reported continuous data on body weight change as a non-serious adverse event.

Seven trials compared antipsychotics to placebo (Bogenschutz 2004; Linehan 2008; Schulz 2007; Soler 2005; Soloff 1993; Zanarini 2001; Zanarini 2007). There was a difference between the two groups regarding body weight change favouring placebo (SMD 0.78, 95% CI 0.44 to 1.12; P < 0.001, I^2 = 74%; 7 trials, 810 participants; Analysis 5.2).

Soloff 1993 also compared an antidepressant to placebo. There was no difference between the two groups regarding body weight change (MD 0.09, 95% CI −0.31 to 0.49; P = 0.66; 1 trial, 62 participants; Analysis 5.3).

Five trials compared mood stabilisers to placebo (Frankenburg 2002; Loew 2006; Nickel 2004; Nickel 2005; Tritt 2005). There was no difference between the two groups regarding body weight change (SMD −0.26, 95% CI −0.72 to 0.20; P = 0.27, I^2 = 55%; 5 trials, 184 participants; Analysis 5.5).

Sensory system

Eye disorders

One trial comparing a pharmacological treatment to placebo reported dichotomous data on eye disorders as a non-serious adverse event. Crawford 2018 compared a mood stabiliser to placebo. There was no difference in eye disorders between the two groups (RR 0.17, 95% CI 0.02 to 1.39; P = 0.10; 1 trial, 276 participants; Analysis 6.1).

Reproductive system

Pregnancy, puerperium and perinatal conditions

One trial comparing a pharmacological treatment to placebo reported dichotomous data on pregnancy, puerperium and perinatal conditions as a non-serious adverse event. Crawford 2018 compared a mood stabiliser to placebo. There was no difference in pregnancy, puerperium and perinatal conditions between the two groups (RR 1.52, 95% CI 0.26 to 8.97; P = 0.64; 1 trial, 276 participants; Analysis 7.1).

Reproductive system and breast disorders

One trial comparing pharmacological treatment to placebo reported dichotomous data on the reproductive system and breast disorders as a non-serious adverse event. Crawford 2018 compared a mood stabiliser to placebo. There was no difference in the reproductive system and breast disorders between the two groups (RR 3.04, 95% CI 0.32 to 28.90; P = 0.33; 1 trial, 276 participants; Analysis 7.1).

Menstrual pain

One trial comparing a pharmacological treatment to placebo reported dichotomous data on menstrual pain as a non-serious adverse event. Loew 2006 compared a mood stabiliser to placebo. There was no difference in menstrual pain between the two groups (RR 1.67, 95% CI 0.44 to 6.31; P = 0.45; 1 trial, 56 participants; Analysis 7.1).

Other

Injury, poisoning or procedural complications

One trial comparing a pharmacological treatment to placebo reported dichotomous data on injuries, poisonings and procedural complications as a non-serious adverse event. Crawford 2018 compared a mood stabiliser to placebo. There was a difference between the two groups regarding injuries, poisonings and procedural complications, with an increased risk of injuries, poisonings and procedural complications in the placebo group (RR 0.44, 95% CI 0.26 to 0.74; P = 0.002; 1 trial, 276 participants; Analysis 8.1).

Skin and subcutaneous tissue disorders

One trial comparing a pharmacological treatment to placebo reported dichotomous data on skin and subcutaneous tissue disorders as a non-serious adverse event. Crawford 2018 compared a mood stabiliser to placebo. There was no difference in skin and subcutaneous tissue disorders between the two groups (RR 1.15, 95% CI 0.75 to 1.75; P = 0.53; 1 trial, 276 participants; Analysis 8.1).

Social circumstances

One trial comparing a pharmacological treatment to placebo reported dichotomous data on social circumstances as a non-serious adverse event. Crawford 2018 compared a mood stabiliser to placebo. There was no evidence of a difference in social circumstances between the two groups (RR 1.01, 95% CI 0.06 to 16.06; P = 0.99; 1 trial, 279 participants; Analysis 8.1).

Surgical and medical procedures

One trial comparing a pharmacological treatment to placebo reported dichotomous data on surgical and medical procedures as a non-serious adverse event. Crawford 2018 compared a mood stabiliser to placebo. There was no difference in surgical and medical procedures between the two groups (RR 4.06, 95% CI 0.46 to 35.85; P = 0.21; 1 trial, 276 participants; Analysis 8.1).

Withdrawal due to adverse events

One trial comparing pharmacological treatment to placebo reported dichotomous data on withdrawal due to adverse events. Kulkarni 2018 compared memantine hydrochloride to placebo. There was no difference in withdrawal due to adverse events between the two groups (RR 2.82, 95% CI 0.33 to 24.43; P = 0.35; 1 trial, 33 participants; Analysis 9.1).

2 Single medications compared with alternate single medications

Primary outcomes

2.1 BPD symptom severity

Three trials compared one medication with another medication and reported continuous data for BPD symptom severity.

Bozzatello 2017 compared two second-generation antipsychotics, olanzapine and asenapine. There was no clear difference between the two treatments regarding the effects on BPD symptom severity (MD −2.23, 95% CI −8.04 to 3.58; P = 0.45; 1 trial, 51 participants; Analysis 10.1).

Soloff 1993 compared the antipsychotic haloperidol with the antidepressant phenelzine sulfate. There was no clear difference between the two treatments regarding BPD symptom severity (MD 5.73, 95% CI −0.33 to 11.79; P = 0.06; 1 trial, 64 participants; Analysis 10.1).

Cowdry 1988 had a cross-over design with four active treatment arms: an arm with a benzodiazepine (alprazolam), an arm with a mood stabiliser (carbamazepine), an arm with an antipsychotic (trifluoperazine hydrochloride) and an arm with an antidepressant (tranylcypromine sulfate). From these, it was possible to make six comparisons: 1) alprazolam compared to carbamazepine; 2) alprazolam compared to trifluoperazine hydrochloride; 3) alprazolam compared to tranylcypromine sulfate; 4) carbamazepine compared to trifluoperazine hydrochloride; 5) carbamazepine compared to tranylcypromine sulfate; and 6) trifluoperazine hydrochloride compared to tranylcypromine sulfate.

There was a difference in BPD symptoms at end of treatment between alprazolam and carbamazepine, favouring alprazolam (MD −1.64, 95% CI −2.71 to −0.57; P = 0.003; 1 trial, 27 participants; Analysis 10.1), as well as between alprazolam and tranylcypromine sulfate, favouring alprazolam (MD −1.58, 95% CI −2.76 to −0.40; P = 0.009; 1 trial, 24 participants; Analysis 10.1).

There were no differences between treatments on BPD symptom severity at end of treatment for any of the other comparisons (alprazolam compared to trifluoperazine hydrochloride: MD −0.80, 95% CI −2.21 to 0.61; P = 0.27; 1 trial, 22 participants; Analysis 10.1; carbamazepine compared to trifluoperazine hydrochloride: MD 0.84, 95% CI −0.41 to 2.09; P = 0.19 ; 1 trial, 25 participants; Analysis 10.1; carbamazepine compared to tranylcypromine sulfate: MD 0.06, 95% CI −0.92 to 1.04; P = 0.90; 1 trial, 27 participants; Analysis 10.1; trifluoperazine hydrochloride compared to tranylcypromine sulfate: MD −0.78, 95% CI −2.13 to 0.57; P = 0.26; 1 trial, 22 participants; Analysis 10.1).

2.2 Self-harm

One trial compared a medication with another medication and reported continuous data for self-harm. Bozzatello 2017 compared two antipsychotics: olanzapine and asenapine. There was no evidence of a difference between the two antipsychotics regarding self-harm (MD 0.21, 95% CI −0.58 to 1.00; P = 0.60; 1 trial, 51 participants; Analysis 10.2).

There were no other trials comparing medications to another medication that reported data on self-harm.

2.3 Suicide-related outcomes

One trial comparing medications to other medications reported continuous data on suicide-related outcomes.

Cowdry 1988 had a cross-over design with four active treatment arms (see above in 2.1).

There was a difference in suicide-related outcomes at end of treatment between alprazolam and carbamazepine, favouring carbamazepine (MD 2.12, 95% CI 1.06 to 3.18; P < 0.001; 1 trial, 27 participants; Analysis 10.3); between alprazolam and trifluoperazine hydrochloride, favouring trifluoperazine hydrochloride (MD 1.73, 95% CI 0.62 to 2.84; P = 0.002; 1 trial, 22 participants; Analysis 10.3); and between alprazolam and tranylcypromine sulfate, favouring tranylcypromine (MD 2.00, 95% CI 0.89 to 3.11; P = 0.0004; 1 trial, 24 participants; Analysis 10.3).

There was no difference between treatments on suicide-related outcomes at end of treatment for any of the other comparisons (carbamazepine compared to trifluoperazine hydrochloride: MD −0.39, 95% CI −1.53 to 0.75; P = 0.50; 1 trial, 25 participants; Analysis 10.3; carbamazepine compared to tranylcypromine sulfate: MD −0.12, 95% CI −1.26 to 1.02; P = 0.84; 1 trial, 27 participants; Analysis 10.3; trifluoperazine hydrochloride compared to tranylcypromine sulfate: MD 0.27, 95% CI −1.00 to 1.54; P = 0.68; 1 trial, 22 participants; Analysis 10.3).

2.4 Psychosocial functioning

Five trials compared a medication with another medication and reported continuous data for psychosocial functioning.

Three trials compared one antipsychotic with another antipsychotic (Bozzatello 2017; Shafti 2010; Shafti 2014). There was no difference between the treatments for any of the comparisons regarding psychosocial functioning; for Bozzatello 2017 comparing olanzapine to asenapine (MD = 0.20, 95% CI −0.23 to 0.63, P = 0.36; 1 trial, 51 participants; Analysis 10.4); for Shafti 2010 comparing olanzapine to haloperidol (MD 0.35, 95% CI −0.45 to 1.15; P = 0.39; 1 trial, 28 participants; Analysis 10.4); or for Shafti 2014 comparing olanzapine to aripiprazole (MD 0.12, 95% CI −0.58 to 0.82; P = 0.74; 1 trial, 24 participants; Analysis 10.4).

Two trials compared an antipsychotic to an antidepressant (Soloff 1989; Soloff 1993). Soloff 1989 compared haloperidol to amitriptyline. There was no difference between the treatments regarding psychosocial functioning (MD −3.87, 95% CI −10.67 to 2.93; P = 0.26; 1 trial, 57 participants; Analysis 10.4). One study, Soloff 1993, compared haloperidol to phenelzine sulfate and found a difference in psychosocial functioning following treatment that favoured phenelzine sulfate (MD 5.15, 95% CI 0.29 to 10.01; P = 0.04; 1 trial, 64 participants; Analysis 10.4).

Secondary outcomes

2.5 Anger

Six trials compared a medication with another medication and reported continuous data for anger.

Three trials compared an antipsychotic to another antipsychotic: Shafti 2010 compared olanzapine to haloperidol, Shafti 2014 compared olanzapine to aripiprazole, and Bozzatello 2017 compared olanzapine to asenapine. There was no difference regarding anger at the end of treatment between

olanzapine and haloperidol (MD 0.21, 95% CI −8.90 to 9.32; P = 0.96; 1 trial, 28 participants; Analysis 10.5) or between olanzapine and aripiprazole (MD −0.40, 95% CI −8.05 to 7.25; P = 0.92, 1 trial, 24 participants; Analysis 10.5). However, there was a difference between asenapine and olanzapine regarding anger at end of treatment, favouring asenapine (MD 1.14, 95% CI 0.31 to 1.97; P = 0.007; 1 trial, 51 participants; Analysis 10.5).

Three trials compared an antipsychotic to an antidepressant. Jariani 2010 compared olanzapine to sertraline, Soloff 1989 compared haloperidol to amitriptyline, and Soloff 1993 compared haloperidol to phenelzine sulfate. There was no difference regarding anger at end of treatment between haloperidol and amitriptyline (MD −0.34, 95% CI −0.82 to 0.14; P = 0.16; 1 trial, 57 participants; Analysis 10.5), or between haloperidol and phenelzine sulfate (MD 0.06, 95% CI −0.31 to 0.43; P = 0.75; 1 trial, 64 participants; Analysis 10.5). However, there was a superior effect of olanzapine compared to sertraline regarding anger at the end of treatment (MD −0.33, 95% CI −0.48 to −0.18; P < 0.001; 1 trial, 120 participants; Analysis 10.5).

Cowdry 1988 had a cross-over design with four active treatment arms (see above in 2.1).

There was a difference in anger at end of treatment between alprazolam and carbamazepine, favouring carbamazepine (MD 1.65, 95% CI 0.80 to 2.50; P = 0.0001; 1 trial, 27 participants; Analysis 10.5), as well as between alprazolam and tranylcypromine sulfate, favouring tranylcypromine sulfate (MD 1.41, 95% CI 0.24 to 2.58; P = 0.02; 1 trial, 24 participants; Analysis 10.5).

There was no difference between treatments in anger at the end of treatment for any of the other comparisons: alprazolam compared to trifluoperazine hydrochloride (MD 0.58, 95% CI −0.77 to 1.93; P = 0.40; 1 trial, 22 participants; Analysis 10.5); carbamazepine compared to trifluoperazine hydrochloride (MD −1.07, 95% CI −2.28 to 0.14; P = 0.08; 1 trial, 25 participants; Analysis 10.5); carbamazepine compared to tranylcypromine sulfate (MD −0.24, 95% CI −1.23 to 0.75; P = 0.64; 1 trial, 27 participants; Analysis 10.5); and trifluoperazine hydrochloride compared to tranylcypromine sulfate (MD 0.83, 95% CI −0.62 to 2.28; P = 0.26; 1 trial, 22 participants; Analysis 10.5).

2.6 Affective instability

One trial compared a medication with another medication and reported continuous data for affective instability. Bozzatello 2017 compared two antipsychotics, olanzapine and asenapine. There was a difference in effects between the two antipsychotics regarding affective instability favouring asenapine (MD 2.28, 95% CI 1.51 to 3.05; P < 0.001; 1 trial, 51 participants; Analysis 10.6).

No other trials comparing medications to alternate medications reported data on affective instability.

2.7 Chronic feelings of emptiness

One trial compared a medication with another medication and reported continuous data for chronic feelings of emptiness. Bozzatello 2017 compared the two antipsychotics, olanzapine and asenapine. There was no difference in effects between the two antipsychotics regarding chronic feelings of emptiness (MD −0.54, 95% CI −1.29 to 0.21; P = 0.16, 1 trial, 51 participants; Analysis 10.7).

No other trials comparing a medication with another medication reported data on chronic feelings of emptiness.

2.8 Impulsivity

Five trials compared a medication with another medication and reported continuous data for impulsivity.

One trial compared two antipsychotics, olanzapine and asenapine (Bozzatello 2017). There was no difference between olanzapine and asenapine regarding impulsivity at the end of treatment (MD −0.78, 95% CI −1.59 to 0.03, P = 0.06; 1 trial, 51 participants; Analysis 10.8).

Three trials compared an antipsychotic with an antidepressant. Soloff 1989 compared haloperidol to amitriptyline, Soloff 1993 compared haloperidol to phenelzine sulfate, and Zanarini 2004 compared olanzapine to fluoxetine. There was no difference between treatments regarding impulsivity at the end of treatment for any of the comparisons (haloperidol versus amitriptyline: MD 3.52, 95% CI −5.52 to 12.56; P = 0.45; 1 trial, 57 participants; Analysis 10.8; haloperidol versus phenelzine sulfate: MD 3.29, 95% CI −14.52 to 21.10; P = 0.72; 1 trial, 64 participants; Analysis 10.8; and olanzapine versus fluoxetine: MD −4.31, 95% CI −19.72 to 11.10; P = 0.58; 1 trial, 29 participants; Analysis 10.8).

Cowdry 1988 had a cross-over design with four active treatment arms (see above in 2.1).

There was a difference in impulsivity at end of treatment in four of the comparisons, specifically between: alprazolam and carbamazepine, favouring carbamazepine (MD 2.18, 95% CI 1.20 to 3.16; P < 0.001; 1 trial, 27 participants; Analysis 10.8); alprazolam and tranylcypromine sulfate, favouring tranylcypromine sulfate (MD 1.83, 95% CI 0.66 to 3.00; P = 0.002; 1 trial, 24 participants; Analysis 10.8); carbamazepine and trifluoperazine hydrochloride, favouring carbamazepine (MD −1.73, 95% CI −2.87 to −0.59; P = 0.003; 1 trial, 25 participants; Analysis 10.8); and trifluoperazine hydrochloride and tranylcypromine sulfate, favouring tranylcypromine sulfate (MD 1.38, 95% CI 0.08 to 2.68; P = 0.04; 1 trial, 22 participants; Analysis 10.8).

There was no difference between treatments in impulsivity at end of treatment for any of the other two comparisons (alprazolam compared to trifluoperazine hydrochloride: MD 0.45, 95% CI −0.87 to 1.77; P = 0.50; 1 trial, 22 participants; Analysis 10.8; and carbamazepine compared to tranylcypromine sulfate: MD −0.35, 95% CI −1.31 to 0.61; P = 0.48; 1 trial, 27 participants; Analysis 10.8).

2.9 Interpersonal problems

Three trials compared a medication with another medication and reported continuous data for interpersonal problems.

One trial (Bozzatello 2017) compared two antipsychotics, olanzapine and asenapine. There was no difference between olanzapine and asenapine regarding interpersonal problems at the end of treatment (MD 0.40, 95% CI −0.35 to 1.15, P = 0.29; 1 trial, 51 participants; Analysis 10.9).

Two trials compared an antipsychotic with antidepressants. Soloff 1989 compared haloperidol to amitriptyline and Soloff 1993 compared haloperidol to phenelzine sulfate. There was no difference between the two treatments regarding interpersonal problems at end of treatment, either when comparing haloperidol

to amitriptyline (MD −0.13, 95% CI −0.62 to 0.36; P = 0.60; 1 trial, 57 participants; Analysis 10.9), or to phenelzine sulfate (MD −0.33, 95% CI −0.68 to 0.02; P = 0.06; 1 trial, 64 participants; Analysis 10.9).

2.10 Abandonment

One trial compared a medication with another medication and reported continuous data for fear of abandonment. Bozzatello 2017 compared two antipsychotics. There was no difference between the two antipsychotics (olanzapine and asenapine) regarding avoidance of abandonment (MD −0.40, 95% CI −1.07 to 0.27, P = 0.24; 1 trial, 51 participants; Analysis 10.10).

No other trials comparing a medication with another medication reported data on fear of abandonment.

2.11 Identity disturbance

One trial compared a medication with another medication and reported continuous data for identity disturbance. Bozzatello 2017 compared the two antipsychotics olanzapine and asenapine. There was no difference in effects between olanzapine and asenapine regarding identity disturbance (MD 0.68, 95% CI −0.12 to 1.48, P = 0.10; 1 trial, 51 participants; Analysis 10.11).

No other trials comparing a medication with another medication reported data on identity disturbance.

2.12 Dissociation and psychotic-like symptoms

Five trials compared a medication with another medication and reported continuous data for dissociation and psychotic-like symptoms.

Three trials compared an antipsychotic to another antipsychotic. Bozzatello 2017 compared olanzapine to asenapine, Shafti 2010 olanzapine to haloperidol, and Shafti 2014 olanzapine to aripiprazole. There was no difference between treatments regarding dissociation and psychotic-like symptoms at the end of treatment for any of the comparisons: olanzapine and asenapine (MD −0.69, 95% CI −1.53 to 0.15; P = 0.11; 1 trial, 51 participants; Analysis 10.12), olanzapine and haloperidol (MD −2.30, 95% CI −10.15 to 5.55; P = 0.57; 1 trial, 28 participants; Analysis 10.12), and olanzapine and aripiprazole (MD −3.30, 95% CI −10.63 to 4.03; P = 0.38; 1 trial, 24 participants; Analysis 10.12).

Two trials compared an antipsychotic with antidepressants. Soloff 1989 compared haloperidol to amitriptyline and Soloff 1993 compared haloperidol to phenelzine sulfate. There was no difference between treatments for any of the comparisons regarding dissociation and psychotic-like symptoms at the end of treatment (haloperidol versus amitriptyline: MD −0.28, 95% CI −0.69 to 0.13; P = 0.18; 1 trial, 57 participants; Analysis 10.12; and haloperidol versus phenelzine sulfate: MD 0.14, 95% CI −0.31 to 0.59; P = 0.54; 1 trial, 64 participants; Analysis 10.12).

2.13 Depression

Six trials compared a medication with another medication and reported continuous data for depression.

Bozzatello 2017 compared the two antipsychotics olanzapine and asenapine. There was a difference in effects between olanzapine and asenapine regarding depression, favouring asenapine (MD 2.90, 95% CI 0.88 to 4.92; P = 0.005; 1 trial, 51 participants; Analysis 10.13).

Four trials compared an antipsychotic with an antidepressant. Jariani 2010 compared olanzapine to sertraline, Soloff 1989 compared haloperidol to amitriptyline, Soloff 1993 compared haloperidol to phenelzine sulfate, and Zanarini 2004 compared olanzapine to fluoxetine. There was no difference between haloperidol and amitriptyline regarding depression at end of treatment (MD 0.88, 95% CI −5.12 to 6.88; P = 0.77; 1 trial, 57 participants; Analysis 10.13); however, a difference between treatments was observed in the comparisons between olanzapine and sertraline, favouring sertraline (MD 0.37, 95% CI 0.22 to 0.52; P < 0.001; 1 trial, 120 participants; Analysis 10.13); haloperidol and phenelzine sulfate, favouring phenelzine sulfate (MD 7.81, 95% CI 2.13 to 13.49; P = 0.007; 1 trial, 64 participants; Analysis 10.13); and olanzapine and fluoxetine, favouring olanzapine (MD −5.40, 95% CI −10.68 to −0.12; P = 0.04; 1 trial, 29 participants; Analysis 10.13).

Cowdry 1988 had a cross-over design with four active treatment arms (see above in 2.1).

There was a difference in depression at the end of treatment between alprazolam and carbamazepine, favouring carbamazepine (MD 1.36, 95% CI 0.37 to 2.35; P = 0.007; 27 participants, 1 trial; Analysis 10.13), as well as between alprazolam and tranylcypromine sulfate, favouring tranylcypromine sulfate (MD 1.67, 95% CI 0.48 to 2.86; P = 0.006; 24 participants, 1 trial; Analysis 10.13).

There was no difference between treatments in terms of depression at end of treatment for any of the other comparisons (alprazolam compared to trifluoperazine hydrochloride: MD 0.90, 95% CI −0.49 to 2.29; P = 0.20; 1 trial, 22 participants; Analysis 10.13; carbamazepine compared to trifluoperazine hydrochloride: MD −0.46, 95% CI −1.81 to 0.89; P = 0.50; 1 trial, 25 participants; Analysis 10.13; carbamazepine compared to tranylcypromine sulfate: MD 0.31, 95% CI −0.82 to 1.44; P = 0.59; 1 trial, 27 participants; Analysis 10.13; and trifluoperazine hydrochloride compared to tranylcypromine sulfate: MD 0.77, 95% CI −0.73 to 2.27; P = 0.31; 1 trial, 22 participants; Analysis 10.13).

2.14 Attrition

Eight trials compared a medication with another medication and reported dichotomous data on attrition.

Four trials compared an antipsychotic to another antipsychotic. Bozzatello 2017 compared olanzapine to asenapine, Leone 1982 compared loxapine to chlorpromazine, Shafti 2010 compared olanzapine to haloperidol, and Shafti 2014 compared olanzapine to aripiprazole. There was no difference between treatments for any of the comparisons on attrition (olanzapine versus asenapine: RR 0.80, 95% CI 0.28 to 2.29; P = 0.68; 1 trial, 51 participants; Analysis 10.14; loxapine versus chlorpromazine: RR 1.14, 95% CI 0.46 to 2.85; P = 0.77; 1 trial, 80 participants; Analysis 10.14; olanzapine versus haloperidol: no events occurred in any of the treatment groups; Analysis 10.14; and olanzapine versus aripiprazole: no events occurred in any of the treatment groups; Analysis 10.14).

Four trials compared an antipsychotic to an antidepressant. Jariani 2010 compared olanzapine to sertraline, Soloff 1989 compared

haloperidol to amitriptyline, Soloff 1993 compared haloperidol to phenelzine sulfate, and Zanarini 2004 compared olanzapine to fluoxetine. There was no difference between treatments for any of the comparisons on attrition (olanzapine versus sertraline: no events occurred in any of the treatment groups; Analysis 10.14; haloperidol versus amitriptyline: RR 2.90, 95% CI 0.32 to 26.38; P = 0.34; 1 trial, 61 participants; Analysis 10.14; haloperidol versus phenelzine sulfate: RR 1.58, 95% CI 0.49 to 5.15; P = 0.45; 1 trial, 75 participants; Analysis 10.14; and olanzapine versus fluoxetine: RR 0.29, 95% CI 0.01 to 6.69; P = 0.44; 1 trial, 30 participants; Analysis 10.14).

2.15 Adverse events

No trials comparing a medication with another medication reported data on non-serious adverse events of the gastrointestinal system, the sensory system or the reproductive system; or on any other adverse events than those suggested in our analysis plan.

Three trials comparing a medication with another medication reported dichotomous data on total non-serious adverse events.

All trials compared an antipsychotic to another antipsychotic. Leone 1982 compared loxapine to chlorpromazine, Shafti 2010 compared olanzapine to haloperidol, and Shafti 2014 compared olanzapine to aripiprazole. There was no difference between treatments regarding adverse events in any of the comparisons i.e. loxapine versus chlorpromazine (RR 1.27, 95% CI 0.66 to 2.45; P = 0.47; 1 trial, 80 participants, Analysis 10.15; olanzapine versus haloperidol (RR 0.75, 95% CI 0.35 to 1.60; P = 0.46; 1 trial, 28 participants; Analysis 10.15; and olanzapine versus aripiprazole (RR 0.75, 95% CI 0.38 to 1.50; P = 0.42; 1 trial, 24 participants; Analysis 10.15). No trials comparing a medication with another medication reported data on serious adverse events.

Withdrawal due to adverse events

One trial comparing a medication with another medication reported dichotomous data on withdrawal due to adverse events. Bozzatello 2017 compared the antipsychotics olanzapine and asenapine. There was no difference between the treatment groups in withdrawal due to adverse events (RR 0.96, 95% CI 0.15 to 6.31; P = 0.97; 1 trial, 51 participants; Analysis 11.1).

Central nervous system

Sedation

One trial comparing a medication with another medication reported dichotomous data on sedation as a non-serious adverse event. Zanarini 2004 compared an antipsychotic with an antidepressant. There was an increased risk of sedation with antipsychotics compared to antidepressants (RR 3.50, 95% CI 1.23 to 9.92; P = 0.02; 1 trial, 30 participants; Analysis 12.1).

Restlessness

Two trials comparing a medication with another medication reported dichotomous data on restlessness as a non-serious adverse event. Leone 1982 compared the antipsychotics loxapine and chlorpromazine, while Zanarini 2004 compared the antipsychotic olanzapine to the antidepressant fluoxetine. None of the analyses showed a difference in restlessness between the groups (loxapine versus chlorpromazine: (RR 1.50, 95% CI 0.26 to 8.50; P = 0.65; 1; I^2 = 0%; 1 trial, 80 participants; Analysis 12.2; and olanzapine versus fluoxetine: RR 0.70, 95% CI 0.23 to 2.11; P = 0.53; 1 trial, 30 participants; Analysis 12.2).

Restlessness/anxiety

One trial comparing a medication with another medication reported dichotomous data on restlessness/anxiety as a non-serious adverse event. Bozzatello 2017 compared two antipsychotics, olanzapine and asenapine. There was no difference in restlessness/anxiety between the two groups (RR 0.19, 95% CI 0.01 to 3.82; P = 0.28; 1 trial, 51 participants; Analysis 12.3).

Sleepiness/drowsiness

Two trials comparing a medication with another medication reported dichotomous data on sleepiness/drowsiness as a non-serious adverse event. Leone 1982 compared the two antipsychotics loxapine and chlorpromazine. There was no difference in sleepiness/drowsiness between the two groups (RR 0.80, 95% CI 0.23 to 2.76; P = 0.72; 1 trial, 80 participants; Analysis 12.4). Bozzatello 2017 compared two second-generation antipsychotics olanzapine and asenapine. There was no difference in sleepiness/drowsiness between the two groups (RR 6.74, 95% CI 0.37 to 124.21; P = 0.20; 1 trial, 51 participants; Analysis 12.4).

Fainting spells

One trial comparing a medication with another medication reported dichotomous data on fainting spells as a non-serious adverse event. Leone 1982 compared the two antipsychotics loxapine and chlorpromazine. There was no difference in fainting spells between the groups (RR 0.14, 95% CI 0.01 to 2.68; P = 0.19; 1 trial, 80 participants; Analysis 12.5).

Akathisia

One trial comparing a medication with another medication reported dichotomous data on akathisia as a non-serious adverse event. Bozzatello 2017 compared the antipsychotics olanzapine and asenapine. There was no difference in akathisia between the two groups (RR 0.19, 95% CI 0.01 to 3.82; P = 0.28; 1 trial, 51 participants; Analysis 12.6).

Moderate anxiety

One trial comparing a medication with another medication reported dichotomous data on moderate anxiety as a non-serious adverse event. Bozzatello 2017 compared the antipsychotics olanzapine and asenapine. There was no difference in moderate anxiety between the two groups (RR 0.32, 95% CI 0.01 to 7.53; P = 0.48; 1 trial, 51 participants; Analysis 12.7).

Fatigue

One trial comparing a medication with another medication reported dichotomous data on fatigue as a non-serious adverse event. Bozzatello 2017 compared the antipsychotics olanzapine and asenapine. There was no difference in fatigue between groups (RR 4.81, 95% CI 0.24 to 95.58; P = 0.30; 1 trial, 51 participants; Analysis 12.8).

Cardiovascular and respiratory system

Oral hypoaesthesia

One trial comparing a medication with another medication reported dichotomous data on oral hypoaesthesia as a non-serious adverse event. Bozzatello 2017 compared the antipsychotics olanzapine and asenapine. There was no difference in oral hypoaesthesia between the two groups (RR 0.32, 95% CI 0.01 to 7.53; P = 0.48; 1 trial, 51 participants; Analysis 13.1).

Musculoskeletal system

Muscle spasms

One trial comparing a medication with another medication reported dichotomous data on muscle spasms as a non-serious adverse event. Leone 1982 compared the two antipsychotics loxapine and chlorpromazine. There was no difference in muscle spasms between the groups (RR 3.00, 95% CI 0.33 to 27.63; P = 0.33; 1 trial, 80 participants; Analysis 14.1).

Body weight change

Two trials comparing a medication with another medication reported continuous data on body weight change as a non-serious adverse event. Both compared an antipsychotic to an antidepressant. Soloff 1993 compared haloperidol to phenelzine sulfate and Zanarini 2004 compared olanzapine to fluoxetine. There was no difference between haloperidol and phenelzine sulfate on body weight change (MD −0.22, 95% CI −0.59 to 0.15; P = 0.25; 1 trial, 64 participants; Analysis 14.2). However, there was a difference between olanzapine and fluoxetine on body weight change favouring fluoxetine (MD 2.50, 95% CI 0.72 to 4.28; P = 0.006; 1 trial, 29 participants; Analysis 14.2).

Weight gain

One trial comparing a medication with another medication reported dichotomous data on weight gain as a non-serious adverse event. Bozzatello 2017 compared the antipsychotics olanzapine and asenapine. There was no difference in weight gain between groups (RR 4.81, 95% CI 0.24 to 95.58; P = 0.30; 1 trial, 51 participants; Analysis 14.3).

3 Single medication compared with combination of medications

Primary outcomes

3.1 BPD symptom severity

One trial compared one medication with a combination of medications and reported continuous data on BPD symptom severity. Bellino 2014 compared the mood stabiliser valproic acid to valproic acid plus omega-3 fatty acids combined. There was a difference between valproic acid alone and valproic acid plus omega-3 fatty acids regarding BPD symptom severity at the end of treatment favouring the mood stabiliser alone (MD 8.48, 95% CI 3.39 to 13.57; P = 0.001; 1 trial, 34 participants; Analysis 15.1).

3.2 Self-harm

One trial compared a pharmacotherapy with a combination of pharmacotherapies and reported continuous data on self-harm. Bellino 2014 compared the mood stabiliser valproic acid to valproic acid plus omega-3 fatty acids combined. There was a difference between valproic acid alone and valproic acid plus omega-3 fatty acids regarding self-harm at the end of treatment favouring the mood stabiliser alone (MD 2.55, 95% CI 0.98 to 4.12; P = 0.001; 1 trial, 34 participants; Analysis 15.2).

3.3 Suicide-related outcomes

One trial compared a pharmacotherapy with a combination of pharmacotherapies and reported continuous data on suicide-related outcomes. Bellino 2014 compared the mood stabiliser valproic acid to valproic acid plus omega-3 fatty acids combined. There was no difference between valproic acid alone and valproic acid plus omega-3 fatty acids regarding suicide-related outcomes at the end of treatment (MD 0.23, 95% CI −0.74 to 1.20; P = 0.64; 1 trial, 34 participants; Analysis 15.3).

3.4 Psychosocial functioning

One trial compared a pharmacotherapy with a combination of pharmacotherapies and reported continuous data on psychosocial functioning. Bellino 2014 compared the mood stabiliser valproic acid to valproic acid plus omega-3 fatty acids combined. There was no difference between valproic acid alone and valproic acid plus omega-3 fatty acids regarding psychosocial functioning at the end of treatment (MD 0.88, 95% CI −6.21 to 7.97; P = 0.81; 1 trial, 34 participants; Analysis 15.4).

Secondary outcomes

3.5 Anger

Two trials compared a pharmacotherapy to a combination of pharmacotherapies and reported continuous data on anger.

Zanarini 2004 compared the antipsychotic olanzapine to olanzapine plus the antidepressant fluoxetine combined. There was no difference between the groups regarding impulsivity at the end of treatment (MD 0.46, 95% CI −12.93 to 13.85; P = 0.95; 1 trial, 29 participants; Analysis 15.5). Zanarini 2004 also compared fluoxetine to fluoxetine plus olanzapine. There was no difference between the groups at the end of treatment (MD 4.77, 95% CI −9.67 to 19.21; P = 0.52; 1 trial, 26 participants; Analysis 15.5).

Bellino 2014 compared the mood stabiliser valproic acid to valproic acid plus omega-3 fatty acids combined. There was no difference between valproic acid alone and valproic acid plus omega-3 fatty acids regarding anger at end of treatment (MD 0.60, 95% CI −0.82 to 2.02; P = 0.41; 1 trial, 34 participants; Analysis 15.5).

3.6 Affective instability

One trial compared a medication with a combination of medications and reported continuous data on affective instability. Bellino 2014 compared the mood stabiliser valproic acid to valproic acid plus omega-3 fatty acids combined. There was a difference between valproic acid alone and valproic acid plus omega-3 fatty acids regarding affective instability at the end of treatment favouring valproic acid combined with omega-3 fatty acids (MD 1.72, 95% CI 0.68 to 2.76; P = 0.001; 1 trial, 34 participants; Analysis 15.6)

3.7 Chronic feelings of emptiness

One trial compared a medication with a combination of medications and reported continuous data on chronic feelings of emptiness. Bellino 2014 compared the mood stabiliser valproic acid to valproic acid plus omega-3 fatty acids combined. There was no difference between valproic acid alone and valproic acid plus

omega-3 fatty acids regarding anger at the end of treatment (MD 0.03, 95% CI −0.97 to 1.03; P = 0.95; 1 trial, 34 participants; Analysis 15.7).

3.8 Impulsivity

Two trials compared a medication with a combination of medications and reported continuous data on impulsivity.

One trial (Zanarini 2004) compared the antipsychotic olanzapine to olanzapine plus the antidepressant fluoxetine combined. There was no difference between treatments regarding impulsivity at the end of treatment (MD 0.46, 95% CI −12.93 to 13.85; P = 0.95; 1 trial, 29 participants; Analysis 15.8). Zanarini 2004 also compared fluoxetine to fluoxetine plus olanzapine. There was no difference between the groups regarding impulsivity at the end of treatment (MD 4.77, 95% CI −9.67 to 19.21; P = 0.52; 1 trial, 26 participants; Analysis 15.8).

Another trial (Bellino 2014), compared the mood stabiliser valproic acid to valproic acid plus omega-3 fatty acids combined. There was a difference between valproic acid alone and valproic acid plus omega-3 fatty acids regarding impulsivity at the end of treatment, favouring valproic acid plus omega-3 fatty acids combined (MD 12.59, 95% CI 6.11 to 19.07; P = 0.0001; 1 trial, 34 participants; Analysis 15.8).

3.9 Interpersonal problems

One trial compared a medication with a combination of medications and reported continuous data on interpersonal problems. Bellino 2014 compared the mood stabiliser valproic acid to valproic acid plus omega-3 fatty acids combined. There was no difference between valproic acid alone and valproic acid plus omega-3 fatty acids regarding interpersonal problems at the end of treatment (MD 0.47, 95% CI −0.41 to 1.35; P = 0.29; 1 trial, 34 participants; Analysis 15.9).

3.10 Abandonment

One trial compared a medication with a combination of medications and reported continuous data on fear of abandonment. Bellino 2014 compared the mood stabiliser valproic acid to valproic acid plus omega-3 fatty acids combined. There was no difference between valproic acid alone and valproic acid plus omega-3 fatty acids regarding fear of abandonment at the end of treatment (MD 0.01, 95% CI −0.83 to 0.85; P = 0.98; 1 trial, 34 participants; Analysis 15.10).

3.11 Identity disturbance

One trial compared a medication with a combination of medications and reported continuous data on identity disturbance. Bellino 2014 compared the mood stabiliser valproic acid to valproic acid plus omega-3 fatty acids combined. There was no difference between valproic acid alone and valproic acid plus omega-3 fatty acids regarding identity disturbances at the end of treatment (MD 0.70, 95% CI −0.34 to 1.74; P = 0.19; 1 trial, 34 participants; Analysis 15.11).

3.12 Dissociation and psychotic-like symptoms

One trial compared a medication with a combination of medications and reported continuous data on dissociation and psychotic-like symptoms. Bellino 2014 compared the mood stabiliser valproic acid to valproic acid plus omega-3 fatty acids combined. There was no difference between valproic acid alone and valproic acid plus omega-3 fatty acids regarding dissociation and psychotic-like symptoms at the end of treatment (MD 0.03, 95% CI −1.09 to 1.15; P = 0.96; 1 trial, 34 participants; Analysis 15.12).

3.13 Depression

Two trials compared pharmacotherapies with combinations of other pharmacotherapies and reported continuous data on depression.

Zanarini 2004 compared the antipsychotic olanzapine to olanzapine plus the antidepressant fluoxetine. There was no difference between olanzapine alone and olanzapine plus fluoxetine regarding depression at the end of treatment (MD −1.78, 95% CI −6.48 to 2.92; P = 0.46; 1 trial, 29 participants; Analysis 15.13). Zanarini 2004 also compared fluoxetine to fluoxetine combined with olanzapine. There was no difference between fluoxetine alone and fluoxetine plus olanzapine regarding depression at the end of treatment (MD 3.62, 95% CI −1.36 to 8.60; P = 0.15; 1 trial, 25 participants; Analysis 15.13).

Bellino 2014 compared the mood stabiliser valproic acid to valproic acid plus omega-3 fatty acids combined. There was no difference between valproic acid alone and valproic acid plus omega-3 fatty acids regarding depression at end of treatment (MD 1.30, 95% CI 0.00 to 2.60; P = 0.05; 1 trial, 34 participants; Analysis 15.13).

3.14 Attrition

Two trials compared a medication with a combination of medications and reported dichotomous data on attrition.

One trial compared the antipsychotic olanzapine to olanzapine plus the antidepressant fluoxetine (Zanarini 2004). There was no difference between olanzapine alone and olanzapine combined with fluoxetine regarding attrition (RR 0.19, 95% CI 0.01 to 3.63; P = 0.27; 1 trial, 31 participants; Analysis 15.14). Zanarini 2004 also compared fluoxetine to fluoxetine plus olanzapine. There was no difference between fluoxetine alone and fluoxetine combined with olanzapine regarding attrition (RR 0.54, 95% CI 0.05 to 5.28; P = 0.59; 1 trial, 29 participants; Analysis 15.14).

One trial compared the mood stabiliser valproic acid to valproic acid plus omega-3 fatty acids combined (Bellino 2014). There was no difference between valproic acid alone and valproic acid combined with omega-3 fatty acids regarding attrition (RR 0.92, 95% CI 0.29 to 2.97; P = 0.89; 1 trial, 43 participants; Analysis 15.14).

3.15 Adverse events

No trials comparing pharmacotherapies to a combination of other pharmacotherapies reported data on total serious or non-serious adverse events; non-serious adverse events of the cardiovascular and respiratory system, the sensory system or the reproductive system; or any other non-serious adverse events than those suggested in our analysis plan. Nor did they report data on withdrawal due to adverse events.

Central nervous system

Sedation

One trial comparing a medication with a combination of medications reported dichotomous data on sedation as a non-serious adverse event. Zanarini 2004 compared the antipsychotic olanzapine to olanzapine plus the antidepressant fluoxetine. There

was no difference in sedation between olanzapine alone and olanzapine plus fluoxetine combined (RR 1.61, 95% CI 0.87 to 2.96; P = 0.13; 1 trial, 31 participants; Analysis 16.1). Zanarini 2004 also compared fluoxetine to fluoxetine plus olanzapine. There was no difference between fluoxetine compared to fluoxetine plus olanzapine (RR 0.46, 95% CI 0.15 to 1.44; P = 0.18; 1 trial, 29 participants; Analysis 16.1).

Gastrointestinal system

Nausea

One trial comparing a medication with a combination of medications reported dichotomous data on nausea as a non-serious adverse event. Bellino 2014 compared the mood stabiliser valproic acid to valproic acid plus omega-3 fatty acids combined. There was no difference between valproic acid alone and valproic acid combined with omega-3 fatty acids regarding nausea (RR 0.22, 95% CI 0.01 to 4.34; P = 0.32; 1 trial, 34 participants; Analysis 17.1).

Dyspepsia

One trial comparing a medication with a combination of medications reported dichotomous data on dyspepsia as a non-serious adverse event. Bellino 2014 compared the mood stabiliser valproic acid to valproic acid plus omega-3 fatty acids combined. There was no difference between valproic acid alone and valproic acid combined with omega-3 fatty acids regarding dyspepsia (RR 1.13, 95% CI 0.08 to 16.55; P = 0.44; 1 trial, 34 participants; Analysis 17.2).

Muscloskeletal system

Akathisia

One trial comparing a medication with a combination of medications reported dichotomous data on akathisia as a non-serious adverse event. Zanarini 2004 compared the antipsychotic olanzapine to olanzapine plus the antidepressant fluoxetine. There was no difference in akathisia between olanzapine alone and olanzapine plus fluoxetine combined (RR 0.75, 95% CI 0.25 to 2.28; P = 0.61; 1 trial, 31 participants; Analysis 18.1). Zanarini 2004 also compared fluoxetine to fluoxetine plus olanzapine. There was no difference in akathisia between fluoxetine alone and the combination of fluoxetine and olanzapine (RR 1.07, 95% CI 0.39 to 2.92; P = 0.89; 1 trial, 29 participants; Analysis 18.1).

Body weight change

Two trials comparing a medication with a combination of medications reported continuous data on body weight change as a non-serious adverse event.

One trial compared the antipsychotic olanzapine to olanzapine plus the antidepressant fluoxetine (Zanarini 2004). There was a difference in body weight change between olanzapine alone and olanzapine plus fluoxetine combined, which favoured the combination of olanzapine and fluoxetine (MD 1.50, 95% CI 0.09 to 2.91; P = 0.04; 1 trial, 29 participants; Analysis 18.3). Zanarini 2004 also compared fluoxetine to fluoxetine plus olanzapine. There was no difference between fluoxetine alone and the combination of fluoxetine and olanzapine in body weight change (MD −1.00, 95% CI −2.39 to 0.39; P = 0.16; 1 trial, 26 participants; Analysis 18.3).

Bellino 2014 compared the mood stabiliser valproic acid to valproic acid plus omega-3 fatty acids combined. There was no difference between valproic acid alone and valproic acid plus omega-3 fatty acids combined for change in body weight (RR 1.13, 95% CI 0.26 to 4.80; P = 0.87; 1 trial, 34 participants; Analysis 18.2).

4. Subgroup analyses

We performed subgroup analyses on substances within each medication type (and type of antipsychotics). Further, we investigated if any subgroup differences between types of medication were present before pooling them into subgroup analyses on psychosocial functioning at baseline (mild, moderate, and seriously impaired), setting (inpatient, outpatient, and mixed setting), funding (publicly funded, and industry funded), trial size (≤ 50 participants, ≤ 99 participants, and > 99 participants) and method of recruitment (advertisement, and referral). There were no differences between antipsychotics, antidepressants, and mood stabilisers in the intervention effects of outcomes for which subgroup analyses were feasible: BPD severity (test for subgroup differences: Chi^2 = 1.42, df = 2 (P = 0.49), I^2 = 0%; Analysis 1.1), suicide-related outcomes (test for subgroup differences: Chi^2 = 0.44, df = 2 (P = 0.80), I^2 = 0%; Analysis 1.5), psychosocial functioning (test for subgroup differences: Chi^2 = 1.48, df = 2 (P = 0.48), I^2 = 0%; Analysis 1.8), and anger (test for subgroup differences: Chi^2 = 6.50, df = 3 (P = 0.09), I^2 = 53.8%; Analysis 1.11).

4.1 Types of medication

4.1.1 Antipsychotics

4.1.1.1 First- versus second-generation antipsychotics

Subgroup analyses were feasible for the primary outcomes of BPD severity, suicide-related outcomes, and psychosocial functioning. The intervention effect varied according to subgroups of antipsychotics indicating inferiority of first-generation antipsychotics (SMD 0.29, 95% CI −0.09 to 0.67; I^2 = 0%; 3 trials, 108 participants) compared to second-generation antipsychotics (SMD -0.36, 95% CI -0.66 to -0.05; I^2 = 74%; 5 trials, 820 participants) regarding BPD severity (test for subgroup differences: Chi^2 = 6.74, df = 1 (P = 0.009), I^2 = 85.2%, Analysis 20.1). There was no indication that intervention effects varied according to subgroups of first- and second-generation antipsychotics neither regarding suicide-related outcomes (test for subgroup differences: Chi^2 = 0.24, df = 1 (P = 0.63), I^2 = 0%; Analysis 20.2), nor psychosocial functioning (test for subgroup differences: Chi^2 = 0.03, df = 1 (P = 0.86), I^2 = 0% Analysis 20.3).

4.1.1.2 Antipsychotics by substance

Subgroup analyses were feasible for the primary outcomes of BPD severity, suicide-related outcomes, and psychosocial functioning.

For BPD severity, subgroups included one trial each (haloperidol, thiothixene, quetiapine, ziprasidone and brexpiprazole) except for olanzapine (two trials). The subgroup analysis revealed that the intervention effect varied according to type of substance (haloperidol; MD 3.95, 95% CI -2.66 to 10.56; 1 trial, 58 participants; olanzapine; SMD -0.15, 95% CI -0.41 to 0.10; I^2 = 60%; 2 trials, 596 participants; thiothixene; MD 1.20, 95% CI -1.19 to 3.60; 1 trial, 50 participants; quetiapine; MD -0.70, 95% CI -2.80 to 1.40; 1 trial, 95 participants; ziprasidone; MD -0.42, 95% CI -0.87 to 0.03; 1 trial, 60 participants; brexpiprazole; MD -5.30, 95% CI -7.56 to -3.04; 1 trial,

69 participants). The test for subgroup differences indicated: Chi^2 = 19.72, df = 5 (P = 0.001), I^2 = 74.6%, Analysis 20.4.

There was no indication that intervention effects varied according to subgroups of substances, olanzapine, ziprasidone, brexpiprazole and alprazolam, either regarding suicide-related outcomes at end of treatment (test for subgroup differences: Chi^2 = 4.30, df = 3 (P = 0.23), I^2 = 30.2%; Analysis 20.6), or between subgroups of haloperidol, olanzapine, quetiapine and thiothixene regarding the outcome of psychosocial functioning (test for subgroup differences: Chi^2 = 1.05, df = 3 (P = 0.79), I^2 = 0%; Analysis 20.7).

4.1.2 Antidepressants

A subgroup analysis of class and substance of antidepressants was only feasible for the primary outcome of psychosocial functioning. There was no indication that the intervention effect on psychosocial functioning varied according to antidepressant class or substance for the subgroups tricyclic antidepressant (amitriptyline) and selective serotonin reuptake inhibitor (fluoxetine). The test for subgroup differences indicated: Chi^2 = 0.25, df = 1 (P = 0.61), I^2 = 0%; Analysis 20.8.

4.1.3 Mood stabilisers

Data permitted a subgroup analysis only for the primary outcome of BPD severity. There was no indication that intervention effects varied according to mood stabiliser substances divalproex and lamotrigine (test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.91), I^2 = 0%; Analysis 20.5).

4.2 Psychosocial functioning at baseline

No subgroup differences were observed for any primary outcome between cohorts of mildly, moderate or seriously impaired individuals (BPD severity: test for subgroup differences: Chi^2 = 1.65, df = 2 (P = 0.44), I^2 = 0%; Analysis 21.1; suicide-related outcomes: test for subgroup differences: Chi^2 = 0.05, df = 1 (P = 0.82), I^2 = 0%; Analysis 21.2; or psychosocial functioning: test for subgroup differences: Chi^2 = 1.66, df = 2 (P = 0.44), I^2 = 0%; Analysis 21.3).

4.3 Setting

The majority of trials included individuals who underwent outpatient treatment. Eight trials were conducted in an inpatient setting, and four trials in mixed in- and outpatient settings (see Table 1). Subgroup analyses were feasible for the primary outcomes of BPD severity, suicide-related outcomes and psychosocial functioning. No differences were observed between setting subgroups (BPD severity: test for subgroup differences: Chi^2 = 1.02, df = 2 (P = 0.60), I^2 = 0%; Analysis 22.1; suicide-related outcomes: test for subgroup differences:Test for subgroup differences: Chi^2 = 0.55, df = 1 (P = 0.46), I^2 = 0%; Analysis 22.2; or psychosocial functioning: test for subgroup differences: Chi^2 = 0.01, df = 2 (P = 1.00), I^2 = 0%; Analysis 22.3).

4.4 Funding

Most trials (16 out of 45), were funded (full or partly) by the pharmaceutical industry. Ten were publicly funded, i.e. by grants from universities, authorities or research foundations, funding for 11 trials was unclear, and eight declared that no funding was received. For BPD severity, the intervention effect varied according to subgroups of funding with a seemingly higher effect of trials partially or fully funded by the pharmaceutical industry (SMD -0.34, 95% CI -0.61 to -0.08; I^2 = 62%, 7 trials, 862 participants) compared to publicly funded trials (SMD 0.04, 95% CI -0.17 to 0.25; I^2 = 0%, 4 trials, 348 participants) and trials with unclear funding (SMD 0.24, 95% CI -0.23 to 0.70; I^2 = 0%, 2 trials, 73 participants). The test for subgroup differences indicated: Chi^2 = 7.00, df = 2 (P = 0.03), I^2 = 71.4%; Analysis 23.1. Intervention effects did not vary according to subgroups of funding sources for the outcome of psychosocial functioning (test for subgroup differences: Chi^2 = 0.23, df = 2 (P = 0.89), I^2 = 0%, Analysis 23.2).

4.5 Trial size

Intervention effects varied according to trial size for the outcome of anger with an equally superior effect from trials with 50 participants or fewer (SMD -0.67, 95% CI -1.00 to -0.34; I^2 = 55%; 13 trials, 377 participants), and with 99 participants or fewer (SMD -0.67, 95% CI -1.14 to -0.20; I^2 = 86%; 9 trials, 546 participants), compared to larger trials with 100 participants or more (SMD -0.25, 95% CI -0.41 to -0.09; I^2 = 0%; 2 trials, 596 participants). The test for subgroup differences indicated: Chi^2 = 6.78, df = 2 (P = 0.03), I^2 = 70.5%; Analysis 24.2 (See Figure 13). Intervention effects did not vary for these groups regarding the outcome of psychosocial functioning (test for subgroup differences: Chi^2 = 2.59, df = 2 (P = 0.27), I^2 = 22.7%, Analysis 24.1) (See Figure 14).

Figure 13. Funnel plot of comparison: 26 Subgroup analyses: trial size, outcome: 26.2 Secondary: Anger at end of treatment SE(SMD): Standard error of the standardised mean difference; SMD: Standardised mean difference

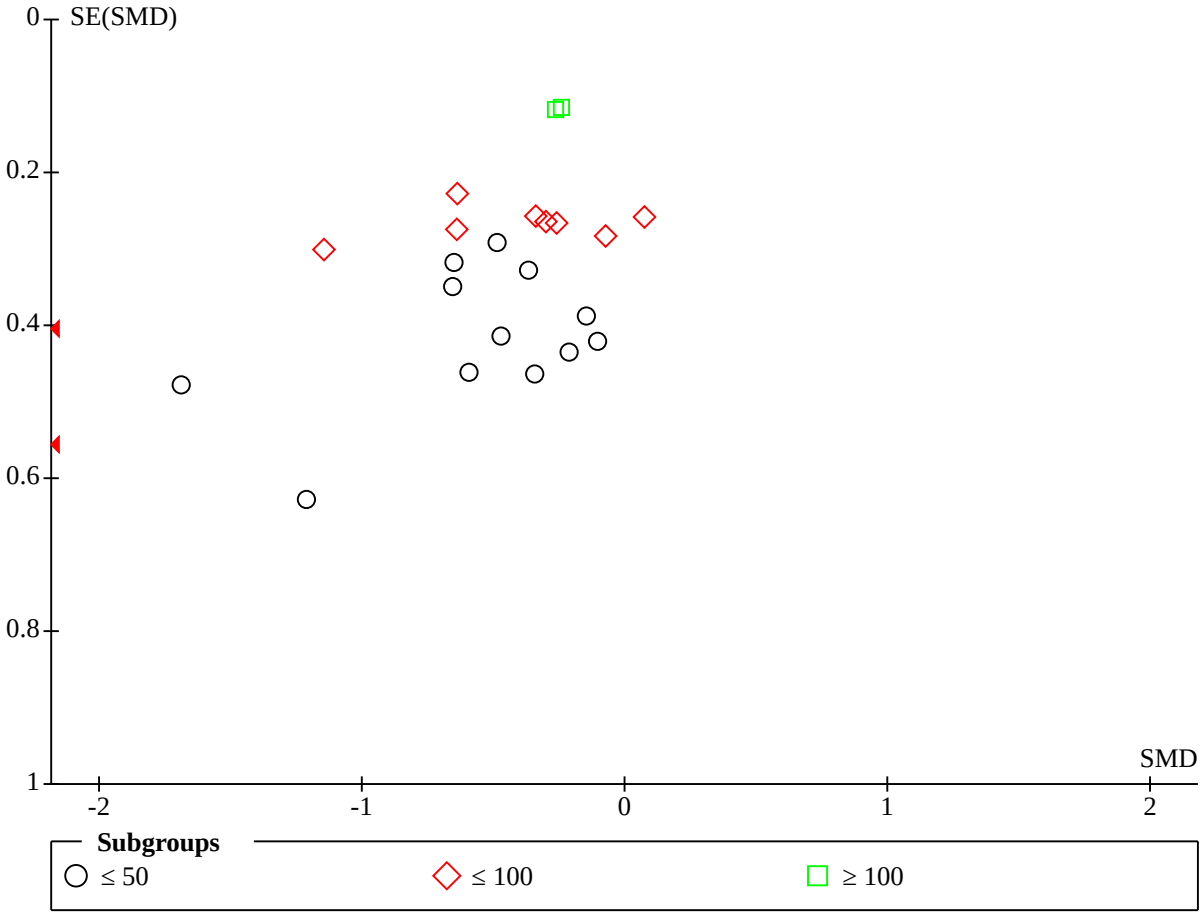
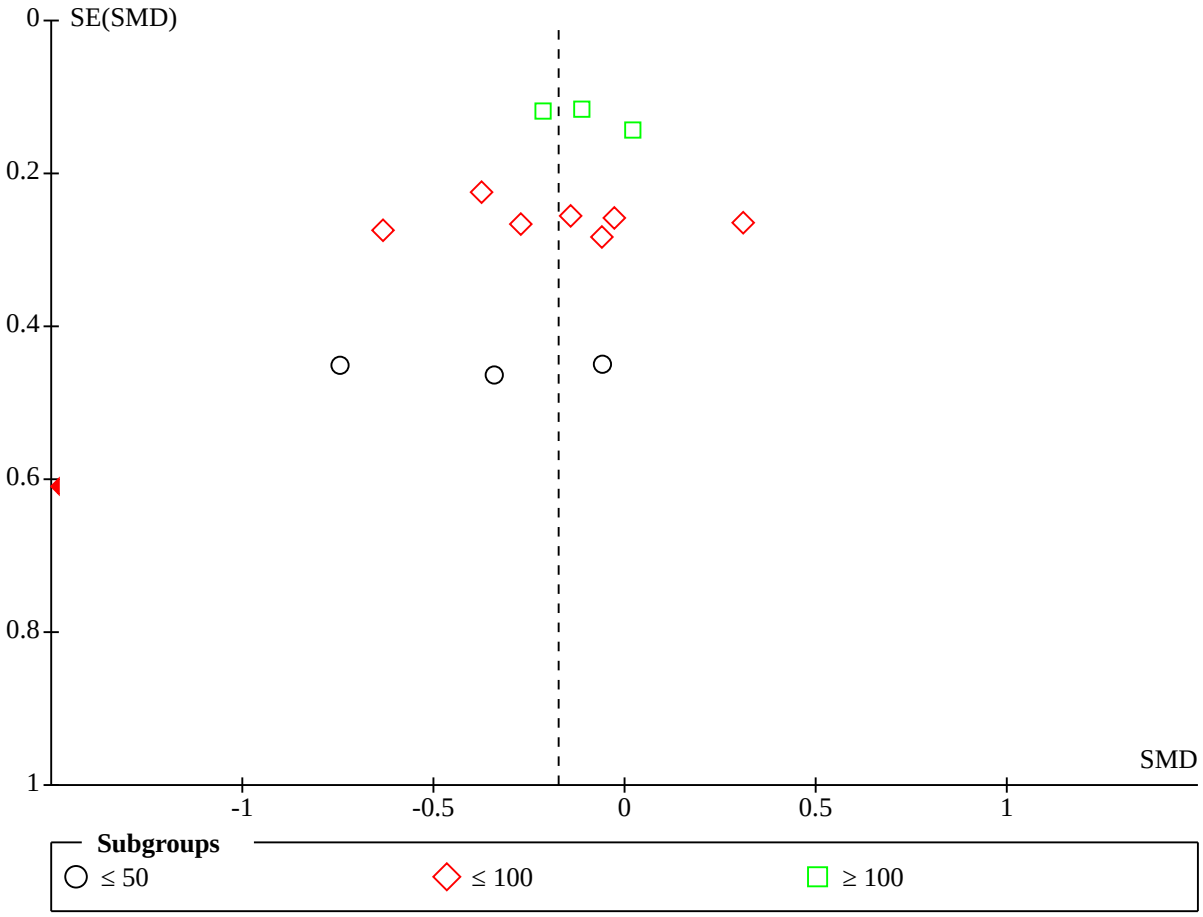


Figure 14. Funnel plot of comparison: 26 Subgroup analyses: trial size, outcome: 26.1 Primary: Psychosocial functioning at end of treatment SE(SMD): Standard error of the standardised mean difference; SMD: Standardised mean difference



4.6 Recruitment

Regarding the effect of antipsychotics on anger at the end of treatment, there were no subgroup differences in intervention effects between trials including participants through referrals or advertisements. The test for subgroup differences indicated: Chi^2 = 0.31, df = 1 (P = 0.58), I^2 = 0%; Analysis 25.1).

5. Sensitivity analyses

5.1 Imprecision

Where we were uncertain about the assessment of imprecision, as assessed by GRADE, we tested for it, by conducting TSAs on the primary and secondary outcomes (for the main comparison versus placebo).

In order to investigate the impact of imprecision, we also drew funnel plots for the primary and secondary outcomes involving the highest number of primary trials comparing active medications to placebo, i.e. psychosocial functioning and anger. Funnel plots revealed a clear trend of more precise estimates by larger trials, and indicated that smaller trials with unfavourable outcomes might be lacking, either due to publication bias or an overestimation of effects by smaller trials (Figure 13; Figure 14).

5.2 Cross-over trials

We found no differences when adding end-of-period data from one cross-over trial to the parallel-group analyses (Cowdry 1988).

5.3 Decisions during the review process

5.3.1 Choice of data sources for Black 2014

For one trial, results were available from a journal publication (Black 2014a) as well as a trial registry entry (NCT00880919). We decided to use the data from the peer-reviewed journal publication, whenever possible. However, for one outcome (Zan-BPD total), data were available from both sources. While those reported in the journal article resulted in a small effect of SMD −0.14 (95% CI −0.58 to 0.29), the data from the trial registry entry would have yielded a very large, clearly outlying large effect of SMD −1.95 (95% CI −2.47 to −1.43). This finding reinforced our decision to primarily use data from peer-reviewed sources, whenever possible.

5.3.2 Exclusion of outliers

For the secondary outcome of anger, heterogeneity was high (87%) due to several trials reporting outstandingly high effect estimates, as the visual inspection of the forest plot indicated. We

decided to exclude the outliers one-by-one, until heterogeneity was low. Therefore, primary analyses resulted in an effect estimate of mood stabilisers compared to placebo of SMD −0.67 (95% CI −1.10 to −0.24; I^2 = 26%; 5 trials, 135 participants), once Loew 2006, Nickel 2004 and Tritt 2005 had been excluded. If all outliers were included, the effect estimate would be more than twice as high, with SMD −1.39 (95% CI −2.16 to −0.61; I^2 = 84%; 8 trials, 247 participants; Analysis 26.1).

The substantial reduction of high statistical heterogeneity from 84% to 27% by excluding those trials with outstanding, exceptionally high effect estimates and the bisection of the pooled effect supports our decision not to include the outliers in the primary analyses in order to avoid an overestimation of intervention effects. All these trials originate from the same working group and had been discussed for possibly biased results previously (NICE 2009, p. 217: "The GDG [guideline development group] [...] took the decision not to consider these trials when drawing up their conclusions."

5.4 Type of model used for analyses

We repeated all analyses of primary outcomes using the fixed-effect model to test the robustness of results. The only relevant difference was that the CI of analysis 1.6.1 (psychosocial functioning, antipsychotics versus placebo) would no longer include zero (95% CI −0.30 to −0.03 instead of 95% CI −0.33 to 0.00).

DISCUSSION

Summary of main results

Comparisons of active medications with placebo

We included 42 trials with a parallel design and 4 trials with a cross-over design (Cowdry 1988; Schmahl 2012a; Schmahl 2012b; Ziegenhorn 2009) in this review. Altogether, these trials randomised 2769 participants, and were reported in 98 publications. The trials compared different types of antipsychotics, antidepressants, mood stabilisers, and miscellaneous medications to placebo, another active treatment or a combination of active treatments. The duration of the trials ranged from four to 52 weeks. The majority of the trials had a duration of three months or less and most of them took place in an outpatient setting. Nineteen trials were from Europe, 17 were from the USA, three trials were from Southwest Asia (the Middle East, all of them from Iran), one trial was from Australia, and two were multi-country trials from nine transcontinental countries.

The mean age of the participants ranged from 16.2 to 39.7 years. Fourteen trials included women only and one trial included only men. All remaining trials included both sexes, but predominantly women. All included trials were assessed to be at high risk of bias overall.

The aim of this review was to determine the effects of pharmacological treatment for individuals with borderline personality disorder (BPD) of any age. We pooled the different types of antipsychotics, antidepressants and mood stabilisers into the respective medication classes.

Compared with placebo, **antipsychotics** may have little to no effect on the primary outcomes of BPD symptoms severity, self-harm, suicide-related outcomes and psychosocial functioning, or the secondary outcomes of attrition or total non-serious adverse events. All primary outcomes are of very low certainty (see Summary of findings 1). Notably, all but one of the RCTs comparing olanzapine to placebo and reporting on suicidality-related outcomes observed heightened suicidality in the olanzapine-treated groups. The evidence is very uncertain about dropout rates and adverse events as compared to placebo.

Antidepressants, when compared to placebo, may result in little to no difference in the primary outcomes of BPD symptom severity, psychosocial functioning, self-harm and suicide-related outcomes, but the evidence is very uncertain. Antidepressants may have no effect on the secondary outcome of interpersonal problems (very low-certainty evidence) or the dropout rate compared with placebo (low-certainty evidence); see Summary of findings 2. Low-certainty evidence suggests that mood stabilisers are not associated with heightened dropout rates. No data are available on non-serious adverse events by antidepressants.

Mood stabilisers, compared with placebo, may result in little to no difference in the primary outcomes of BPD symptom severity, self-harm, suicide-related outcomes, and psychosocial functioning (all very low-certainty evidence). Mood stabilisers may reduce interpersonal problems, but the evidence is uncertain again (low-certainty). Low-certainty evidence suggests that mood stabilisers are not associated with heightened dropout rates. Regarding non-serious adverse events, the evidence is very uncertain (very low-certainty evidence, see Summary of findings 3).

We also included trials with **miscellaneous** medications (i.e. those not classified as antipsychotics, antidepressants or mood stabilisers). With the exception of omega-3 fatty acids, none of these drugs (the antidementia drug memantine hydrochloride, the opioid antagonist naltrexone, the antihypertensive alpha-2A adrenergic agonist clonidine, or the opioid antagonist naltrexone) were observed to have an effect on any of the primary or secondary outcomes compared to placebo. Omega-3 fatty acids might have an effect on suicide-related outcomes compared to placebo. Furthermore, in the analysis of omega-3 fatty acids on psychosocial functioning, there might be an increase in psychosocial function at the end of treatment in favour of placebo.

We did not find any differences in the presence of total adverse events between groups for any of the medications that reported adverse events. Only one trial reported total serious adverse events. Kulkarni 2018 compared memantine hydrochloride to placebo and reported no serious adverse events in the experimental or the placebo group (Analysis 1.29). No other trial specifically reported data on serious adverse events. However, we did find evidence of a difference between groups for some individual non-serious adverse events; for example, antipsychotics on somnolence, increased appetite, dry mouth and body weight change; and mood stabilisers on gastrointestinal disorders. We also found evidence of a difference between groups on a range of laboratory values when comparing antipsychotics to placebo; for example, mean change in AST/SGOT and ALT/SGPT as well as LDL and HDL cholesterol. Please refer to the section, Effects of interventions, for a full overview of adverse events.

Head-to-head comparisons of active medications

Head-to-head comparisons of active medications compared antipsychotics to antidepressants (Jariani 2010; Soloff 1989; Soloff

1993; Zanarini 2004) or different antipsychotics (Bozzatello 2017; Leone 1982; Shafti 2010; Shafti 2014). When comparing the two antipsychotics, olanzapine and asenapine, there was a difference in effects on the secondary outcomes of anger and depression, favouring asenapine over olanzapine. No differences in effects were observed for any other comparison of any primary or secondary outcome. Regarding adverse events, the only difference between any two treatments was observed in the comparison of an antipsychotic (olanzapine) and an antidepressant (fluoxetine), where the comparison showed a higher risk for somnolence with olanzapine than with fluoxetine.

Comparison of active medications to combinations of medications

The combination of an antidepressant (fluoxetine) and an antipsychotic (olanzapine) was compared to each of its two individual components in one trial, with the evidence indicating little to no difference between single and combined treatment for any clinical outcome (Zanarini 2004). However, higher body weight gain was observed in those who were treated with olanzapine, compared to those who received olanzapine plus fluoxetine.

Another trial compared valproic acid alone against valproic acid plus omega-3 fatty acids (Bellino 2014). Effects were observed for the combined treatment of valproic acid plus omega-3 fatty acids for the primary outcomes of BPD severity and self-harm, as well as for the secondary outcomes of affective instability and impulsivity.

Subgroup analyses

We conducted subgroup analyses on types of medication, substances, psychosocial functioning at baseline, setting, funding and trial size. The evidence indicated inferiority of first-generation antipsychotics compared to second-generation antipsychotics regarding the outcome of BPD severity. The intervention effect on BPD severity was also influenced by the type of substance with a seemingly superior effect of brexpiprazole; however, this analysis contained sparse data in each subgroup and for this reason caution should be given to the reliability of its results.

For BPD severity, the intervention effect also varied according to subgroups of funding, with a seemingly higher effect of trials partially or fully funded by the pharmaceutical industry.

For the outcome of anger, trial size affected the intervention effect, with an unsurprising superior effect of smaller trials (those with 50 participants or less and those with 99 participants of less) compared to larger trials (those with 100 or more participants). No other subgroup analyses showed a difference in intervention effects on the investigated outcomes.

Overall completeness and applicability of evidence

Participants

A third of the included trials consisted of female participants only, while just one trial solely included males. For the trials that did include both sexes, the majority of participants were female. This situation resembles the situation in clinical settings, where higher rates of BPD are found in women than men (Ellison 2018; Newton-Howes 2021). However, evidence from representative community trials suggest that the true prevalence is even in men and women, though findings are mixed (Eaton 2018; Ellison 2018). It has been suggested that neurobiological differences between men and women may lead to different manifestations, with men tending to show more externalised patterns (explosive, aggressive, antisocial, disruptive, impulsive behaviour, novelty seeking) and different co-occurring disorders (men: substance use, intermittent explosive disorder, paranoid, passive-aggressive, narcissistic, sadistic, and antisocial PDs; women: eating, mood, anxiety, somatoform and post-traumatic stress disorders, histrionic PD) (Bohus 2021; Neacsiu 2017; Newton-Howes 2021). Therefore, the generalisability of the findings to men with BPD may be limited. Furthermore, clinical characteristics in men may be displayed differently than in women (e.g. with antisocial features; Mancke 2015; Sher 2019), and the under-representation of male participants in the included trials could potentially have affected the effects of medications on some outcomes. All included trials took binary approaches to the gender variable, which restrains applicability to those that are gender diverse. Additionally, it is not uncommon for people affected by BPD to experience gender dysphoria (Neacsiu 2017).

Only one trial had a mean age below 18 years (Amminger 2013: 16.2 years); the remaining trials included adult populations. Six of these included populations with a mean age below 26 years (Bellino 2014; Bozzatello 2017; Loew 2006; Nickel 2006; Soloff 1989; Zanarini 2004). Therefore, around one-sixth (16%) of all trials reporting the mean age of their samples were conducted in young people below 26 years old, and five-sixths in mature adult populations. Taking into account the early onset of BPD symptoms and the symptom threshold for an official BPD diagnosis, these results may not be applicable for adolescent populations.

Generally, the impairment of psychosocial functioning at baseline was moderate to mild in most trials. Notably, individuals with actively suicidal behaviour were not included in around one third of all primary trials. Therefore, the applicability of findings to people with more severe BPD, highly impaired psychosocial functioning, or suicidal ideation and/or behaviour is limited.

Comorbid disorders and substance use dependence are highly prevalent in people with BPD. However, the applicability of findings to routine settings is limited, given that the majority of trials excluded individuals with concurrent major depression, bipolar affective disorders or psychotic disorders, as well as those with alcohol or substance abuse or dependence. Similarly, in many included trials, co-medication was not allowed. However, clinically polypharmacy is common for many people with BPD and often for substantial periods of time.

Interventions

Antidepressants and antipsychotics are the most prevalent medications in inpatients with BPD (Bridler 2015). Both medications are prescribed to around 70% of individuals each (which also illustrates the high prevalence of polypharmacy in this group). According to Bridler 2015, the most frequently prescribed antidepressants are SSRIs. However, neither the corresponding number of trials nor the pooled findings of the trials support the high use of these medications. The only possible effect of (any) antidepressants compared to placebo was found for anger (small effect size: SMD −0.33, 95% CI −0.61 to −0.05; 5 trials, 199 participants; I^2 = 0%). Confining this analysis to SSRIs alone, the effect estimate would be SMD −0.38 (95% CI −0.82 to 0.07; 3 trials, 80 participants; I^2 = 0%). Among antipsychotics (and psychotropic medications in general), quetiapine is the medication most often

used in BPD inpatients in Europe (Bridler 2015). In contrast, only one RCT evaluating the effects of quetiapine in individuals with BPD has ever been published in full (Black 2014), while others (e.g. AstraZeneca 2007) have been completed but not published (Stoffers 2015; Stoffers-Winterling 2020). Therefore, the findings on quetiapine use in BPD are very uncertain.

Mood stabilisers are prescribed to one-third (33%) of European BPD inpatients (Bridler 2015). In this review, we found moderate effects on two secondary outcomes (interpersonal problems and anger), but not on any of the primary outcomes. Another 30% receive tranquillisers, 30% benzodiazepines, and still another 16% hypnotics (Bridler 2015). We have only identified one RCT testing benzodiazepine medication (Cowdry 1988). This may be due to the eligibility criteria of this review, which focuses on continuous, not crisis medication.

Outcomes

The most commonly assessed primary outcomes were BPD severity and psychosocial functioning, and the most prevalently assessed secondary outcomes were anger and depression. The use of BPD-specific assessment scales (e.g. Zan-BPD, BPDSI-IV, CGI-BPD) has increased in the last decade, allowing for differentiated assessment of BPD symptoms. Oftentimes, if BPD-specific outcome scales have been assessed, outcome reporting is limited to general BPD severity, while more specific reporting on individual BPD symptoms is not given. BPD-specific criteria have been found, however, to be significant predictors of the long-term course of the disorder, and should be considered more thoroughly. Specifically, identity disturbance, chronic feelings of emptiness, or frantic efforts to avoid abandonment have emerged as significant, independent factors associated with suicide attempts (Yen 2021), as they tend to persist, even after more impulsivity-related symptoms such as impulsivity, self-harm, or anger have diminished, and individuals no longer meet criteria for a BPD diagnosis. However, the suffering remains (Ng 2016), and psychosocial functioning, specifically vocational functioning, remains substantially impaired. Therefore, important outcomes were not considered by the majority of trials that reported only generic, BPD-non-specific psychiatric scales. Regarding individual outcomes, it is apparent that there are few data on the primary outcome of self-harm: only seven out of 45 included RCTs reported on this outcome. Individuals with active self-harm were often ineligible for study inclusion. However, these behaviours are highly prevalent in individuals with BPD (around 80% report suicidal and self-harming behaviour; Soloff 2012), and they constitute important treatment outcomes. In addition, some of the evidence was indirect, coming from surrogate outcomes. For example, many of the included RCTs used the Overt Aggression Scale-Modified (OAS-M; Coccaro 2020) to measure anger; however, this instrument actually assesses impulsive-aggressive behaviour. The SCL-90-R (Derogatis 1994) subscale 'anger/hostility' covers irritability, general mental imbalance and aggressiveness. The DSM, however, specifies the corresponding diagnostic criterion as "inappropriate, intense anger OR difficulty controlling anger" (APA 2013). The 'appropriateness' of anger and facets of self-inflicted anger, therefore, are not adequately reflected by non-BPD-specific anger outcome scales.

This review is based on the idea of covering all DSM-defined BPD criteria, as they represent the 'least common denominator' among the heterogeneous population of individuals with a diagnosis of BPD. Still, each of the nine criteria include diverse facets, and so a review like this requires the use of a somewhat 'broader lens' when synthesising study outcomes; thus, the pooled findings are always composite measures of individual scales measuring somewhat heterogeneous outcomes. Pooling the data in the way that we did seemed appropriate to us as it directly reflects symptoms covered by the DSM IV-5 criterion 9. Notably, older trials, in the absence of BPD-specific scales like the BPDSI-IV or the Zan-BPD, used assessment instruments that are usually used to measure psychotic symptoms, like the BPRS (Overall 1962) or the PANSS (Kay 1987), and somewhat exceed what is covered by the DSM criterion 9. However, recent research has found that psychotic phenomena in BPD actually equal those that people with 'traditional' psychotic disorders experience, as they are stress-reactive, but more persisting and enduring than previously thought (e.g. Cavelti 2019; Cavelti 2021; Herpertz 2007; Thompson 2019). Future versions of this review should consider analysing these outcomes separately (see Appendix 7).

Observation periods in the included trials did not fully match clinical routines, where individuals with BPD usually take (several) medications for sustained periods of time. In 34 out of 46 included RCTs (74%), treatment effects were assessed after just three months or less.

Quality of the evidence

We rated the certainty of the evidence using the GRADE approach, giving considerations to each of the following: risk of bias, inconsistency, indirectness, imprecision and publication bias. The results of this assessment are provided in Summary of findings 1, Summary of findings 2, and Summary of findings 3. Mostly, the evidence was of very low certainty, with few exemptions of low-certainty evidence.

We assessed the risk of bias in all trials in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). The majority of trials were prone to selection bias as well as attrition, reporting bias, and vested interests. High risk of bias in randomised clinical trials has been shown to overestimate benefits and underestimate harms (Kjaergard 2001; Lundh 2012; Moher 1998; Savović 2012a; Savović 2012b; Schulz 1995; Wood 2008). We considered all trials to be at high risk of bias overall. However, we used all eligible trials in the meta-analyses, as the *Cochrane Handbook for Systematic Reviews of Interventions* recommends doing when all trials are assigned the same risk of bias.

The results are based on 46 trials, 45 of which were eligible for quantitative analysis, and involved 2769 participants with BPD. Most trials included small sample sizes. The total number of included participants ranged from 13 to 451 in the individual trials.

We tested imprecision, assessed as part of the GRADE approach, by conducting TSAs on the primary outcomes and for some of the secondary outcomes (interpersonal problems, attrition and non-serious adverse events) for the main comparison versus placebo where we were uncertain about the assessment of imprecision. The result of the TSAs did not change any imprecision rated by GRADE on any of the outcomes. In order to investigate the impact of imprecision, we also drew funnel plots for the primary and secondary outcomes involving the highest number of primary trials comparing active agents to placebo (i.e. psychosocial functioning and anger). Funnel plots revealed a clear trend of more precise estimates by larger trials, and indicated that smaller trials without

statistically significant effects might be lacking, either due to publication bias or an overestimation of effects by smaller trials.

Potential biases in the review process

This review was conducted in a way where we tried to minimise the risk of potential biases. We developed a protocol, Stoffers-Winterling 2018, for this review in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). We conducted extensive searches of relevant databases. There were no restrictions on publication formats, publication periods or language. In order to assure a comprehensive selection of relevant RCTs, based on the pre-defined eligibility criteria, guarantee a fair and consistent rating of bias, and collection of any relevant study results for use in the synthesis, any steps from study selection to rating of the overall quality of the evidence were done in duplicate by two reviewers each. All analyses had been pre-defined (Stoffers-Winterling 2018), and any methods that could not be used are reported in Appendix 8, with reasons why. We also went to a great effort to try and obtain unpublished data pertaining to BPD subsamples where the full sample included fewer than 70% of participants with full BPD. We were able to obtain such subsample data from some trials, but in other cases, trial authors did not respond. We do not know why they did not respond, and it is possible that the subsample data we received are biased in a positive way (i.e. being associated with desired findings). We included four cross-over trials using end-of-period data as we did not have data from the first period. It is possible to use end-of-period data from cross-over trials and to include these data as if they were parallel-group data (Curtin 2002), but doing so might increase the risk of carry-over effects and a unit of analysis error. We did, however, test this in a sensitivity analysis. Some might take issue with this, but we believe this was a sensible approach. We conducted Trial Sequential Analyses to control the risk of type I errors and to estimate how far we were from obtaining the DARIS to detect or reject a certain plausible intervention effect. Lastly, as we wished to investigate differences between new subgroups post hoc, we conducted some exploratory subgroup analyses where we pooled different classes of medication because of the limited data available. As this highly inflates the risk of bias in these analyses, we advise caution when interpreting these results; they serve mainly as exploratory analyses.

Agreements and disagreements with other studies or reviews

There are three other meta-analyses of medications for BPD available. Two of them date back 10 years now (Ingenhoven 2011; Vita 2011) and one is from 2021 (Gartlehner 2021a).

Regarding the review by Ingenhoven 2011, which focused on the effects of antipsychotics in BPD, only one more placebo-controlled RCT has become available since (Black 2014, on quetiapine). The findings presented by Ingenhoven 2011 and the findings of this review regarding the effects on BPD symptoms are similar; however, the evidence differs with regards to global functioning. Ingenhoven 2011 classified SCL-90 GSI scores as measures of functioning, while we did not do so in this review. From our point of view, the SCL-90 is a measure of general psychopathology, but does not detail how severely these symptoms actually impair a person´s functioning. Therefore, we did not replicate the finding of Ingenhoven 2011 of a small effect of antipsychotics on global functioning. However, we agree that the "wide and long-term use of antipsychotics in these patients remains controversial" (Ingenhoven 2011, p. 489).

Vita 2011 investigated the effects of antipsychotics, antidepressants and mood stabilisers by means of a meta-analysis of randomised controlled and open-label trials. Outcomes were pooled into three domains; affective dysregulation, impulsive-behavioural dyscontrol, and cognitive-perceptual symptoms. Due to the inclusion of other study designs that are more prone to risk of bias, the pooling of measures into broader outcome categories and not excluding statistical outliers with SMD > 1.5, Vita 2011 found more favourable results, with small- to medium-size effects of antipsychotics on all three outcome domains, and moderate effects (antidepressants) and very large effects (mood stabilisers) on affective dysregulation.

Gartlehner 2021a investigated the effects of various pharmacological treatments for BPD on the basis of RCT evidence. Their work was conducted for APA in connection to the development of clinical practice guidelines on treatment for BPD. Gartlehner and colleagues included data on nine different medications (second-generation antipsychotics, anticonvulsants, and second-generation antidepressants) from 21 RCTs. They concluded that the evidence does not support the use of these medications alone to reduce the severity of BPD. This conclusion by Gartlehner and colleagues is in agreement with the findings of this review; however, there are some methodological issues that we do not agree with (Gartlehner 2021b; Pereira Ribeiro 2021). Most prominent is the exclusion of studies with a duration less than eight weeks. Such an exclusion criterion effectively omits many trials that could have provided valuable information and does not, in return, provide insight on long-term effects, especially considering that some patients with BPD continuously receive pharmacological treatment for their symptomatology for years.

Three more recent systematic reviews have been published that outline and evaluate the published and unpublished evidence from RCTs on this topic (Hancock-Johnson 2017; Stoffers 2015; Stoffers-Winterling 2020). All three have pointed to the dearth of trials and concluded that the evidence did not support the use of any medication for BPD treatment. However, none of these systematic reviews included quantitative meta-analyses of outcomes.

This review is an update and replaces the previous versions (Binks 2006; Stoffers 2010). The current review includes 18 more RCTs compared to Stoffers 2010. The new findings, however, do not lead to substantially different conclusions, and the evidence is still of low and very low quality. The authors of the 2010 review concluded that there were some beneficial effects of antipsychotics, mood stabilisers and dietary supplementation by omega-3 fatty acids for people with BPD, and that antidepressants may be helpful for comorbid conditions. However, they also concluded that none of these medications had an effect on total BPD severity, and that there seemed to be no promising results for the BPD core symptoms: chronic feelings of emptiness, identity disturbance and fear of abandonment. The results from this current review are in accordance with conclusions from Stoffers 2010.

AUTHORS' CONCLUSIONS

Implications for practice

Conclusions about the usefulness of medications in the continued treatment of BPD require a trade-off between estimated benefits and harms.

We assessed the beneficial and harmful effects of medications in the continued treatment of borderline personality disorder regarding the BPD symptoms, psychosocial functioning, depression, tolerability in terms of attrition, and adverse events. The evidence was very uncertain about the beneficial effects of antipsychotics, antidepressants and mood stabilisers for all primary outcomes of this review (borderline symptoms severity, self-harm, suicide-related outcomes, and psychosocial functioning). As regards secondary outcomes, the evidence suggested small (antipsychotics, antidepressants) to medium-size effects (mood stabilisers, dietary supplementation with omega-3 fatty acids) by medication, but these effects were of very low certainty and confined to few outcomes (anger: mood stabilisers, omega-3 fatty acids, antipsychotics, antidepressants; interpersonal problems: mood stabilisers, antipsychotics; brief psychotic-like symptoms and dissociative phenomena: antipsychotics, omega-3 fatty acids). On the side of potential harms, adverse effects, especially serious events, were scarcely and unsystematically reported across included trials. The only exception was olanzapine, which had (among others) been tested in two large-scale clinical studies intended for marketing authorisation (Schulz 2007; Zanarini 2007), and for which detailed marketing authorisation reports were available. For remaining medications, clinicians and consumers will need to consider the adverse effects of medications observed in other conditions.

As the evidence is very uncertain, the findings of this review do not allow for a trade-off of benefits and harms of medications in BPD in general. Informed decisions whether to start or continue drug treatment must (as usual in practical evidence-based medicine) consider the individual context of a person, the somatic condition (given substantially heightened rates of physical illness in BPD; Schneider 2019), and the treatment targets, values and preferences. Still, the person who is about to undergo medical treatment must be informed about the certainty of the evidence.

Implications for research

The current review supports the continued understanding that no pharmacological therapy seems effective in specifically treating BPD pathology. As long as there is no clear evidence of superiority of any medication over placebo, head-to-head comparisons of active medications or combinations of medications do not add much to the current understanding of medication effects.

Placebo-controlled trials of medication in combination with psychotherapeutic interventions could be interesting to investigate, to assess the potential additive effect of medication to psychotherapy or psychosocial interventions, given the encouraging evidence of the beneficial effects of psychotherapy (Andrews 2013a; Cristea 2017; NHMRC 2013; Oud 2017; Storebø 2020) and guidelines recommending disorder-specific psychotherapies as first-line treatment for BPD (NHMRC 2013; NICE 2009; NICE 2018). Outcomes should include BPD symptoms but also psychosocial functioning, which has been found to be severely affected in the long run. There is also a need to extend observation periods in order to rule out time effects and reflect the situation of individuals with BPD adequately, as many take medications for sustained periods of time (Zanarini 2015). BPD-specific measurement scales should be used to assess the impact of treatments on individual BPD symptoms. Individuals with lived experience should also be involved in the design of new trials in order to consider outcomes that are of importance to those who are directly affected by BPD.

When future medication trials are planned, they should also assess effects on males, adolescents, and individuals with defined comorbid mental disorders. To arrive at better drug treatments, it is necessary to understand the pathophysiology of BPD in order to develop drugs specifically acting at crucial pathophysiological pathways. Given the urge to detect and treat BPD early (Chanen 2017), more trials in young populations, including adolescents, are needed. Also, treatment targets should be considered when defining inclusion criteria for pharmacologic intervention trials, given that BPD in itself is a very heterogeneous disorder; for example, if impulsivity is the main target of a medication, it should be tested in individuals with BPD plus pronounced such symptoms. In particular, trials investigating the effects of medications in samples with, for example, comorbid depression and substance use are lacking. Since comorbidity is highly prevalent in individuals with BPD, there is a clear need to enhance the applicability of findings at this point. At least, individuals with common comorbid disorders or symptoms such as aggressive or suicidal symptoms, which are core symptoms of BPD, should not be excluded from trial participation.

We need more high-quality trials, at low risk of bias and with sufficient sample sizes (at least 200 participants) to investigate pharmacological treatment versus placebo for people with BPD. Such trials should aim to include adolescents, since only one study in this review assessed this age group. Lastly, future trials should be based on pre-published protocols to combat the problem of publication bias.

There might be new evidence on the way in the future giving a larger evidence base as there are some large ongoing trials in process (See Characteristics of ongoing studies).

ACKNOWLEDGEMENTS

We thank Signe Sofie Nielsen and Maja Lærke Kielsholm for their contribution wíth screening titles and abstracts of records. We thank the Cochrane Developmental, Psychosocial and Learning Problems (CDPLP) Editorial Team, Joanne Duffield (Managing Editor), Sarah Davies (Deputy Managing Editor), Margaret Anderson (Information Specialist), and Geraldine Macdonald (Coordinating Editor).

The CRG Editorial Team are grateful to the following peer reviewers for their time and comments: Dr Nicholas Bendit, Staff Specialist Psychiatrist, Hunter New England Area Health, Newcastle, Australia; Andrew Chanen, Orygen, Melbourne, Australia, and The University of Melbourne, Australia; David Alejandro Pérez Ferrara, Mexico; and Katharine J Nelson MD, Associate Professor, Department of Psychiatry & Behavioral Sciences, University of Minnesota Medical School, Minneapolis, MN, USA. They also thank Anne Lethaby for copyediting the review.

We thank professor Christian Gluud, Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region, Copenhagen University Hospital — Rigshospitalet, Copenhagen, Denmark for his kind support with the TSA analyses.

Cochrane DPLP supported the authors in the development of this intervention review.

The following people conducted the editorial process for this article:

Sign-off Editor (final editorial decision): Professor Geraldine Macdonald, Cochrane DPLP; University of Bristol, UK;
Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Dr Joanne Duffield, Cochrane DPLP; Queen's University Belfast, NI;
Deputy Managing Editor (conducted editorial policy checks, provided editorial guidance to authors, edited the article): Dr Sarah Davies, Cochrane DPLP; University of Bristol, UK;
Copy Editor (copy editing and production): Anne Lethaby;
Peer-reviewers (provided comments and recommended an editorial decision): Dr Nicholas Bendit, Staff Specialist Psychiatrist, Hunter New England Area Health, Newcastle, Australia (clinical/content review); Andrew Chanen, Orygen, Melbourne, Australia, and The University of Melbourne, Australia (clinical/content review); David Alejandro Pérez Ferrara, Mexico (consumer review); Katharine J Nelson MD, Associate Professor, Department of Psychiatry & Behavioral Sciences, University of Minnesota Medical School, Minneapolis, MN, USA (clinical/content review); and Margaret Anderson, Cochrane DPLP; Queen's University Belfast, NI (search review). One additional peer reviewer provided statistical peer review, but chose not to be publicly acknowledged.

REFERENCES

References to studies included in this review

Amminger 2013 *{published data only}*

* Amminger GP, Chanen AM, Ohmann S, Klier CM, Mossaheb N, Bechdolf A, et al. Omega-3 fatty acid supplementation in adolescents with borderline personality disorder and ultra-high risk criteria for psychosis: a post hoc subgroup analysis of a double-blind, randomized controlled trial. *Canadian Journal of Psychiatry [Revue Canadienne de Psychiatrie]* 2013;**58**(7):402-8. [DOI: 10.1177/070674371305800705] [PMID: 23870722]

Amminger GP, Schäfer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, et al. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. *Archives of General Psychiatry* 2010;**67**(2):146-54. [DOI: 10.1001/archgenpsychiatry.2009.192] [PMID: 20124114]

AstraZeneca 2007 *{published data only}*

* NCT00254748. Verkes Borderline Study: the effect of quetiapine on borderline personality disordered patients [The effect of quetiapine on psychotic-like symptoms in borderline personality disordered patients: a randomised placebo-controlled trial]. clinicaltrials.gov/ct2/show/NCT00254748 (first received 15 November 2005).

Van den Broek PJ, Penterman EJ, Hummelen JW, Verkes RJ. P.3.c.038. The effect of quetiapine on psychotic-like symptoms in borderline personality disorder. A placebo-controlled trial. *European Neuropsychopharmacology* 2008;**18**(Suppl 4):S425-6. [DOI: 10.1016/S0924-977X(08)70622-9]

Bellino 2014 *{published data only}*

Bellino S, Bozzatello P, Brunetti C, De Grandi E, Bogetto F. Omega-3 fatty acids associated with valproate in the treatment of borderline personality disorder: a controlled study [Acidi grassi omega-3 associati alvalproato nel trattamento del disturbo borderlinedi personalità: uno studio controllato]. *Journal of Psychopathology* 2013;**19**(4):296-303. [WEB PAGE: Available at www.jpsychopathol.it/wp-content/uploads/2015/07/02-Bellino-acidi1.pdf]

* Bellino S, Bozzatello P, Rocca G, Bogetto F. Efficacy of omega-3 fatty acids in the treatment of borderline personality disorder: a study of the association with valproic acid. *Journal of Psychopharmacology* 2014;**28**(2):125-32. [DOI: 10.1177/0269881113510072] [PMID: 24196948]

Bozzatello P, Rocca P, Bellino S. Combination of omega-3 fatty acids and valproic acid in treatment of borderline personality disorder: a follow-up study. *Clinical Drug Investigation* 2018;**38**(4):367-72. [DOI: 10.1007/s40261-017-0617-x] [PMID: 29302857]

Black 2014 *{published data only}*

Bellino S. Inclusion of study in Cochrane review. Email to: A Tadorovac 31 January 2019.

* Black DW, Zanarini MC, Romine A, Shaw M, Allen J, Schulz SC. Comparison of low and moderate dosages of extended-release quetiapine in borderline personality disorder: a randomized, double-blind, placebo-controlled trial. *American Journal of Psychiatry* 2014;**171**(11):1174-82. [DOI: 10.1176/appi.ajp.2014.13101348] [PMID: 24968985]

Lee SS, Allen J, Black DW, Zanarini MC, Schulz SC. Quetiapine's effect on the SCL-90-R domains in patients with borderline personality disorder. *Annals of Clinical Psychiatry* 2016;**28**(1):4-10. [PMID: 26855980]

NCT00880919. Seroquel extended release (XR) for the management of borderline personality disorder (BPD) [Seroquel XR for the management of borderline personality disorder (BPD)]. clinicaltrials.gov/ct2/show/NCT00880919 (first received 10 April 2009).

Bogenschutz 2004 *{published data only}*

* Bogenschutz MP, Nurnberg HG. Olanzapine versus placebo in the treatment of borderline personality disorder. *Journal of Clinical Psychiatry* 2004;**65**(1):104-9. [DOI: 10.4088/jcp.v65n0118] [PMID: 14744178]

Nurnberg HG, Bogenschutz MP. Atypical antipsychotic treatment of BPD: a 12-week, double-blind, placebo-control trial with olanzapine. In: 156th Annual Meeting of the American Psychiatric Association; 2003 May 17-22; San Fransisco (CA). 2003.

Bozzatello 2017 *{published data only}***ACTRN12614000551695**

ACTRN12614000551695. Efficacy and tolerability of asenapine compared with olanzapine in borderline personality disorder: a randomized controlled trial [Asenapine versus olanzapine in the treatment of impulsivity, aggression, and self injuries in patients with borderline personality disorder]. www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=365182 (first received 12 May 2014).

* Bozzatello B, Rocca P, Uscinska M, Bellino S. Efficacy and tolerability of asenapine compared with olanzapine in borderline personality disorder: an open-label randomized controlled trial. *Central Nervous System Drugs* 2017;**31**(9):801-19. [DOI: 10.1007/s40263-017-0458-4] [PMID: 28741044]

Cowdry 1988 *{published data only}*

* Cowdry RW, Gardner DL. Pharmacotherapy of borderline personality disorder. Alprazolam, carbamazepine, trifluoperazine, and tranylcypromine. *Archives of General Psychiatry* 1988;**45**(2):111-9. [DOI: 10.1001/archpsyc.1988.01800260015002] [PMID: 3276280]

Gardner DL, Cowdry RW. Alprazolam-induced dyscontrol in borderline personality disorder. *American Journal of Psychiatry* 1985;**142**(1):98-100. [DOI: 10.1176/ajp.142.1.98] [PMID: 2857071]

Gardner DL, Cowdry RW. Development of melancholia during carbamazepine treatment in borderline personality disorder. *Journal of Clinical Psychopharmacology* 1986;**6**(4):236-9. [PMID: 3525615]

Gardner DL, Cowdry RW. Positive effects of carbamazepine on behavioral dyscontrol in borderline personality disorder.

American Journal of Psychiatry 1986;**143**(4):519-22. [DOI: 10.1176/ajp.143.4.519] [PMID: 3513634]

Crawford 2018 *{published data only}*

Crawford MJ, Sanatinia R, Barrett B, Byford S, Cunningham G, Gakhal K, et al. Lamotrigine versus inert placebo in the treatment of borderline personality disorder: study protocol for a randomized controlled trial and economic evaluation. *Trials* 2015;**16**:308. [DOI: 10.1186/s13063-015-0823-x] [PMCID: PMC4506596] [PMID: 26187496]

* Crawford MJ, Sanatinia R, Barrett B, Cunningham G, Dale O, Ganguli P, et al. Lamotrigine for people with borderline personality disorder: a RCT. *Health Technology Assessment* 2018;**22**(17):1-68. [DOI: 10.3310/hta22170] [PMCID: PMC5925438] [PMID: 29651981]

Crawford MJ. Inclusion of your study in Cochrane review. Email to: A Pathmanathan Ratnam 09 November 2020.

De la Fuente 1994 *{published data only}*

* De la Fuente JM, Lotstra F. A trial of carbamazepine in borderline personality disorder. *European Neuropsychopharmacology* 1994;**4**(4):479-86. [DOI: 10.1016/0924-977x(94)90296-8] [PMID: 7894258]

De la Fuente JM, Lotstra F. Carbamazepine in borderline personality disorder. *European Neuropsychopharmacology* 1993;**3**(3):350. [DOI: 10.1016/0924-977X(93)90132-6]

Frankenburg 2002 *{published data only}*

Frankenburg FR, Zanarini MC. Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: a double-blind placebo-controlled pilot study. *Journal of Clinical Psychiatry* 2002;**63**(5):442-6. [DOI: 10.4088/jcp.v63n0511] [PMID: 12019669]

Goldberg 1986 *{published data only}*

Goldberg SC, Schulz SC, Schulz PM, Resnick RJ, Hamer RM, Friedel RO. Borderline and schizotypal personality disorders treated with low-dose thiothixene vs placebo. *Archives of General Psychiatry* 1986;**43**(7):680-6. [DOI: 10.1001/archpsyc.1986.01800070070009] [PMID: 3521531]

Grant 2022 *{published data only}*

* Grant J, Valle S, Chesivoir E, Ehsan D, Chamberlain S. A double-blind placebo-controlled study of brexpiprazole for the treatment of borderline personality disorder. *British Journal of Psychiatry* 2022;**220**(2):58-63. [CENTRAL: PMC7612273] [DOI: 10.1192/bjp.2021.159] [PMID: 35049469]

Hallahan 2007 *{published data only}*

Hallahan B, Hibbeln JR, Davis JM, Garland MR. Omega-3 fatty acid supplementation in patients with recurrent self-harm. Single-centre double-blind randomised controlled trial. *British Journal of Psychiatry* 2007;**190**:118-22. [DOI: 10.1192/bjp.bp.106.022707] [PMID: 17267927]

Hollander 2001 *{published data only}*

Hollander E, Allen A, Lopez RP, Bienstock CA, Grossman R, Siever LJ, et al. A preliminary double-blind, placebo-controlled trial of divalproex sodium in borderline personality disorder. *Journal of Clinical Psychiatry* 2001;**62**(3):199-203. [DOI: 10.4088/jcp.v62n0311] [PMID: 11305707]

Jariani 2010 *{published data only}*

Jariani M, Saaki M, Nazari H, Birjandi M. The effect of olanzapine and sertraline on personality disorder in patients with methadone maintenance therapy. *Psychiatria Danubina* 2010;**22**(4):544-7. [PMID: 21169896]

Kulkarni 2018 *{published data only}*

* Kulkarni J, Thomas N, Hudaib AR, Gavrilidis E, Grigg J, Tan R, et al. Effect of the glutamate NMDA receptor antagonist memantine as adjunctive treatment in borderline personality disorder: an exploratory, randomised, double-blind, placebo-controlled trial. *Central Nervous System Drugs* 2018;**32**(2):179-87. [DOI: 10.1007/s40263-018-0506-8] [PMID: 29549516]

Kulkarni J [pers comm]. Re: Your Request. Email to: A Pathmanatan Ratnam 14 December 2020.

NCT02097706. A novel drug for borderline personality disorder [A randomised double-blind placebo controlled investigation of the efficacy of a novel drug as an adjunct in patients with borderline personality disorder]. clinicaltrials.gov/ct2/show/study/NCT02097706 (first received 25 March 2014).

Leone 1982 *{published data only}*

Leone NF. Response of borderline patients to loxapine and chlorpromazine. *Journal of Clinical Psychiatry* 1982;**43**(4):148-50. [PMID: 7040351]

Linehan 2008 *{published data only}*

Linehan M. Update on dialectical behavioral therapy for BPD. In: 158th Annual Meeting of the American Psychiatric Association; 2005 May 21-26; Atlanta (GA). 2005.

* Linehan MM, McDavid JD, Brown MZ, Sayrs JH, Gallop RJ. Olanzapine plus dialectical behavior therapy for women with high irritability who meet criteria for borderline personality disorder: a double-blind, placebo-controlled pilot study. *Journal of Clinical Psychiatry* 2008;**69**(9):999-1005. [DOI: 10.4088/jcp.v69n0617] [PMID: 18466045]

Loew 2006 *{published data only}*

* Loew TH, Nickel MK, Muehlbacher M, Kaplan P, Nickel C, Kettler C, et al. Topiramate treatment for women with borderline personality disorder: a double-blind, placebo-controlled study. *Journal of Clinical Psychopharmacology* 2006;**26**(1):61-6. [DOI: 10.1097/01.jcp.0000195113.61291.48] [PMID: 16415708]

Loew TH, Nickel MK. Topiramate treatment of women with borderline personality disorder, part II: an open 18-month follow-up. *Journal of Clinical Psychopharmacology* 2008;**28**(3):355-7. [DOI: 10.1097/JCP.0b013e318173a8fb] [PMID: 18480701]

Markovitz 1995a *{published data only}*

Markovitz PJ. Pharmacotherapy of impulsivity, aggression, and related disorders. In: Hollander E, Stein DJ, editors(s). Impulsivity and Aggression. New York (NY): Wiley, 1995:263-87.

Moen 2012 *{published data only}*

* Moen R, Freitag M, Miller M, Lee S, Romine A, Song S, et al. Efficacy of extended-release divalproex combined with "condensed" dialectical behavior therapy for individuals with borderline personality disorder. *Annals of Clinical Psychiatry* 2012;**24**(4):255-60. [PMID: 23145381]

NCT00222482. Depakote ER in borderline personality disorder [A double-blind and placebo controlled assessment of depakote ER in borderline personality disorder]. clinicaltrials.gov/ct2/show/NCT00222482 (first received 14 September 2005).

Montgomery 1982a *{published data only}*

* Montgomery SA, Montgomery D. Pharmacological prevention of suicidal behaviour. *Journal of Affective Disorders* 1982;**4**(4):291-8. [DOI: 10.1016/0165-0327(82)90026-x] [PMID: 6131083]

Montgomery SA, Montgomery DB, Janyanthi Rani S, Roy DH, Shaw PJ, McAuley R. Maintenance therapy in repeat suicidal behaviour: a placebo controlled trial. In: 10th International Congress for Suicide Prevention and Crisis Intervention; 1979 Jun 17-20; Ottawa (ON). 1979.

Montgomery 1982b *{published data only}*

Montgomery D, Montgomery S, Roy D. Mianserin in the prophylaxis of suicidal behaviour: a double-blind placebo controlled trial. In: Soubrier JP, Vedrinne J, editors(s). Depression and Suicide: Aspects Medicaux, Psychologiques et Socio-Culturels. Paris (FR): Pergamon, 1983:786-90. [DOI: 10.1016/B978-0-08-027080-7.50130-0]

* Montgomery SA, Montgomery D. Pharmacological prevention of suicidal behaviour. *Journal of Affective Disorders* 1982;**4**(4):291-8. [DOI: 10.1016/0165-0327(82)90026-x] [PMID: 6131083]

Montgomery SA, Roy D, Montgomery DB. The prevention of recurrent suicidal acts. *British Journal of Clinical Pharmacology* 1983;**15**(Suppl 2):183-8S. [DOI: 10.1111/j.1365-2125.1983.tb05864.x] [PMCID: PMC1427879] [PMID: 6824553]

NCT00533117 *{published data only}*

Fertuck EA, Keilp J, Song I, Morris MC, Wilson ST, Brodsky BS, et al. Higher executive control and visual memory performance predict treatment completion in borderline personality disorder. *Psychotherapy and Psychosomatics* 2012;**81**(1):38-43. [DOI: 10.1159/000329700] [PMCID: PMC3242704] [PMID: 22116411]

* NCT00533117. Treating suicidal behavior and self-mutilation in people with borderline personality disorder [Treating suicidal behavior and self-mutilation in borderline personality disorder]. clinicaltrials.gov/ct2/show/results/NCT00533117?sect=X043716&view=results#part (first received 19 September 2007).

Nickel 2004 *{published data only}*

Nickel M. Topiramate reduced aggression in female patients with borderline personality disorder. *European Archives of Psychiatry and Clinical Neuroscience* 2007;**257**(7):432-3. [DOI: 10.1007/s00406-007-0735-1] [PMID: 17902007]

* Nickel MK, Nickel C, Mitterlehner FO, Tritt K, Lahmann C, Leiberich PK, et al. Topiramate treatment of aggression in female borderline personality disorder patients: a double-blind, placebo-controlled study. *Journal of Clinical Psychiatry* 2004;**65**(11):1515-9. [DOI: 10.4088/jcp.v65n1112] [PMID: 15554765]

Nickel 2005 *{published data only}*

Nickel MK, Loew TH. Treatment of aggression with topiramate in male borderline patients, part II: 18-month follow-up. *European Psychiatry* 2008;**23**(2):115-7. [DOI: 10.1016/j.eurpsy.2007.09.004] [PMID: 18024088]

* Nickel MK, Nickel C, Kaplan P, Lahmann C, Mühlbacher M, Tritt K, et al. Treatment of aggression with topiramate in male borderline patients: a double-blind, placebo-controlled study. *Biological Psychiatry* 2005;**57**(5):495-9. [DOI: 10.1016/j.biopsych.2004.11.044] [PMID: 15737664]

Nickel MK. Topiramate treatment of aggression in male borderline patients. *Australian and New Zealand Journal of Psychiatry* 2007;**41**(5):461-2. [DOI: 10.1080/00048670701261251] [PMID: 17464743]

Nickel 2006 *{published data only}*

Nickel MK, Loew TH, Pedrosa Gil F. Aripiprazole in treatment of borderline patients, part II: an 18-month follow-up. *Psychopharmacology* 2007;**191**(4):1023-6. [DOI: 10.1007/s00213-007-0740-0] [PMID: 17318503]

* Nickel MK, Mühlbacher M, Nickel C, Kettler C, Pedrosa Gil F, Bachler E, et al. Aripiprazole in the treatment of patients with borderline personality disorder: a double-blind, placebo-controlled study. *American Journal of Psychiatry* 2006;**163**(5):833-8. [DOI: 10.1176/ajp.2006.163.5.833] [PMID: 16648324]

Nickel MK. Aripiprazole treatment of patients with borderline personality disorder. *Journal of Clinical Psychiatry* 2007;**68**(11):1815-6. [DOI: 10.4088/jcp.v68n1124f] [PMID: 18052583]

Pascual 2008 *{published data only}*

NCT00635921. Ziprasidone in the treatment of borderline personality disorder [Ziprasidone in the treatment of borderline personality disorder: a double-blind, placebo-controlled, randomized study]. clinicaltrials.gov/ct2/show/NCT00635921 (accessed 9 September 2009).

* Pascual JC, Soler J, Puigdemont D, Pérez-Egea R, Tiana T, Alvarez E, et al. Ziprasidone in the treatment of borderline personality disorder: a double-blind, placebo-controlled, randomized study. *Journal of Clinical Psychiatry* 2008;**69**(4):603-8. [PMID: 10.4088/jcp.v69n0412]

Reich 2009 *{published data only}*

NCT00634062. Study of lamotrigine treatment of affective instability in borderline personality disorder. clinicaltrials.gov/ct2/show/NCT00634062 (first received 4 March 2008). [NCT00634062]

* Reich DB, Zanarini MC, Bieri KA. A preliminary study of lamotrigine in the treatment of affective instability in borderline personality disorder. *International Clinical Psychopharmacology* 2009;**24**(5):270-5. [DOI: 10.1097/YIC.0b013e32832d6c2f] [PMID: 19636254]

Rinne 2002 *{published data only}*

Rinne T, Van den Brink W, Wouters L, Van Dyck R. SSRI treatment of borderline personality disorder: a randomized, placebo-controlled clinical trial for female patients with borderline personality disorder. *American Journal of Psychiatry* 2002;**159**(12):2048-54. [DOI: 10.1176/appi.ajp.159.12.2048] [PMID: 12450955]

Salzman 1995 *{published data only}*

Salzmann C, Wolfson AN, Schatzberg A, Looper J, Henke R, Albanese M, et al. Effect of fluoxetine on anger in symptomatic volunteers with borderline personality disorder. *Journal of Clinical Psychopharmacology* 1995;**15**(1):23-9. [DOI: 10.1097/00004714-199502000-00005] [PMID: 7714224]

Schmahl 2012a *{published data only}*

NCT01133301. Naltrexone in the treatment of dissociative symptoms in patients with borderline personality disorder. clinicaltrials.gov/ct2/show/NCT01133301 (first received 17 May 2010).

* Schmahl C, Kleindienst N, Limbergera M, Ludäscher P, Mauchnika J, Deiblera P, et al. Evaluation of naltrexone for dissociative symptoms in borderline personality disorder. *International Clinical Psychopharmacology* 2012;**27**(1):61-8. [DOI: 10.1097/YIC.0b013e32834d0e50] [PMID: 22002175]

Schmahl 2012b *{published data only}*

NCT00124839. Naltrexone in borderline personality disorder [Evaluation of the efficacy of the opioid antagonist naltrexone on the incidence and intensity of flashbacks and dissociative states in patients with borderline personality disorder]. clinicaltrials.gov/ct2/show/NCT00124839 (first received 27 July 2005).

NCT01133301. Naltrexone in the treatment of dissociative symptoms in patients with borderline personality disorder. clinicaltrials.gov/ct2/show/record/NCT01133301 (first received 17 May 2010).

* Schmahl C, Kleindienst N, Limbergera M, Ludäscher P, Mauchnika J, Deiblera P, et al. Evaluation of naltrexone for dissociative symptoms in borderline personality disorder. *International Clinical Psychopharmacology* 2012;**27**(1):61-8. [DOI: 10.1097/YIC.0b013e32834d0e50] [PMID: 22002175]

Schulz 2007 *{published data only}*

* Eli Lilly and Company. Efficacy and safety of olanzapine in patients with borderline personality disorder: a randomized, flexible-dose, double-blind comparison with placebo [Summary ID #6257. Clinical Study Summary: F1D-MC-HGKL]. www.lillytrials.com/results_files/zyprexa/zyprexa_summary_6257 (accessed 14 February 2008).

NCT00091650. Olanzapine in patients with borderline personality disorder [Efficacy and safety of olanzapine in patients with borderline personality disorder: a randomized flexible dose double-blind comparison with placebo]. clinicaltrials.gov/ct2/show/NCT00091650 (first accessed 14 September 2004).

Schulz SC, Zanarini M, Detke H, Trzaskoma Q, Lin D, DeBerdt W, et al. P02.101 Olanzapine for the treatment of borderline personality disorder: a flexible-dose 12-week randomized double-blind placebo-controlled study. *International Journal of Neuropsychopharmacology* 2006;**9**(Suppl 1):S191. [DOI: 10.1017/S1461145706007292]

Schulz SC, Zanarini MC, Bateman A, Bohus M, Detke HC, Trzaskoma Q, et al. Olanzapine for the treatment of borderline personality disorder: variable dose, 12-week randomised double-blind placebo-controlled study. *British Journal of Psychiatry* 2008;**193**(6):485-92. [DOI: 10.1192/bjp.bp.107.037903] [PMID: 19043153]

Schulz SC, Zanarini MC, Detke HC, Trzaskoma Q, Lin D, DeBerdt W, et al. Olanzapine for the treatment of borderline personality disorder: a flexible-dose, 12-week, randomized, double-blind, placebo-controlled study. In: Association of European Psychiatrsts. 15th European Congress of Psychiatry; 2007 Mar 17-21; Madrid, Spain. 2007.

Schulz SC, Zanarini MC, Detke HC, Trzaskoma Q, Lin D, DeBerdt W, et al. P248 Olanzapine for the treatment of borderline personality disorder: a flexible-dose 12-week randomized double-blind placebo-controlled study. *European Psychiatry* 2007;**22**(Suppl 1):S172. [DOI: 10.1016/j.eurpsy.2007.01.564]

Zanarini MC, Schulz SC, Detke HC, Tanaka Y, Zhao F, Trzaskoma Q, et al. 80. Olanzapine for the treatment of borderline personality disorder: two 12-week randomized double-blind placebo-controlled trials. *Neuropsychopharmacology* 2006;**31**(Suppl 1):S229-30. [DOI: 10.1017/S1461145706007292]

Shafti 2010 *{published data only}*

Shafti SS, Shaveisi B. Olanzapine versus haloperidol in the management of borderline personality disorder. *Journal of Clinical Psychopharmacology* 2010;**30**(1):44-7. [DOI: 10.1097/JCP.0b013e3181c826ff] [PMID: 20075647]

Shafti 2014 *{published data only}*

Shafti SS, Kaviani H. A comparative study on olanzapine and aripiprazole for symptom management in female patients with borderline personality disorder. *Klinik Psikofarmakoloji Bülteni [Bulletin of Clinical Psychopharmacology]* 2015;**25**(1):38-43. [DOI: 10.5455/bcp.20140923100030]

* Shafti SS, Kaviani H. Olanzapine vs aripiprazole in the management of borderline personality disorder. *Current Psychopharmacology* 2014;**3**(2):132-6. [DOI: 10.2174/2211556003666140912223626]

Simpson 2004 *{published data only}*

Simpson EB, Yen S, Costello E, Rosen K, Begin A, Pistorello J, et al. Combined dialectical behavior therapy and fluoxetine in the treatment of borderline personality disorder. *Journal of Clinical*

Psychiatry 2004;**65**(3):379-85. [DOI: 10.4088/jcp.v65n0314] [PMID: 15096078]

Soler 2005 *{published data only}*

Pascual JC, Soler J, Barrachina J, Campins J, Puigdemont D, Alvarez E, et al. Olanzapine plus dialectical behavior therapy of patients with BPD. In: Psychotherapy and Psychopharmacology: Dissolving the Mind-Brain Barrier. 157th Annual Meeting of the American Psychiatric Association; 2004 May 1-6; New York (NY). 2004.

* Soler J, Pascual JC, Campins J, Barrachina J, Puigdemont D, Alvarez E, et al. Double-blind, placebo-controlled study of dialectical behavior therapy plus olanzapine for borderline personality disorder. *American Journal of Psychiatry* 2005;**162**(6):1221-4. [DOI: 10.1176/appi.ajp.162.6.1221] [PMID: 15930077]

Soloff 1989 *{published data only}*

Soloff PH, George A, Nathan RS, Schulz PM, Perel JM. Behavioral dyscontrol in borderline patients treated with amitriptyline. *Psychopharmacology Bulletin* 1987;**23**(1):177-81. [PMID: 3602316]

Soloff PH, George A, Nathan RS, Schulz PM, Perel JM. Paradoxical effects of amitriptyline on borderline patients. *American Journal of Psychiatry* 1986;**143**(12):1603-5. [DOI: 10.1176/ajp.143.12.1603] [PMID: 3538914]

Soloff PH, George A, Nathan RS, Schulz PM, Ulrich RF, Perel JM. Progress in pharmacotherapy of borderline disorders. A double-blind study of amitriptyline, haloperidol, and placebo. *Archives of General Psychiatry* 1986;**43**(7):691-7. [DOI: 10.1001/archpsyc.1986.01800070081010] [PMID: 3521532]

* Soloff PH, George A, Nathan S, Schulz PM, Cornelius JR, Herring J, et al. Amitriptyline versus haloperidol in borderlines: final outcomes and predictors of response. *Journal of Clinical Psychopharmacology* 1989;**9**(4):238-46. [DOI: 10.1097/00004714-198908000-00002] [PMID: 2768542]

Soloff PH, George A, Nathan S, Schulz PM, Ulrich RF, Perel JM. Amitriptyline and haloperidol in unstable and schizotypal borderline disorders. *Psychopharmacology Bulletin* 1986;**22**(1):177-82. [PMID: 3523575]

Soloff 1993 *{published data only}*

Cornelius JR, Soloff PH, George A, Ulrich RF, Perel JM. Haloperidol vs phenelzine in continuation therapy of borderline disorder. *Psychopharmacology Bulletin* 1993;**29**(2):333-7. [PMID: 8290683]

Cornelius JR, Soloff PH, Perel JM, Ulrich RF. Continuation pharmacotherapy of borderline personality disorder with haloperidol and phenelzine. *American Journal of Psychiatry* 1993;**150**(12):1843-8. [DOI: 10.1176/ajp.150.12.1843] [PMID: 8238640]

* Soloff PH, Cornelius J, George A, Nathan S, Perel JM, Ulrich RF. Efficacy of phenelzine and haloperidol in borderline personality disorder. *Archives of General Psychiatry* 1993;**50**(5):377-85. [DOI: 10.1001/archpsyc.1993.01820170055007] [PMID: 8489326]

Tritt 2005 *{published data only}*

Leiberich P, Nickel MK, Tritt K, Pedrosa Gil F. Lamotrigine treatment of aggression in female borderline patients, part II: an 18-month follow-up. *Journal of Psychopharmacology* 2008;**22**(7):805-8. [DOI: 10.1177/0269881107084004] [PMID: 18308777]

* Tritt K, Nickel C, Lahmann C, Leiberich PK, Rother WK, Loew TH, et al. Lamotrigine treatment of aggression in female borderline-patients: a randomized, double-blind, placebo-controlled study. *Journal of Psychopharmacology* 2005;**19**(3):287-91. [DOI: 10.1177/0269881105051540] [PMID: 15888514]

Zanarini 2001 *{published data only}*

Zanarini MC, Frankenburg FR. Olanzapine treatment of female borderline personality disorder patients: a double-blind, placebo-controlled pilot study. *Journal of Clinical Psychiatry* 2001;**62**(11):849-54. [DOI: 10.4088/jcp.v62n1103] [PMID: 11775043]

Zanarini 2003 *{published data only}*

Zanarini MC, Frankenburg FR. Omega-3 fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. *American Journal of Psychiatry* 2003;**160**(1):167-9. [DOI: 10.1176/appi.ajp.160.1.167] [PMID: 12505817]

Zanarini 2004 *{published data only}*

Zanarini MC, Frankenburg FR, Parachini EA. A preliminary, randomized trial of fluoxetine, olanzapine, and the olanzapine-fluoxetine combination in women with borderline personality disorder. *Journal of Clinical Psychiatry* 2004;**65**(7):903-7. [DOI: 10.4088/jcp.v65n0704] [PMID: 15291677]

Zanarini 2007 *{published data only}*

* Eli Lilly and Company. Efficacy and safety of olanzapine in patients with borderline personality disorder: a randomized double-blind comparison with placebo [Summary ID # 6253. Clinical Study Summary: Study F1D-MC-HGKK]. www.lillytrials.com/results_files/zyprexa/zyprexa_summary_6523/ (accessed 14 February 2008).

NCT00088036. Efficacy and safety of olanzapine in patients with borderline personality disorder [Efficacy and safety of olanzapine in patients with borderline personality disorder: a randomized double-blind comparison with placebo]. clinicaltrials.gov/ct2/show/NCT00088036 (first received 19 July 2004).

Zanarini MC, Schulz SC, Detke HC, Tanaka Y, Zhao F, Lin D, et al. A dose comparison of olanzapine for the treatment of borderline personality disorder: a 12-week randomized, double-blind, placebo controlled study. *European Psychiatry* 2007;**22**(Suppl 1):S172-3. [DOI: 10.1016/j.eurpsy.2007.01.565]

Zanarini MC, Schulz SC, Detke HC, Tanaka Y, Zhao F, Lin D, et al. A dose comparison of olanzapine for the treatment of borderline personality disorder: a 12-week randomized, double-blind, placebo-controlled study. In: Association of European Psychiatrists. 15th European Congress of Psychiatry; 2007 Mar 17-21; Madrid, Spain. 2007.

Zanarini MC, Schulz SC, Detke HC, Tanaka Y, Zhao F, Lin D, et al. P02.102 A dose comparison of olanzapine for the treatment of borderline personality disorder: a 12-week randomized double-blind placebo-controlled study. *International Journal of Neuropsychopharmacology* 2006;**9**(Suppl 1):S191. [DOI: 10.1017/S1461145706007450]

Zanarini MC, Schulz SC, Detke HC, Tanaka Y, Zhao F, Trzaskoma Q, et al. 80. Olanzapine for the treatment of borderline personality disorder: two 12-week randomized double-blind placebo-controlled trials. *Neuropsychopharmacology* 2006;**31**(Suppl 1):S229-30. [DOI: 10.1017/S1461145706007292]

Ziegenhorn 2009 *{published data only}*

Ziegenhorn AA, Roepke S, Schommer NC, Merkl A, Danker-Hopfe H, Perschel FH, et al. Clonidine improves hyperarousal in borderline personality disorder with or without comorbid posttraumatic stress disorder: a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Psychopharmacology* 2009;**29**(2):170-3. [DOI: 10.1097/JCP.0b013e31819a4bae] [PMID: 19512980]

References to studies excluded from this review

ACTRN12615000705583 *{published data only}*

ACTRN12615000705583. Investigation of the benefits of using quetiapine as an adjunct treatment in addition to psychotherapy in patients diagnosed with severe Borderline Personality Disorder. www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=368589 (first received 8 July 2015).

Bellino 2006b *{published data only}*

Bellino S, Zizza M, Rinaldi C, Bogetto F. Combined treatment of major depression in patients with borderline personality disorder: a comparison with pharmacotherapy. *Canadian Journal of Psychiatry* 2006;**51**(7):453-60. [DOI: 10.1177/070674370605100707] [PMID: 16838827]

Coccaro 1997 *{published data only (unpublished sought but not used)}*

Coccaro EF, Kavoussi RJ. Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. *Archives of General Psychiatry* 1997;**54**(12):1081-8. [DOI: 10.1001/archpsyc.1997.01830240035005] [PMID: 9400343]

Hollander 2005 *{published data only}*

* Hollander E, Swann AC, Coccaro EF, Jiang P, Smith TB. Impact of trait impulsivity and state aggression on divalproex versus placebo response in borderline personality disorder. *American Journal of Psychiatry* 2005;**162**(3):621-4. [DOI: 10.1176/appi.ajp.162.3.621] [PMID: 15741486]

Hollander E, Tracy KA, Swann AC, Coccaro EF, McElroy SL, Wozniak P, et al. Divalproex in the treatment of impulsive aggression: efficacy in cluster B personality disorders. *Neuropsychopharmacology* 2003;**28**(6):1186-97. [DOI: 10.1038/sj.npp.1300153] [PMID: 12700713]

ISRCTN11135486 *{published data only}***11135486**

* ISRCTN11135486. Quetiapine versus sertraline as the pharmacological component in a standardised psychopharmacological and psychotherapeutic treatment of borderline personality disorder: a randomised, rater-blinded study. www.isrctn.com/ISRCTN11135486 (first received 1 August 2006). [ISRCTN11135486]

Malevani J. AW: Cochrane review: RCT zu Quetapin und Sertraline bei BPS [personal communication]. Email to: J Stoffers-Winterling 17 June 2020.

Koenigsberg 2003 *{published data only}*

Koenigsberg HW, Reynolds D, Goodman M, New AS, Mitropoulou V, Trestman RL, et al. Risperidone in the treatment of schizotypal personality disorder. *Journal of Clinical Psychiatry* 2003;**64**(6):628-34. [DOI: 10.4088/jcp.v64n0602] [PMID: 12823075]

La Malfa 2003 *{published data only}*

La Malfa G, Lampronti L, Bertelli M, Conte M, Cabras P. Aggressiveness and personality disorders: evaluation of efficacy and existence of predictors in the treatment with fluvoxamine and lithium [Aggressività e disturbi della personalità]. *Minerva Psychiatrica* 2003;**44**(2):75-82. [WEB PAGE: Available at www.minervamedica.it/en/journals/minerva-psychiatry/article.php?cod=R17Y2003N02A0075]

Links 1990 *{published data only}*

Links PS, Steiner M, Boiago I, Irwin D. Lithium therapy for borderline patients: preliminary findings. *Journal of Personality Disorders* 1990;**4**(2):173-81. [DOI: 10.1521/pedi.1990.4.2.173]

Marchesi 2006 *{published data only}*

Marchesi C, De Panfilis C, Cantoni A, Fontò S, Giannelli MR, Maggini C. Personality disorders and response to medication treatment in panic disorder: a 1-year naturalistic study. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2006;**30**(7):1240-5. [DOI: 10.1016/j.pnpbp.2006.03.010] [PMID: 16678956]

NCT00255554 *{published data only}*

Goodman M, New AS, Koenigsberg HW, Hazlett E, Flory J, Siever L. Psychotherapy and combined treatment in BPD: possible effects. In: Psychosomatic Medicine. Integrating Psychiatry & Medicine. 158th Annual Meeting of the American Psychiatric Association; 2005 May 21-26; Atlanta (GA). 2005:126-7. [ABSTRACT #: No. 19F] [PDF: www.psychiatry.org/File%20Library/Psychiatrists/Directories/Library-and-Archive/syllabus/am_syllabus_2005.pdf]

Goodman M. RE: [EXTERNAL] Cochrane Colllaboration review [personal communication]. Email to: J Stoffers-Winterling 16 June 2018.

* NCT00255554. DBT and escitalopram in borderline personality disorder [Effects of dialectical behavioral therapy and escitalopram on impulsive aggression, affective instability and cognitive processing in borderline personality disorder]. clinicaltrials.gov/ct2/show/NCT00255554 (first received 17 November 2005). [NCT00255554]

NCT00463775 *{published data only}*

NCT00463775. Topiramate for treatment of patients with borderline personality disorder and alcohol dependence. clinicaltrials.gov/ct2/show/NCT00463775 (first received 18 April 2007).

NCT00633802 *{published data only}*

Bloch M. Re: RCT of Risperidone in borderline PD [pers commun]. Email to: J. Stoffers-Winterling 15 August 2018.

* NCT00633802. Low-dose risperidone treatment for subjects suffering from borderline personality disorder. clinicaltrials.gov/ct2/show/NCT00633802 (first received 4 March 2008).

NCT01103180 *{published data only}*

McCloskey M. Fwd: Cochrane Collaboration review - RCT of escitalopram in BPD. Email to: J Stoffers-Winterling 15 August 2018.

NCT01103180. Selective serotonin reuptake inhibitors (SSRIs) in borderline personality disorder [SSRIs and self-harm in borderline personality disorder]. clinicaltrials.gov/ct2/show/NCT01103180 (first received 12 April 2010).

NCT03395314 *{published data only}*

NCT03395314. Ketamine in borderline personality disorder [A randomized active placebo controlled trial of ketamine in borderline personality disorderKetamine in Borderline Personality Disorder]. clinicaltrials.gov/ct2/show/NCT03395314 (first received 10 January 2018). [NCT03395314]

Parsons 1989 *{published data only}*

Parsons B, Quitkin FM, McGrath PJ, Stewart JW, Tricamo E, Ocepek-Welikson K, et al. Phenelzine, imipramine, and placebo in borderline patients meeting criteria for atypical depression. *Psychopharmacology Bulletin* 1989;**25**(4):524-34. [PMID: 2698483]

Rombold 2014 *{published data only}*

Rombold F, Lauterbach E, Felber W, Mueller-Oerlinghausen B, Ahrens B, Bronisch T, et al. Adjunctive lithium treatment in the prevention of suicidal behavior in patients with depression and comorbid personality disorders. *International Journal of Psychiatry in Clinical Practice* 2014;**18**(4):300-3. [DOI: 10.3109/13651501.2014.940052] [PMID: 24994476]

Russell 2003 *{published data only}*

Russell JM, Kornstein SG, Shea MT, McCullough JP, Harrison WM, Hirschfeld RM, et al. Chronic depression and comorbid personality disorders: response to sertraline versus imipramine. *Journal of Clinical Psychiatry* 2003;**64**(5):554-61. [DOI: 10.4088/jcp.v64n0510] [PMID: 12755659]

Serban 1984 *{published data only}*

Serban G, Siegel S. Response of borderline and schizotypal patients to small doses of thiothixene and haloperidol. *American Journal of Psychiatry* 1984;**141**(11):1455-8. [DOI: 10.1176/ajp.141.11.1455] [PMID: 6388363]

Verkes 1998 *{published data only}*

Verkes RJ, Van der Mast RC, Hengeveld MW, Tuyl JP, Zwinderman AH, Van Kempen GM. Reduction by paroxetine of suicidal behavior in patients with repeated suicide attempts but not major depression. *American Journal of Psychiatry* 1998;**155**(4):543-7. [DOI: 10.1176/ajp.155.4.543] [PMID: 9546002]

Wollmer 2022 *{published data only}***10.1177/02698811211069108**

Wollmer MA, Neumann I, Jung S, Bechinie A, Herrmann J, Müller A, et al. Clinical effects of glabellar botulinum toxin injections on borderline personality disorder: a randomized controlled trial. *Journal of Psychopharmacology* 2022;**36**(2):159-69. [DOI: 10.1177/02698811211069108] [PMID: 35102782]

References to studies awaiting assessment

NCT00437099 *{published data only}*

NCT00437009. Efficacy of omega-3 fatty acids on borderline personality disorder: a randomised, double blind clinical trial. clinicaltrials.gov/ct2/show/NCT00437099 (first received 16 February 2007).

NCT01912391 *{published data only}*

NCT01912391. Clinical research study to evaluate selegiline in the treatment of borderline personality disorder [A phase III randomized double-blind, 12 week, placebo controlled trial of transdermal selegiline in borderline personality disorder (BPD) to evaluate efficacy and safety]. clinicaltrials.gov/ct2/show/NCT01912391 (first received 16 July 2013).

References to ongoing studies

ACTRN12617001317381 *{published data only}***ACTRN12617001317381**

ACTRN12617001317381. Estrogen for the treatment of borderline personality disorder [A randomised placebo controlled trial of estradiol for the treatment of women with borderline personality disorder]. anzctr.org.au/Trial/Registration/TrialReview.aspx?id=373455 (first received 10 August 2017).

Arteaga-Henríquez 2020 *{published data only}*

* Arteaga-Henríquez G, Rosales-Ortiz SK, Arias-Vásquez A, Bitter I, Ginsberg Y, Ibañez-Jimenez P, et al. Treating impulsivity with probiotics in adults (PROBIA): study protocol of a multicenter, double-blind, randomized, placebo-controlled trial. *Trials* 2020;**21**(1):161. [DOI: 10.1186/s13063-019-4040-x] [PMCID: PMC7014653] [PMID: 32046750]

NCT03495375. Treating impulsivity in adults with probiotics (PROBIA) [Randomized placebo-controlled treatment of impulsivity in adults with probiotics]. clinicaltrials.gov/ct2/show/NCT03495375 (first received 26 February 2018).

Chanen 2019 *{published data only}***ACTRN12616001192471**

ACTRN12616001192471. VERBATIM: a randomised controlled trial of aripiprazole for the treatment of auditory verbal hallucinations in borderline personality disorder [A randomised

controlled trial of aripiprazole for the treatment of auditory verbal hallucinations in borderline personality disorder]. anzctr.org.au/Trial/Registration/TrialReview.aspx?id=371038 (first received 26 August 2016).

* Chanen AM, Betts J, Jackson H, McGorry P, Nelson B, Cotton SM, et al. Ripiprazole compared with placebo for auditory verbal hallucinations in youth with borderline personality disorder: protocol for the VERBATIM randomized controlled trial. *Early Intervention in Psychiatry* 2019;**13**(6):1373-81. [DOI: 10.1111/eip.12774] [PMID: 30689305]

DRKS00015817 *{published data only}*

DRKS00015817. Stellate ganglion block in patients with borderline personality disorder and posttraumatic stress disorder. www.drks.de/DRKS00015817 (first received 31 October 2018).

EUCTR2020-003469-20-ES *{published data only}*

EUCTR2020-003469-20-ES. A phase IIb study to evaluate the safety and efficacy of vafidemstat in an adult borderline personality disorder population [A double blind, randomized, placebo-controlled, adaptive 14-week phase IIb trial to evaluate the efficacy and safety of vafidemstat in an adult borderline personality disorder (BPD) population (PORTICO)]. trialsearch.who.int/?TrialID=EUCTR2020-003469-20-ES (first received 19 November 2020). [EUCTR2020-003469-20-ES]

EudraCT 2018-002471-18-GB *{published data only}***ISRCTN18352058**

* EudraCT 2018-002471-18. Clozapine in the treatment of borderline personality disorder [The clinical effectiveness and cost effectiveness of clozapine for inpatients with borderline personality disorder: randomised controlled trial]. clinicaltrialsregister.eu/ctr-search/search?query=2018-002471-18/GB (first received 19 June 2019).

ISRCTN18352058. Clozapine in the treatment of borderline personality disorder. The CALMED study [The clinical effectiveness and cost effectiveness of clozapine for inpatients with borderline personality disorder: randomised controlled trial]. www.isrctn.com/ISRCTN18352058 (first received 18 March 2019).

IRCT20210106049948N1 *{published data only}***IRCT20210106049948N1**

IRCT20210106049948N1. Memantine and borderline personality disorder [The effect of memantine on the symptoms of Borderline personality disorder in the Iranian population]. trialsearch.who.int/?TrialID=IRCT20210106049948N1 (first received 21 February 2021). [IRCT20210106049948N1]

IRCT20210531051453N1 *{published data only}***IRCT20210531051453N1**

IRCT20210531051453N1. Effect of omega 3 fatty acid in borderline personality disorder [Study the effectiveness of omega 3 fatty acid as adjuvant treatment on depression, aggression and poor impuls control in hospitalized patients of borderline personality disorder]. trialsearch.who.int/Trial2.aspx?TrialID=IRCT20210531051453N1 (first received 30 July 2021). [IRCT20210531051453N1]

NCT04100096 *{published data only}*

NCT04100096. A trial of brexpiprazole in the treatment of borderline personality disorder [A multicenter, randomized, flexible-dose, double-blind trial of brexpiprazole versus placebo for the treatment of adults with borderline personality disorder]. clinicaltrials.gov/ct2/show/NCT04100096 (first received 20 September 2019).

NCT04566601 *{published data only}*

NCT04566601. A study to test different doses of BI 1358894 and find out whether they reduce symptoms in people with borderline personality disorder [A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of 4 oral doses of BI 1358894 once daily over 12 week treatment period in patients with borderline personality disorder]. clinicaltrials.gov/ct2/show/NCT04566601 (first received 28 September 2020).

NCT05356013 *{published data only}*

NCT05356013. Caplyta in borderline personality disorder. clinicaltrials.gov/ct2/show/NCT05356013 (first received 02 May 2022).

Additional references

Aguglia 2019

Aguglia A, Serafini G, Nebbia J, Salvi V, Martinotti G, Corbo M, et al. Off-label use of second-generation antipsychotics in borderline personality disorder: a survey of Italian psychiatrists. *Journal of Personality Disorders* 2021;**35**(3):321-5.

Alvarez-Tomas 2017

Alvarez-Tomás I, Soler J, Bados A, Martín-Blanco A, Elices M, Carmona C, et al. Long-term course of borderline personality disorder: a prospective 10-year follow-up study. *Journal of Personality Disorders* 2017;**31**(5):590-605.

Alvarez-Tomas 2019

Álvarez-Tomás I, Ruiz J, Guilera G, Bados A. Long-term clinical and functional course of borderline personality disorder: a meta-analysis of prospective studies. *European Psychiatry* 2019;**56**:75-83. [DOI: 10.1016/j.eurpsy.2018.10.010] [PMID: 30599336]

Amminger 2010

Amminger GP, Schäfer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, et al. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. *Archives of General Psychiatry* 2010;**67**(2):146-54. [DOI: 10.1001/archgenpsychiatry.2009.192] [PMID: 20124114]

Andrews 2013a

Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *Journal of Clinical Epidemiology* 2013;**66**(7):719–25. [DOI: 10.1016/j.jclinepi.2012.03.013] [PMID: 23312392]

Andrews 2013b

Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation - determinants of a recommendation's direction and strength. *Journal of Clinical Epidemiology* 2013;**66**(7):726–35. [DOI: 10.1016/j.jclinepi.2013.02.003] [PMID: 23570745]

Ansell 2007

Ansell EB, Sanislow CA, McGlashan TH, Grilo CM. Psychosocial impairment and treatment utilization by patients with borderline personality disorder, other personality disorders, mood and anxiety disorders, and a healthy comparison group. *Comprehensive Psychiatry* 2007;**48**(4):329–36. [DOI: 10.1016/j.comppsych.2007.02.001] [PMID: 17560953]

APA 1980

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-III). 3rd edition. Washington (DC): American Psychiatric Association, 1980. [ISBN: 978-0-89042-0416]

APA 1987

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R). 3rd edition. Washington (DC): American Psychiatric Association, 1987. [ISBN: 978-0-89042-0195]

APA 1994

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). 4th edition. Washington (DC): American Psychiatric Association, 1994. [ISBN: 978-0-89042-0610]

APA 2000

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). 4th edition. Washington (DC): American Psychiatric Association, 2000. [ISBN: 978-0-89042-0256]

APA 2001

American Psychiatric Association. Practice guideline for the treatment of patients with borderline personality disorder. *American Journal of Psychiatry* 2001;**158**(10 Suppl):1-52. [PMID: 11665545]

APA 2013

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). 5 edition. Washington (DC): American Psychiatric Association, 2013. [ISBN: 978-0-89042-554-1]

Arntz 2003

Arntz A, Van den Hoorn M, Cornelis J, Verheul R, Van den Bosch W, De Bie AJHT. Reliability and validity of the borderline personality disorder severity index. *Journal of Personality Disorders* 2003;**17**(1):45-59. [PMID: 12659546]

Atkins 2004

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(7454):1490-9. [DOI: 10.1136/bmj.328.7454.1490] [PMCID: PMC428525] [PMID: 15205295]

Ayodeji 2015

Ayodeji E, Green J, Roberts C, Trainor G, Rothwell J, Woodham A, et al. The influence of personality disorder on outcome in adolescent self-harm. *British Journal of Psychiatry* 2015;**207**(4):313-9. [DOI: 10.1192/bjp.bp.113.138941] [PMID: 26250743]

Balshem 2011

Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology* 2011;**64**(4):401–6. [DOI: 10.1016/j.jclinepi.2010.07.015] [PMID: 21208779]

Barrett 1995

Barrett ES, Stanford MS. Impulsiveness. In: Costello CG, editors(s). Personality Characteristics of the Personality Disordered. New York (NY): Wiley, 1995:91-118. [ISBN: 978-0-471-01529-1]

Bateman 2015

Bateman AW, Gunderson J, Mulder R. Treatment of personality disorder. *Lancet* 2015;**385**(9969):735-43. [PMID: 10.1016/S0140-6736(14)61394-5] [PMID: 25706219]

Beck 1961

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Archives of General Psychiatry* 1961;**4**:561-71. [PMID: 13688369]

Beck 1979

Beck AT, Kovacs M, Weissman A. The assessment of suicidal intention: the Scale for Suicide Ideation. *Journal of Consulting and Clinical Psychology* 1979;**47**(2):343-52. [PMID: 469082]

Bellino 2019 [pers comm]

Bellino S. Inclusion of study in Cochrane review. Email to: A Tadorovac 31 January 2019.

Bender 2001

Bender DS, Dolan RT, Skodol AE, Sanislow CA, Dyck IR, McGlashan TH, et al. Treatment utilization by patients with personality disorders. *American Journal of Psychiatry* 2001;**158**(2):295–302. [DOI: 10.1176/appi.ajp.158.2.295] [PMID: 11156814]

Bender 2006

Bender DS, Skodol AE, Pagano ME, Dyck IE, Grilo CM, Shea MT, et al. Prospective assessment of treatment use by patients with personality disorders. *Psychiatric Services* 2006;**57**(2):254–7. [DOI: 10.1176/appi.ps.57.2.254] [PMCID: PMC2705621] [PMID: 16452705]

Berkey 1996

Berkey CS, Mosteller F, Lau J, Antman E. Uncertainty of the time of first significance in random effects cumulative meta-analysis. *Controlled Clinical Trials* 1996;**17**(5):357-71. [PMID: 8932970]

Bernstein 1986

Bernstein EM, Putnam FW. Development, reliability, and validity of a dissociation scale. *Journal of Nervous and Mental Disease* 1986;**174**(12):727-35. [PMID: 3783140]

Bero 2013

Bero L. Why the Cochrane risk of bias tool should include funding source as a standard item. Cochrane Database of Systematic Reviews 2013;(12):ED000075. [DOI: 10.1002/14651858.ED000075] [PMID: 24575439]

Biskin 2015

Biskin RS. The lifetime course of borderline personality disorder. *Canadian Journal of Psychiatry* 2015;**60**(7):303-8. [DOI: 10.1177/070674371506000702] [PMCID: PMC4500179] [PMID: 26175388]

Black 2014a

Black DW, Zanarini MC, Romine A, Shaw M, Allen J, Schulz SC. Comparison of low and moderate dosages of extended-release quetiapine in borderline personality disorder: a randomized, double-blind, placebo-controlled trial. *American Journal of Psychiatry* 2014;**171**(11):1174-82. [DOI: 10.1176/appi.ajp.2014.13101348] [PMID: 24968985]

Bode 2017

Bode K, Vogel R, Walker J, Kröger C. Health care costs of borderline personality disorder and matched controls with major depressive disorder: a comparative study based on anonymized claims data. *European Journal of Health Economics* 2017;**18**(9):1125-35.

Bohus 2021

Bohus M, Stoffers-Winterling JM, Sharp C, Krause-Utz A, Schmahl C, Lieb K. Borderline personality disorder. *Lancet* 2021;**398**:1528-40.

Borschmann 2012

Borschmann R, Henderson C, Hogg J, Phillips R, Moran P. Crisis interventions for people with borderline personality disorder. *Cochrane Database of Systematic Reviews* 2012, Issue 6. Art. No: CD009353. [DOI: 10.1002/14651858.CD009353.pub2] [PMID: 22696385]

Bridler 2015

Bridler R, Häberle A, Müller ST, Cattapan K, Grohmann R, Toto S, et al. Psychopharmacological treatment of 2195 in-patients with borderline personality disorder: a comparison with other psychiatric disorders. *European Neuropsychopharmacology* 2015;**25**(6):763-72. [PMID: 10.1016/j.euroneuro.2015.03.017] [PMID: 25907249]

Brok 2008

Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *Journal of Clinical Epidemiology* 2008;**61**(8):763-9. [DOI: 10.1016/j.jclinepi.2007.10.007] [PMID: 18411040]

Brok 2009

Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analysis may be inconclusive -- trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *International Journal of Epidemiology* 2009;**38**(1):287-98. [DOI: 10.1093/ije/dyn188] [PMID: 18824466]

Brühl 2017

Brühl AB, Sahakian BJ. Neuroscience-based nomenclature: improving clinical and scientific terminology in research and clinical psychopharmacology. *Psychological Medicine* 2017;**47**(8):1339-41.

Brunetti 2013

Brunetti M, Shemilt I, Pregno S, Vale L, Oxman AD, Lord J, et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. *Journal of Clinical Epidemiology* 2013;**66**(2):140–50. [DOI: 10.1016/j.jclinepi.2012.04.012] [PMID: 22863410]

Cailhol 2015

Cailhol L, Thalamas C, Garrido C, Birmes P, Lapeyre-Mestre M. Mental health service utilization among borderline personality disorder inpatients [Utilisation des services de soin par les patients hospitalisés, présentant un trouble de personnalité borderline en Midi-Pyrénées]. *L'Encéphale* 2015;**41**(2):115-22. [DOI: 10.1016/j.encep.2014.10.008] [PMID: 25526809]

Cavelti 2019

Cavelti M, Thompson K, Hulbert C, Betts J, Jackson H, Francey S, et al. Preliminary evidence for the cognitive model of auditory verbal hallucinations in youth with borderline personality disorder. *Front Psychiatry* 2019;**10**:292. [PMID: 31156473]

Cavelti 2021

Cavelti M, Thompson K, Chanen AM, Kaess M. Psychotic symptoms in borderline personality disorder: developmental aspects. *Current Opinion in Psychology* 2021;**37**:26-31. [PMID: 32771980]

Chanen 2012

Chanen AM, Kaess M. Developmental pathways to borderline personality disorder. *Current Psychiatry Reports* 2012;**14**(1):45-53. [DOI: 10.1007/s11920-011-0242-y] [PMID: 22009682]

Chanen 2013

Chanen AM, McCutcheon L. Prevention and early intervention for borderline personality disorder: current status and recent evidence. *British Journal of Psychiatry* 2013;**Supplement**(54):s24-9.

Chanen 2017

Chanen A, Sharp C, Hoffman P, Global Alliance for Prevention and Early Intervention for Borderline Personality Disorder. Prevention and early intervention for borderline personality disorder: a novel public health priority. *World Psychiatry* 2017;**16**(2):215-6.

Coccaro 1991

Coccaro EF, Harvey PD, Kupsaw-Lawrence E, Herbert JL, Bernstein DP. Development of neuropharmacologically-based behavioral assessments of impulsive aggressive behavior. *Journal of Neuropsychiatry and Clinical Neurosciences* 1991;**3**(2):S44-51. [PMID: 1821222]

Coccaro 2020

Coccaro EF. The Overt Aggression Scale Modified (OAS-M) for clinical trials targeting impulsive aggression and intermittent explosive disorder: validity, reliability, and correlates. *Journal of Psychiatric Research* 2020;**124**:50-7. [DOI: 10.1016/j.jpsychires.2020.01.007] [PMID: 32114032]

Coid 2006

Coid J, Yang M, Tyrer P, Roberts A, Ullrich S. Prevalence and correlates of personality disorder in Great Britain. *British Journal of Psychiatry* 2006;**188**:423-31. [DOI: 10.1192/bjp.188.5.423] [PMID: 16648528]

Crawford 2020 [pers comm]

Crawford M. Inclusion of your study in Cochrane review. Email to: A Pathmanathan Ratnam 09 November 2020.

Cristea 2017

Cristea IA, Gentili C, Cotet CD, Palomba D, Barbui C, Cuijpers P. Efficacy of psychotherapies for borderline personality disorder: a systematic review and meta-analysis. *JAMA Psychiatry* 2017;**74**(4):319-28. [DOI: 10.1001/jamapsychiatry.2016.4287] [PMID: 28249086]

CTU 2011

Copenhagen Trial Unit. TSA - Trial Sequential Analysis. www.ctu.dk/tsa (accessed 12 December 2016).

Curtin 2002

Curtin F, Elbourne D, Altman DG. Meta-analysis combining parallel and cross-over clinical trials. III: the issue of carry-over. *Statistics in Medicine* 2002;**21**(15):2161-73. [DOI: 10.1002/sim.1207] [PMID: 12210631]

Deeks 2021

Deeks JJ, Higgins JP, Altman DG, editor(s). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 6.2 (updated February 2021), Cochrane 2021. Available from www.training.cochrane.org/handbook.

Derogatis 1994

Derogatis LR, Lazarus L. SCL-90-R, Brief Symptom Inventory, and matching clinical rating scales. In: Maruish ME, editors(s). The Use of Psychological Testing for Treatment Planning and Outcome Assessment. 1st edition. Hillsdale (NJ): Lawrence Erlbaum Associates, 1994. [ISBN: 978-0-80581-1629]

DGPPN 2009

Deutsche Gesellschaft für Psychiatrie und Psychotherapie Psychosomatik und Nervenheilkunde (DGPPN) [German Association for Psychiatry, Psychotherapy and Psychosomatics]. S2-Praxisleitlinien in Psychiatrie und Psychotherapie. Band 1: Behandlungsleitlinie Persönlichkeitsstörungen [S2 Practical Guidelines in Psychiatry and Psychotherapy. Treatment Guideline Personality Disorders]. Vol. **1**. Heidelberg (DE): Steinkopff Verlag, 2009. [ISBN: 978-3-7985-1853-7]

Donner 2002

Donner A, Klar N. Issues in the meta-analysis of cluster randomized trials. *Statistics in Medicine* 2002;**21**(19):2971-80. [DOI: 10.1002/sim.1301] [PMID: 12325113]

Eaton 2018

Eaton NR, Greene AL. Personality disorders: community prevalence and socio-demographic correlates. *Current Opinion in Psychology* 2018;**21**:28-32. [DOI: 10.1016/j.copsyc.2017.09.001] [PMID: 28961462]

Elbourne 2002

Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140-9.

Eli Lilly 2008

Eli Lilly and Company. Efficacy and safety of olanzapine in patients with borderline personality disorder: a randomized, flexible-dose, double-blind comparison with placebo [Summary ID #6257. Clinical Study Summary: F1D-MC-HGKL]. www.lillytrials.com/results_files/zyprexa/zyprexa_summary_6257 (accessed 14 February 2008).

Ellison 2018

Ellison WD, Rosenstein LK, Morgan TA, Zimmerman M. Community and clinical epidemiology of borderline personality disorder. *Psychiatric Clinics of North America* 2018;**41**(4):561-73. [DOI: 10.1016/j.psc.2018.07.008] [PMID: 30447724]

Endicott 1976

Endicott J, Spitzer RL, Fleiss JL, Cohen J. The Global Assessment scale: a procedure for measuring overall severity of psychiatric disturbance. *Archives of General Psychiatry* 1976;**33**(6):766-71. [PMID: 938196]

Fonagy 2009

Fonagy P, Luyten P. A developmental, mentalization-based approach to the understanding and treatment of borderline personality disorder. *Development and Psychopathology* 2009;**21**(4):1355-81. [DOI: 10.1017/S0954579409990198] [PMID: 19825272]

Garner 2016

Garner P, Hopewell S, Chandler J, MacLehose H, Schünemann HJ, Akl EA, et al. When and how to update systematic reviews: consensus and checklist. *BMJ* 2016;**354**:i3507. [PMCID: PMC4955793] [PMID: 27443385]

Gartlehner 2021a

Gartlehner G, Crotty K, Kennedy S, Edlund MJ, Ali R, Siddiqui M, et al. Pharmacological treatments for borderline personality disorder: a systematic review and meta-analysis. *Central Nervous System Drugs* 2021;**35**(10):1053-67. [CENTRAL:

PMC8478737] [DOI: 10.1007/s40263-021-00855-4] [PMID: 34495494]

Gartlehner 2021b

Gartlehner G, Crotty K, Edlund MJ, Viswanathan M. Authors' reply to Pereira Ribeiro et al: comment on "Pharmacological Treatments for Borderline Personality Disorder: A Systematic Review and Meta-Analysis". *Central Nervous System Drugs* 2021;**35**:1335-6. [DOI: https://doi.org/10.1007/s40263-021-00873-2]

Goodman 2012

Goodman M, Roiff T, Oakes AH, Paris J. Suicidal risk and management in borderline personality disorder. *Current Psychiatry Reports* 2012;**14**(1):79-85. [DOI: 10.1007/s11920-011-0249-4] [PMID: 22113831]

GRADEpro 2021 [Computer program]

GRADEpro GDT (guideline development tool). Version accessed prior to 18 October 2022. Hamilton (Ontario): Grade Working Group, McMaster University and Evidence Prime, 2021.

Grant 2008

Grant BF, Chou SP, Goldstein RB, Huang B, Stinson FS, Saha TD, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of Clinical Psychiatry* 2008;**69**:533-45.

Gratz 2001

Gratz KL. Meausrement of deliberate self-harm: preliminary data on the deliberate self-harm inventory. *Journal of Psychopathology and Behavioral Assessment* 2001;**23**(4):253-63. [DOI: 10.1023/A:1012779403943]

Gunderson 2011a

Gunderson JG. Borderline personality disorder. *New England Journal of Medicine* 2011;**364**(21):2037-42. [DOI: 10.1056/NEJMcp1007358]

Gunderson 2011b

Gunderson JG, Stout RL, McGlashan TH, Shea MT, Morey LC, Grilo CM, et al. Ten-year course of borderline personality disorder: psychopathology and function from the Collaborative Longitudinal Personality Disorders study. *Archives of General Psychiatry* 2011;**68**(8):827-37. [DOI: 10.1001/archgenpsychiatry.2011.37] [PMCID: PMC3158489] [PMID: 21464343]

Guttierez 2001

Guttierez PM, Osman A, Barrios FX, Kopper BA. Development and initial validation of the Self-Harm Behavior Questionnaire. *Journal of Personality Assessment* 2001;**77**(3):475-90. [DOI: 10.1207/S15327752JPA7703_08] [PMID: 11781034]

Guyatt 2011a

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383–94. [DOI: 10.1016/j.jclinepi.2010.04.026] [PMID: 21195583]

Guyatt 2011b

Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *Journal of Clinical Epidemiology* 2011;**64**(4):395–400. [DOI: 10.1016/j.jclinepi.2010.09.012] [PMID: 21194891]

Guyatt 2011c

Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence - study limitations (risk of bias). *Journal of Clinical Epidemiology* 2011;**64**(4):407–15. [DOI: 10.1016/j.jclinepi.2010.07.017] [PMID: 21247734]

Guyatt 2011d

Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence - publication bias. *Journal of Clinical Epidemiology* 2011;**64**(12):1277–82. [DOI: 10.1016/j.jclinepi.2011.01.011] [PMID: 21802904]

Guyatt 2011e

Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence - imprecision. *Journal of Clinical Epidemiology* 2011;**64**(12):1283–93. [DOI: 10.1016/j.jclinepi.2011.01.012] [PMID: 21839614]

Guyatt 2011f

Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence - inconsistency. *Journal of Clinical Epidemiology* 2011;**64**(12):1294–302. [DOI: 10.1016/j.jclinepi.2011.03.017] [PMID: 21803546]

Guyatt 2011g

Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence - indirectness. *Journal of Clinical Epidemiology* 2011;**64**(12):1303–10. [DOI: 10.1016/j.jclinepi.2011.04.014] [PMID: 21802903]

Guyatt 2011h

Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. *Journal of Clinical Epidemiology* 2011;**64**(12):1311–6. [DOI: 10.1016/j.jclinepi.2011.06.004] [PMID: 21802902]

Guyatt 2013a

Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):151–7. [DOI: 10.1016/j.jclinepi.2012.01.006] [PMID: 22542023]

Guyatt 2013b

Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables - binary outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):158–72. [DOI: 10.1016/j.jclinepi.2012.01.012] [PMID: 22609141]

Guyatt 2013c

Guyatt GH, Thorlund K, Oxman AD, Walter SD, Patrick D, Furukawa TA, et al. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles - continuous outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):173–83. [DOI: 10.1016/j.jclinepi.2012.08.001] [PMID: 23116689]

Gøtzsche 2015

Gøtzsche P. Re: Why the Cochrane risk of bias tool should include funding source as a standard item. Response to JAC Sterne. cochranelibrary.com/editorial/10.1002/14651858.ED000076 (accessed 19 January 2018).

Hancock-Johnson 2017

Hancock-Johnson E, Griffiths C, Picchioni M. A focused systematic review of pharmacological treatment for borderline personality disorder. *Central Nervous System Drugs* 2017;**31**(5):345-56. [DOI: 10.1007/s40263-017-0425-0] [PMID: 28353141]

Hastrup 2019a

Hastrup LH, Kongerslev MT, Simonsen E. Low vocational outcome among people diagnosed with borderline personality disorder during first admission to mental health services in Denmark: a nationwide 9-year register-based study. *Journal of Personality Disorders* 2019;**33**(3):326-40. [DOI: 10.1521/pedi_2018_32_344]

Hastrup 2019b

Hastrup LH, Jennum P, Ibsen R, Kjellberg J, Simonsen E. Societal costs of borderline personality disorders: a matched-controlled nationwide study of patients and spouses. *Acta Psychiatrica Scandinavica* 2019;**140**(5):458-67. [DOI: 10.1111/acps.13094] [PMID: 31483859]

Herpertz 2007

Herpertz SC, Zanarini M, Schulz CS, Siever L, Lieb K, Möller H-J, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of personality disorders. *World Journal of Biological Psychiatry* 2007;**8**(4):212-44. [DOI: 10.1080/15622970701685224] [PMID: 17963189]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [DOI: 10.1136/bmj.327.7414.557] [PMCID: PMC192859] [PMID: 12958120]

Higgins 2017

Higgins JPT, Altmand DG, Sterne JAC, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Churchill R, Chandler J, Cumpston M, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 (updated June 2017). Cochrane, 2017. Available from www.training.cochrane.org/handbook/archive/v5.2.

Higgins 2019

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions. 2nd edition. Chichester (UK): John Wiley & Sons, 2019. [WEB PAGE: Available from www.training.cochrane.org/handbook]

Higgins 2022

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane 2022. Available from www.training.cochrane.org/handbook.

Horowitz 1988

Horowitz LM, Rosenberg SE, Baer BA, Ureño G, Villaseñor VS. Inventory of interpersonal problems: psychometric properties and clinical applications. *Journal of Consulting and Clinical Psychology* 1988;**56**(6):885-92. [PMID: 3204198]

Hörz 2010

Hörz S, Zanarini MC, Frankenburg FR, Reich DB, Fitzmaurice G. Ten-year use of mental health services by patients with borderline personality disorder and with other axis II disorders. *Psychiatric Services* 2010;**61**(6):612-6. [DOI: 10.1176/ps.2010.61.6.612] [PMCID: PMC3889171] [PMID: 20513685]

Ingenhoven 2011

Ingenhoven TJ, Duivendvoorden HJ. Differential effectiveness of antipsychotics in borderline personality disorder: Meta-analyses of placebo-controlled, randomized clinical trials on symptomatic outcome domains. *Journal of Clinical Psychopharmacology* 2011;**31**(4):489-96. [DOI: 10.1097/JCP.0b013e3182217a69] [PMID: 21694626]

Ingenhoven 2015

Ingenhoven T. Pharmacotherapy for borderline patients: business as usual or by default? *Journal of Clinical Psychiatry* 2015;**76**(4):e522-3. [DOI: 10.4088/JCP.14com09522] [PMID: 25919847]

Jacobi 2021

Jacobi F, Grafiadeli R, Volkmann H, Schneider I. Disease burden of borderline personality disorder: cost of illness, somatic comorbidity and mortality [[Krankheitslast der Borderline-Persönlichkeitsstörung: Krankheitskosten, somatische Komorbidität und Mortalität]]. *Nervenarzt* 2021;**92**(7):660-9.

Jakobsen 2014

Jakobsen JC, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. *BMC Medical Research Methodology* 2014;**14**:120. [DOI: 10.1186/1471-2288-14-120] [PMCID: PMC4251848] [PMID: 25416419]

Kay 1987

Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;**13**(2):261-76. [PMID: 3616518]

Kjaergard 2001

Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Annals of Internal Medicine* 2001;**135**(11):982-9. [PMID: 11730399]

Knappich 2014

Knappich M, Hörz-Sagstetter S, Schwerthöffer D, Leucht S, Rentrop M. Pharmacotherapy in the treatment of patients with borderline personality disorder: results of a survey among psychiatrists in private practices. *International Clinical Psychopharmacology* 2014;**29**(4):224-8. [DOI: 10.1097/YIC.0000000000000021] [PMCID: PMC4047315] [PMID: 24896541]

Kongerslev 2015

Kongerslev MT, Chanen AM, Simonsen E. Personality disorder in childhood and adolescence comes of age: a review of the current evidence and prospects for future research. *Scandinavian Journal of Child and Adolescent Psychiatry and Psychology* 2015;**3**(1):31-48. [DOI: 10.21307/sjcapp-2015-004]

Korang 2020

Korang Steven Kwasi, Juul Sophie, Nielsen Emil Eik, Feinberg Joshua, Siddiqui Faiza, Ong Giok, et al. Vaccines to prevent COVID-19: a protocol for a living systematic review with network meta-analysis including individual patient data (The LIVING VACCINE Project). *Systematic Reviews* 2020;**9**(1):1-15.

Kulkarni 2020 [pers comm]

Kulkarni J. Re: Your Request. Email to: A Pathmanathan Ratnam 14 December 2020.

Lau 1995

Lau J, Schmid CH, Chalmers TC. Cumulative meta-analysis of clinical trials builds evidence for exemplary medical care. *Journal of Clinical Epidemiology* 1995;**48**(1):45-57. [PMID: 7853047]

Lenzenweger 2007

Lenzenweger MF, Lane MC, Loranger AW, Kessler RC. DSM-IV personality disorders in the National Comorbidity Survey Replication. *Biological Psychiatry* 2007;**62**(6):553-64. [DOI: 10.1016/j.biopsych.2006.09.019] [PMCID: PMC2044500] [PMID: 17217923]

Levine 1986

Levine J, Schooler NR. SAFTEE: a technique for the systematic assessment of side effects in clinical trials. *Psychopharmacology Bulletin* 1986;**22**(2):343-81. [PMID: 3774930]

Lieb 2004

Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M. Borderline personality disorder. *Lancet* 2004;**364**(9432):453-61. [DOI: 10.1016/S0140-6736(04)16770-6] [PMID: 15288745]

Linehan 1997

Linehan MM. Behavioral treatments of suicidal behaviors: definitional obfuscation and treatment outcomes. *Annals of the New York Academy of Sciences* 1997;**836**:302-28. [PMID: 9616806]

Links 2009

Links PS, Kolla N. Assessing and managing suicide risk. In: Oldham JM, Skodol AE, Bender DS, editors(s). Essentials of Personality Disorders. 1st edition. Arlington (VA): American Psychiatric Publishing, Inc, 2009:343-60. [ISBN: 978-1-58562-358-7]

Lundh 2017

Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. *Cochrane Database of Systematic Reviews* 2017, Issue 2. Art. No: MR000033. [DOI: 10.1002/14651858.MR000033.pub3] [PMCID: PMC8132492] [PMID: 28207928]

Lundh 2018

Lundh Andreas, Lexchin Joel, Mintzes Barbara, Schroll Jeppe B, Bero Lisa. Industry sponsorship and research outcome: systematic review with meta-analysis. *Intensive care medicine* 2018;**44**(10):1603-1612.

Makela 2006

Makela EH, Moeller KE, Fullen JE, Gunel E. Medication utilization patterns and methods of suicidality in borderline personality disorder. *Annals of Pharmacotherapy* 2006;**40**(1):49-52. [DOI: 10.1345/aph.1E479] [PMID: 16303987]

Mancke 2015

Mancke F, Bertsch K, Herpertz SC. Gender differences in aggression of borderline personality disorder. *Borderline Personal Disord Emot Dysregul* 2015;**9**(2):7.

Meuldijk 2017

Meuldijk D, McCarthy A, Bourke ME, Grenyer BF. The value of psychological treatment for borderline personality disorder: Systematic review and cost offset analysis of economic evaluations. *PLoS One* 2017;**1**(12(3)):e0171592.

Moher 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad A, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;**352**(9128):609-13. [DOI: 10.1016/S0140-6736(98)01085-X] [PMID: 9746022]

Moher 1999

Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999;**354**(9193):1896-900. [PMID: 10584742]

Montgomery 1979

Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* 1979;**134**:382-9. [DOI: 10.1192/bjp.134.4.382] [PMID: 444788]

Montgomery 1983

Montgomery D, Montgomery S, Roy D. Mianserin in the prophylaxis of suicidal behaviour: a double-blind placebo controlled trial. In: Soubrier JP, Vedrinne J, editors(s). Dépression et Suicide: Aspects Medicaux, Psychologiques et Socio-Culturels. Paris (FR): Pergamon Press, 1983:786-90. [DOI: 10.1016/B978-0-08-027080-7.50130-0]

Mulder 2021

Mulder RT. CD-11 personality disorders: utility and implications of the new model. *Front Psychiatry* 2021;**12**:655548.

[DOI: 0.3389/fpsyt.2021.655548] [PMID: 34040555] [PMID: PMC8141634]

Munk-Jørgensen 2010

Munk-Jørgensen P, Najarraq Lund M, Bertelsen A. Use of ICD-10 diagnoses in Danish psychiatric hospital-based services in 2001-2007. *World Psychiatry* 2010;**9**(3):183-4. [PMCID: PMC2948730] [PMID: 20975866]

Mustafa 2013

Mustafa RA, Santesso N, Brozek J, Akl EA, Walter SD, Norman G, et al. The GRADE approach is reproducible in assessing the quality of evidence of quantitative evidence syntheses. *Journal of Clinical Epidemiology* 2013;**66**(7):736-42. [DOI: 10.1016/j.jclinepi.2013.02.004] [PMID: 23623694]

NbN3 2021

Neuroscience-Based Nomenclature. Neuroscience-Based Nomenclature, Second Edition-reivsed. https://nbn2r.com/search (accessed 02 December 2021).

NCT00880919

NCT00880919. Seroquel extended release (XR) for the management of borderline personality disorder (BPD) [Seroquel XR for the management of borderline personality disorder (BPD)]. clinicaltrials.gov/ct2/show/NCT00880919 (first received 10 April 2009).

Neacsiu 2017

Neacsiu DA, Eberle WJ, Keng SL, Fang MC, Rosenthal ZM. Understanding borderline personality disorder across sociocultural groups: findings, issues, and future directions. *Current Psychiatry Reviews* 2017;**13**(3):188-223. [PMID: 10.2174/1573400513666170612122034]

Newton-Howes 2021

Newton-Howes G, Cunningham R, Atkinson J. Personality disorder prevalence and correlates in a whole of nation dataset. *Soc Psychiatry Psychiatr Epidemiol* 2021;**56**(4):679-85.

Ng 2016

Ng FY, Bourke ME, Grenyer BF. Recovery from borderline personality disorder: a systematic review of the perspectives of consumers, clinicians, family and carers. *PLoS One* 2016;**11**(8):e0160515. [DOI: 10.1371/journal.pone.0160515] [PMCID: PMC4978398] [PMID: 27504634]

NHMRC 2013

National Health and Medical Research Council. Clinical Practice Guideline for the Management of Borderline Personality Disorder. Melbourne: National Health and Medical Research Council, 2013. [WEB PAGE: Available from www.nhmrc.gov.au/guidelines/publications/mh25]

NICE 2009

National Institute for Health and Clinical Excellence. Borderline personality disorder: recognition and management. NICE clinical guideline 78; 28 January 2009. Available at www.nice.org.uk/guidance/cg78 (accessed 29 June 2021).

NICE 2018

National Instiute for Health and Care Excellence (NICE). 2018 surveillance of personality disorders (NICE guidelines CG77 and CG78). Surveillance report. Published 19 July 2018. Available from www.nice.org.uk/guidance/cg78/resources/2018-surveillance-of-personality-disorders-nice-guidelines-cg77-and-cg78-4906490080/chapter/Surveillance-decision?tab=evidence. (accessed 05 December 2021).

Niesten 2016

Niesten IJ, Karan E, Frankenburg FR, Fitzmaurice GM, Zanarini MC. Description and prediction of the income status of borderline patients over 10 years of prospective follow-up. *Personality and Mental Health* 2016;**10**(4):285-92. [DOI: 10.1002/pmh.1331] [PMID: 26864557]

Norman 2004

Norman GR, Sloan JA, Wyrwich KW. The truly remarkable universality of half a standard deviation: confirmation through another look. *Expert Review of Pharmacoeconomics & Outcomes Research* 2004;**4**(5):581-5. [DOI: 10.1586/14737167.4.5.581] [PMID: 19807551]

Ose 2021

Ose SO, Tveit T, Mehlum L. Non-suicidal self-injury (NSSI) in adult psychiatric outpatients - a nationwide study. *Journal of Psychiatric Research* 2021;**133**:1-9. [DOI: 10.1016/j.jpsychires.2020.11.031] [PMID: 33296801]

Osman 2001

Osman A, Bagge CL, Gutierrez PM, Konick LC, Kopper BA, Barrios FX. The Suicidal Behaviors Questionnaire-Revised (SBQ-R): validation with clinical and nonclinical samples. *Assessment* 2001;**8**(4):443-54. [DOI: 10.1177/107319110100800409] [PMID: 11785588]

Ottosson 2002

Ottosson HA, Ekselius LA, Grann MA, Kullgren G. Cross-system concordance of personality disorder diagnoses of DSM-IV and diagnostic criteria for research of ICD-10. *Journal of Personality Disorders* 2002;**16**(3):283-92. [DOI: 10.1521/pedi.16.3.283.22537] [PMID: 12136684]

Oud 2017

Oud M, Arntz A, Hermens ML, Verhoef R, Kendall T. Specialized psychotherapies for adults with borderline personality disorder: A systematic review and meta-analysis. *Aust N Z J Psychiatry* 2018;**52**(10):949-61.

Overall 1962

Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychological Reports* 1962;**10**(3):799-812. [DOI: 10.2466/pr0.1962.10.3.799]

Paris 2015

Paris J. Why patients with severe personality disorders are overmedicated. *Journal of Clinical Psychiatry* 2015;**76**(4):e521. [DOI: 10.4088/JCP.14com09441] [PMID: 25919846]

Pascual 2021

Pascual JC, Martín-Blanco A, Soler J. Twenty-Year Trends in the Psychopharmacological Treatment of Outpatients with Borderline Personality Disorder: A Cross-Sectional Naturalistic Study in Spain.. *CNS Drugs* 2021;**35**(9):1023-32.

Paton 2015

Paton C, Crawford MJ, Bhatti SF, Patel MX, Barnes TE. The use of psychotropic medication in patients with emotionally unstable personality disorder under the care of UK Mental Health Services. *Journal of Clinical Psychiatry* 2015;**76**(4):e512–8. [DOI: 10.4088/JCP.14m09228] [PMID: 25919844]

Pereira Ribeiro 2021

Pereira Ribeiro, J, Sedoc Jørgensen, M, Storebø, OJ. Comment on: "Pharmacological Treatments for Borderline Personality Disorder: A Systematic Review and `Meta-Analysis`" . *CNS Drugs* 2021 Nov;**35**:1333-1334. [https://doi.org/10.1007/s40263-021-00872-3]

Perez 2007

Perez V, Barrachina J, Soler J, Pascual JC, Campins MJ, Puigdemont D, et al. The clinical global impression scale for borderline personality disorder patients (CGI-BPD): a scale sensible to detect changes [Impresión clínica global para pacientes con trastorno límite de la personalidad (ICG-TLP): una escala sensible al cambio]. *Actas Españolas de Psiquiatría* 2007;**35**(4):229-35. [PMID: 17592784]

RevMan Web 2020 [Computer program]

Review Manager Web (RevMan Web). Version 3.2.1. The Cochrane Collaboration, 2020. Available at revman.cochrane.org.

Riffer 2019

Riffer F, Farkas M, Streibl L, Kaiser E, Sprung M. Psychopharmacological treatment of patients with borderline personality disorder: comparing data from routine clinical care with recommended guidelines. *International Journal of Psychiatry in Clinical Practice* 2019;**23**(3):178-88. [DOI: 10.1080/13651501.2019.1576904] [PMID: 31140337]

Rossouw 2012

Rossouw TI, Fonagy P. Mentalization-based treatment for self-harm in adolescents: a randomized controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry* 2012;**51**(12):1304-13. [DOI: 10.1016/j.jaac.2012.09.018] [PMID: 23200287]

Sansone 2003

Sansone RA, Rytwinski D, Gaither GA. Borderline personality and psychotropic medication prescription in an outpatient psychiatry clinic. *Comprehensive Psychiatry* 2003;**44**(6):454-8. [DOI: 10.1016/S0010-440X(03)00147-0] [PMID: 14610722]

Savović 2012a

Savović J, Jones H, Altman D, Harris R, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomised controlled trials: combined analysis of meta-epidemiological studies. *Health Technology Assessment* 2012;**16**(35):1-82. [DOI: 10.3310/hta16350] [PMID: 22989478]

Savović 2012b

Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Annals of Internal Medicine* 2012;**157**(6):429-38. [DOI: 10.7326/0003-4819-157-6-201209180-00537] [PMID: 22945832]

Schneider 2019

Schneider F, Erhart M, Hewer W, Loeffler LA, Jacobi F. Mortality and medical comorbidity in the severely mentally ill. *Deutsches Arzteblatt International* 2019;**116**(23-24):405-11. [DOI: 10.3238/arztebl.2019.0405] [PMCID: PMC6683445] [PMID: 31366432]

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408-12. [DOI: 10.1001/jama.273.5.408] [PMID: 7823387]

Schulz 2008

Schulz SC, Zanarini MC, Bateman A, Bohus M, Detke HC, Trzaskoma Q, et al. Olanzapine for the treatment of borderline personality disorder: variable dose, 12-week, randomised double-blind placebo-controlled study. *British Journal of Psychiatry* 2008;**193**(6):485-92. [DOI: 10.1192/bjp.bp.107.037903] [PMID: 19043153]

Shea 2017

Shea Beverley J, Reeves Barnaby C, Wells George, Thuku Micere, Hamel Candyce, Moran Julian, Moher David, Tugwell Peter, Welch Vivian, Kristjansson Elizabeth. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *bmj* 2017;**358**:j4008.

Sher 2019

Sher L, Rutter SB, New AS, Siever LJ, Hazlett EA. Gender differences and similarities in aggression, suicidal behaviour, and psychiatric comorbidity in borderline personality disorder. *Acta Psychiatr Scand* 2019;**139**(2):145-53.

Silk 2015

Silk KR. Management and effectiveness of psychopharmacology in emotionally unstable and borderline personality disorder. *Journal of Clinical Psychiatry* 2015;**76**(4):e524–5. [DOI: 10.4088/JCP.14com09534] [PMID: 25919848]

Simonsen 2019

Simonsen S, Bateman A, Bohus M, Dalewijk HJ, Doering S, Kaera A, et al. European guidelines for personality disorders: past, present and future. *Borderline Personality Disorder and Emotion Dysregulation* 2019;**6**:9. [DOI: 10.1186/s40479-019-0106-3] [PMCID: PMC6530178] [PMID: 31143448]

Skodol 2002

Skodol AE, Gunderson JG, McGlashan TH, Dyck IR, Stout RL, Bender DS, et al. Functional impairment in patients with

schizotypal, borderline, avoidant, or obsessive-compulsive personality disorder. *American Journal of Psychiatry* 2002;**159**(2):276-83. [DOI: 10.1176/appi.ajp.159.2.276] [PMID: 11823271]

Soetmann 2008a

Soeteman DI, Hakkaart-van Roijen L, Verheul R, Busschbach JJ. The economic burden of personality disorders in mental health care. *Journal of Clinical Psychiatry* 2008;**69**(2):259–65. [PMID: 18363454]

Soetmann 2008b

Soeteman DI, Verheul R, Busschbach JJ. The burden of disease in personality disorders: diagnosis-specific quality of life. *Journal of Personality Disorders* 2008;**22**(3):259-68. [DOI: 10.1521/pedi.2008.22.3.259] [PMID: 18540798]

Soloff 2002

Soloff PH, Lynch KG, Kelly TM. Childhood abuse as a risk factor for suicidal behavior in borderline personality disorder. *Journal of Personality Disorders* 2002;**16**(3):201-14. [DOI: 10.1521/pedi.16.3.201.22542] [PMID: 12136678]

Soloff 2012

Soloff PH, Chiappetta L. Prospective predictors of suicidal behavior in borderline personality disorder at 6-year follow-up. *Am J Psychiatry* 2012;**169**(5):484-90.

Spielberger 1988

Spielberger CD. Manual for the State-Trait Anger Expression Inventory. Odessa (Fl): Psychological Assessment Resources, 1988.

Stepp 2012

Stepp SD. Development of borderline personality disorder in adolescence and young adulthood: introduction to the special section. *Journal of Abnormal Child Psychology* 2012;**40**(1):1-5. [DOI: 10.1007/s10802-011-9594-3] [PMCID: PMC3865353] [PMID: 22116635]

Sterne 2013

Sterne JA. Why the Cochrane risk of bias tool should not include funding source as a standard item. Cochrane Database of Systematic Reviews 2013;**12**:ED000076. [DOI: 10.1002/14651858.ED000076] [PMID: 24575440]

Sterne 2017

Sterne JAC, Egger M, Moger D, Boutron I, editor(s). Chapter 10: Addressing reporting biases. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 (updated June 2017). Cochrane, 2017. Available from www.training.cochrane.org/handbook.

Stiglmayr 2005

Stiglmayr CE, Grathwol T, Linehan MM, Ihorst G, Fahrenberg J, Bohus M. Aversive tension in patients with borderline personality disorder: a computer-based controlled field study. *Acta Psychiatrica Scandinavica* 2005;**111**(5):372-9. [DOI: 10.1111/j.1600-0447.2004.00466.x] [PMID: 15819731]

Stoffers 2015

Stoffers JM, Lieb K. Pharmacotherapy for borderline personality disorder--current evidence and recent trends. *Current Psychiatry Reports* 2015;**17**(1):534. [DOI: 10.1007/s11920-014-0534-0] [PMID: 25413640]

Stoffers-Winterling 2018

Stoffers-Winterling JM, Storebø OJ, Völm BA, Mattivi JT, Nielsen SS, Kielsholm ML, et al. Pharmacological interventions for people with borderline personality disorder. *Cochrane Database of Systematic Reviews* 2018, Issue 2. Art. No: CD012956. [DOI: 10.1002/14651858.CD012956]

Stoffers-Winterling 2020

Stoffers-Winterling J, Storebø OJ, Lieb K. Pharmacotherapy for borderline personality disorder: an update of published, unpublished and ongoing studies. *Current Psychiatry Reports* 2020;**22**(8):37. [DOI: 10.1007/s11920-020-01164-1] [PMCID: PMC7275094] [PMID: 32504127]

Stoffers-Winterling J 2018 [pers comm]

Stoffers-Winterling J. Cochrane Collaboration review - RCT of escitalopram in BPD. Email to: E Coccaro 13 August 2018.

Stone 1993

Stone MH. Long-term outcome in personality disorders. *British Journal of Psychiatry* 1993;**162**:299-313. [DOI: 10.1192/bjp.162.3.299] [PMID: 8453424]

Storebø 2014

Storebø OJ, Simonsen E. Is ADHD an early stage in the development of borderline personality disorder? *Nordic Journal of Psychiatry* 2014;**68**(5):289-95. [DOI: 10.3109/08039488.2013.841992] [PMID: 24117059]

Storebø 2018

Storebø¸ OJ, Stoffers-Winterling JM, Völlm BA, Kongerslev MT, Mattivi JT, Kielsholm ML, et al. Psychological therapies for people with borderline personality disorder. *Cochrane Database of Systematic Reviews* 2018, Issue 2. Art. No: CD012955. [DOI: 10.1002/14651858.CD012955]

Storebø 2020

Storebø OJ, Stoffers-Winterling JM, Völm BA, Kongerslev MT, Mattivi JT, Jørgensen MS, et al. Psychological therapies for people with borderline personality disorder. *Cochrane Database of Systematic Reviews* 2020, Issue 5. Art. No: CD012955. [DOI: 10.1002/14651858.CD012955.pub2] [PMCID: PMC7199382] [PMID: 32368793]

Ten Have 2016

Ten Have M, Verheul R, Kaasenbrood A, Van Dorsselaer S, Tuithof M, Kleinjan M, et al. Prevalence rates of borderline personality disorder symptoms: a study based on the Netherlands Mental Health Survey and Incidence Study-2. *BMC Psychiatry* 2016;**16**:249. [DOI: 10.1186/s12888-016-0939-x] [PMCID: PMC4949762] [PMID: 27435813]

Thomas 2021

Thomas J, Askie LM, Berlin JA, Elliott JH, Ghersi D, Simmonds M, Takwoingi Y, Tierney JF, Higgins HPT. Prospective approaches

to accumulating evidence.. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors(s). Cochrane 2021. Cochrane Handbook for Systematic Reviews of Interventions version 6.2. Vol. **Chapter 22**. Wiley. Available from: www.training.cochrane.org/handbook, Updated February 2021.

Thompson 2019

Thompson KN, Cavelti M, Chanen AM. Psychotic symptoms in adolescents with borderline personality disorder features. *Eur Child Adolesc Psychiatry* 2019;**28**(7):985-92. [PMID: 30511234]

Thorlund 2009

Thorlund K, Devereaux PJ, Wetterslev J, Guyatt G, Ioannidis JP, Thabane L, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analysis? *International Journal of Epidemiology* 2009;**38**(1):276-86. [DOI: 10.1093/ije/dyn179] [PMID: 18824467]

Tomko 2014

Tomko RL, Trull TJ, Wood PK, Sher KJ. Characteristics of borderline personality disorder in a community sample: comorbidity, treatment utilization, and general functioning. *Journal of Personality Disorders* 2014;**28**(5):734-50. [DOI: 10.1521/pedi_2012_26_093] [PMCID: PMC3864176] [PMID: 25248122]

Torgersen 2001

Torgersen S, Kringlen E, Cramer V. The prevalence of personality disorders in a community sample. *Archives of General Psychiatry* 2001;**58**(6):590–6. [DOI: 10.1001/archpsyc.58.6.590] [PMID: 11386989]

Torgersen 2012

Torgersen S. Epidemiology. In: Widiger TA, editors(s). The Oxford Handbook of Personality Disorders. New York (NY): Oxford University Press, 2012:186-205. [DOI: 10.1093/oxfordhb/9780199735013.013.0009] [ISBN: 978-0-19-973501-3]

Trull 2010

Trull TJ, Jahng S, Tomko RL, Wood PK, Sher KJ. Revised NESARC personality disorder diagnoses: gender, prevalence, and comorbidity with substance dependence disorders. *Journal of Personality Disorders* 2010;**24**(4):412-26. [DOI: 10.1521/pedi.2010.24.4.412] [PMCID: PMC3771514] [PMID: 20695803]

Tyrer 2005

Tyrer P, Nur U, Crawford M, Karlsen S, McLean C, Rao B, et al. The Social Functioning Questionnaire: a rapid and robust measure of perceived functioning. *International Journal of Social Psychiatry* 2005;**51**(3):265-75. [PMID: 16252794]

Tyrer 2015

Tyrer P, Reed GM, Crawford MJ. Classification, assessment, prevalence, and effect of personality disorders. *Lancet* 2015;**385**(9969):717-26. [DOI: 10.1016/S0140-6736(14)61995-4]

Van Asselt 2007

Van Asselt AD, Dirksen CD, Arntz A, Severens JL. The cost of borderline personality disorder: societal cost of illness in BPD-patients. *European Psychiatry* 2007;**22**(6):354-61. [DOI: 10.1016/j.eurpsy.2007.04.001] [PMID: 17544636]

Vita 2011

Vita A, De Peri L, Sacchetti E. Antipsychotics, antidepressants, anticonvulsants, and placebo on the symptom dimensions of borderline personality disorder: a meta-analysis of randomized controlled and open-label trials. *Journal of Clinical Psychopharmacology* 2011;**31**(5):613-24. [DOI: 10.1097/JCP.0b013e31822c1636] [PMID: 21869691]

Wetterslev 2008

Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *Journal of Clinical Epidemiology* 2008;**61**(1):64-75. [DOI: 10.1016/j.jclinepi.2007.03.013] [PMID: 18083463]

Wetterslev 2009

Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Medical Research Methodology* 2009;**9**:86. [DOI: 10.1186/1471-2288-9-86.] [PMCID: PMC2809074] [PMID: 20042080]

WHO 1993

World Health Organisation. The ICD-10 Classification of Mental and Behavioral Disorders: Diagnostic Criteria for Research. Geneva (CH): World Health Organization, 1993.

WHO 2021

World Health Organisation. ICD-11 for Mortality and Morbidity Statistics (Version: 05/2021). icd.who.int/browse11/l-m/en (accessed 6 June 2021).

WHO Collaborating Center for Drug Statistics.

WHO Collaborating Center for Drug Statistics. ATC/DDD Index 2021. https://www.whocc.no/atc_ddd_index/ (accessed 03 December 2021).

Widiger 1993

Widiger TA, Trull TJ. Borderline and Narcissistic Personality Disorders. In: PB Sutker, HE Adams, editors(s). Comprehensive Handbook of Psychopathology. New York, NY: Plenum, 1993:371-94.

Widiger 1998

Widiger TA. Invited essay: Sex biasesin the diagnosis of personality disorders. *Journal of Personality Disorders* 1998;**12**(2):95-118.

Wood 2008

Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008;**336**(7644):601-5. [DOI: 10.1136/bmj.39465.451748.AD] [PMCID: PMC2267990] [PMID: 18316340]

Yen 2021

Yen S, Peters JR, Nishar S, Grilo CM, Sanislow CA, Shea MT, et al. Association of borderline personality disorder criteria with suicide attempts: findings from the Collaborative Longitudinal Study of Personality Disorders over 10 years of follow-up. *JAMA Psychiatry* 2021;**78**(2):187-94. [DOI: 10.1001/jamapsychiatry.2020.3598] [PMCID: PMC7675214] [PMID: 33206138]

Zanarini 1998

Zanarini MC, Frankenburg FR, DeLuca CJ, Hennen J, Khera GS, Gunderson JG. The pain of being borderline: dysphoric states specific to borderline personality disorder. *Harvard Review of Psychiatry* 1998;**6**(4):201-7. [DOI: 10.3109/10673229809000330] [PMID: 10370445]

Zanarini 2004a

Zanarini MC, Frankenburg FR, Hennen J, Silk KR. Mental health service utilization by borderline personality disorder patients and Axis II comparison subjects followed prospectively for 6 years. *Journal of Clinical Psychiatry* 2004;**65**(1):28-36. [DOI: 10.4088/jcp.v65n0105] [PMID: 14744165]

Zanarini 2004b

Zanarini MC, Frankenburg FR, Hennen J, Reich DB, Silk KR. Axis I comorbidity in patients with borderline personality disorder: 6-year follow-up and prediction of time to remission. *American Journal of Psychiatry* 2004;**161**(11):2108-14. [DOI: 10.1176/appi.ajp.161.11.2108] [PMID: 15514413]

Zanarini 2005

Zanarini MC, Frankenburg FR, Hennen J, Reich DB, Silk KR. The McLean Study of Adult Development (MSAD): overview and implications of the first six years of prospective follow-up. *Journal of Personality Disorders* 2005;**19**(5):505-23. [DOI: 10.1521/pedi.2005.19.5.505] [PMID: 16274279]

Zanarini 2010

Zanarini MC, Frankenburg FR, Reich DB, Fitzmaurice G. The 10-year course of psychosocial functioning among patients with borderline personality disorder and axis II comparison subjects. *Acta Psychiatrica Scandinavica* 2010;**122**(2):103-9. [DOI: 10.1111/j.1600-0447.2010.01543.x] [PMCID: PMC3876887] [PMID: 20199493]

Zanarini 2012

Zanarini MC, Frankenburg FR, Reich B, Fitzmaurice G. Attainment and stability of sustained symptomatic remission and recovery among patients with borderline personality disorder and axis II comparison subjects: a 16-year prospective follow-up study. *American Journal of Psychiatry* 2012;**169**(5):476-83. [DOI: 10.1176/appi.ajp.2011.11101550] [PMCID: PMC3509999] [PMID: 22737693]

Zanarini 2015

Zanarini MC, Frankenburg FR, Reich DB, Harned AL, Fitzmaurice GM. Rates of psychotropic medication use reported by borderline patients and axis II comparison subjects over 16 years of prospective follow-up. *Journal of Clinical Psychopharmacology* 2015;**35**(1):63-7. [DOI: 10.1097/JCP.0000000000000232] [PMCID: PMC4276426] [PMID: 25384261]

Zanarini 2018

Zanarini MC, Temes CM, Frankenburg FR, REich DB, Fitzmaurice GM. Description and prediction of time-to-attainment of excellent recovery for borderline patients followed prospectively for 20 years. *Psychiatry Research* 2018;**262**:40-45.

References to other published versions of this review

Binks 2006

Binks C, Fenton M, McCarthy L, Lee T, Adams CE, Duggan C. Pharmacological interventions for people with borderline personality disorder. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No: CD005653. [DOI: 10.1002/14651858.CD005653] [PMID: 16437535]

Stoffers 2010

Stoffers J, Völlm BA, Rücker G, Timmer A, Huband N, Lieb K. Pharmacological interventions for borderline personality disorder. *Cochrane Database of Systematic Reviews* 2010, Issue 6. Art. No: CD005653. [DOI: 10.1002/14651858.CD005653.pub2] [PMCID: PMC4169794] [PMID: 20556762]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Amminger 2013

Study characteristics	
Methods	12-week trial with 2 arms: 1. concentrated fish oil (long-chain omega-3 polyunsaturated fatty acids) 2. placebo **Duration of trial**: 12 weeks **Country:** Austria

Amminger 2013 *(Continued)*

	Setting: outpatient
Participants	**Method of recruitment of participants:** "All patients were consecutive referrals to a psychosis detection unit at the Department of Child and Adolescent Psychiatry, Medical University of Vienna between May 2004 and May 2006" (Amminger 2013, p. 404) **Overall sample size:** 15 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** no structured interview used, consensus **Mean age:** 16.2 years (SD 2.1; range = 13-25) **Sex:** 93.33% women **Comorbidity:** no information **Inclusion criteria** 1. Aged 13 to 25 2. 1 or more of 3 groups of risk factors for psychotics 3. BPD **Exclusion criteria** 1. History of psychotic or manic episode 2. Acute suicidal or aggressive behaviour 3. Dependency on morphine, cocaine and amphetamine, but not cannabis 4. Previous treatment with an antipsychotic or mood-stabilising agent 5. Having taken omega-3 supplements within 8 weeks of being included in the trial
Interventions	**Experimental group** **Treatment name:** concentrated fish oil (long-chain omega-3 polyunsaturated fatty acids) **Number randomised to group:** 8 **Duration:** 12 weeks **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 7 **Duration:** 12 weeks **Both groups** **Concomitant psychotherapy:** "All patients were offered 7 sessions of needs-based psychological and psychosocial interventions, concurrently with the research follow-up interviews at baseline, 1, 2, 3, 4, 8, and 12 weeks" (Amminger 2013, p. 405) **Concomitant pharmacotherapy:** Antidepressants and benzodiazepines were allowed. **Proportions of participants taking standing medication during trial observation period:** antidepressants = 25% of treatment group, 14.3% of placebo group; benzodiazepines = 12.5% of treatment group, 14.3% of placebo group
Outcomes	**Primary outcomes** 1. BPD severity, measured by PANSS items of suspiciousness, tension and poor impulse control. Assessed at baseline and at 12 weeks (EOT) 2. Mental health status (functioning), measured by GAF. Assessed at baseline and at 12 weeks (EOT) **Secondary outcomes** 1. Impulsivity, measured by PANSS subscale. Assessed at baseline and at 12 weeks (EOT) 2. Interpersonal problems, measured Tension subscale of PANSS. Assessed at baseline and at 12 weeks (EOT)

Amminger 2013 *(Continued)*

3. Depression, measured by MADRS and PANSS subscale. Assessed at baseline and at 12 weeks (EOT)
4. Attrition – no attrition; post hoc subgroup analysis
5. Adverse effects, measured by 'udvalg for kliniske undersogelser' (UKU) side effect scale; no data on this post hoc. Assessed at baseline and at 12 weeks (EOT)

Notes	**Sample size calculation:** no information **Ethics approval:** yes **Funding source:** funded by grants from universities, authorities or research foundations **Conflicts of interest:** No conflicts of interest reported. **Comments from trial authors (limitations)** 1. "A secondary analysis was conducted within a trial of indicated prevention of psychosis" (p. 404). 2. The number of participants was small. 3. All but one participant were females.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "A computer-generated random sequence based on a block randomized design (2 strata with block size of 4 within each stratum) was kept in a remote secure location and administered by an independent third party until all study data were collected and verified. Participants, parents, and those involved in administering interventions, assessing outcomes, data entry, and/or data analyses were blind to group assignments." (Amminger 2010, p. 148)
Allocation concealment (selection bias)	Low risk	**Quote:** “was kept in a remote secure location and administered by an independent third party until all study data were collected and verified” (Amminger 2010, p. 148)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** “Placebo capsules were carefully matched in appearance and flavour with the active treatment; they also contained the same amount of vitamin E as the n-3 capsules, and 1% fish oil to mimic taste” (Amminger 2013, p. 405).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** “Participants, parents, and those involved in administering interventions, assessing outcomes, data entry and/or data analyses were blind to the group assignments” (Amminger 2010, p. 148). **Comment:** The intervention treatment was not associated with specific adverse effects that would allow for singling out participants with active treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Quote:** "All analyses were performed on an intent-to-treat basis" (Amminger 2010, p. 149).
Selective reporting (reporting bias)	High risk	**Comment:** NCT00396643 - The protocol had lipid metabolism as a secondary outcome but this was not mentioned in Amminger 2010 or Amminger 2013. No outcome on adverse effects included in the post hoc analysis
Vested Interest (funding and/or author affiliations)	Low risk	**Comment:** grant from the Stanley Medical Research Institute; grant from the National Health and Medical Research Council Australia; career development fellowship. All authors reported no biomedical financial interest or potential conflicts of interest.

Amminger 2013 *(Continued)*

Other bias	Low risk	**Comment:** no indication of other bias

AstraZeneca 2007

Study characteristics	
Methods	8-week trial with 2 arms: 1. quetiapine fumarate 2. placebo **Duration of trial:** 8 weeks + 10 weeks follow-up **Country:** The Netherlands **Setting:** no information
Participants	**Methods of recruitment of patients:** no information **Overall sample size:** 24 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** SCID-II **Mean age:** no information **Sex:** no information **Comorbidity:** no information **Inclusion criteria** 1. BPD according to DSM-IV, including criterion 9: transient, stress-related paranoid ideation or severe dissociative symptoms 2. Aged 18-55 years 3. In- or outpatients **Exclusion criteria** 1. Depressive disorder 2. Bipolar disorder 3. Schizoaffective disorder/schizophrenia/delusional disorder/schizotypal personality disorder 4. Alcohol or substance dependence 5. quetiapine doses > 100 mg od use in the past 6. History of trauma capitis 7. Visual and auditive disorders 8. Neurological disorders (epilepsy) 9. Pregnancy 10. No adequate contraception 11. History of cardial complaints/cardiological disorder 12. Known sensitivity for quetiapine
Interventions	**Experimental group** **Treatment name:** quetiapine fumarate **Number randomised to group:** 13 **Duration:** 8 weeks

AstraZeneca 2007 *(Continued)*

	Control/comparison group **Comparison name:** placebo **Number randomised to group:** 11 **Duration:** 8 weeks **Both groups** **Concomitant psychotherapy:** no information **Concomitant pharmacotherapy:** not allowed, except for SSRIs and benzodiazepines, with doses stabilised 8 weeks before start of trial period **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary outcomes:** none **Secondary outcomes** 1. Dissociation and psychotic-like symptoms, measured by the BPRS, PANSS and the Dissociation Questionnaire (DIS-Q). Assessed at baseline and at 1, 2, 4, 6 and 8 weeks 2. Attrition, measured in terms of patients lost after randomisation in each group
Notes	**Sample size calculation:** no information **Ethic approval:** no information **Funding source:** funded or partially funded by pharmaceutical industry **Conflicts of interest:** The trial director is affiliated with AstraZeneca who produces the medication tested. **Comments from review authors (limitations)** 1. Small sample, underpowered 2. Key trial dates are a considerable duration of time apart

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** no information
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** Trial registration stated that the study had triple blinding (participant, care provider and investigator), however, there was no information on how the blinding was secured or if it was adequately maintained throughout the study to permit a judgement of low or high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** Trial registration stated that the study had triple blinding (participant, care provider and investigator), however, there was no information on how the blinding was secured or if it was adequately maintained throughout the study to permit a judgement of low or high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** dropout 5/13 in experimental intervention and 3/11 in placebo group. No information on reasons for dropout or imputation method

AstraZeneca 2007 *(Continued)*

Selective reporting (reporting bias)	High risk	**Comment:** The protocol mentioned psychotic-like symptoms and severity of psychiatric symptoms + mood, anger, impulsiveness, hostility and anxiety in patients with BPD. Only psychotic and dissociative symptoms were reported.
Vested Interest (funding and/or author affiliations)	High risk	**Comment:** Trial director is from AstraZeneca and the medication tested is from AstraZeneca.
Other bias	Low risk	**Comment:** no indication of other bias

Bellino 2014

Study characteristics	
Methods	12-week trial with 2 arms: 1. EPA (1.2 g/day) and DHA (0.8 g/day), in combination with the same dose of valproic acid 2. valproic acid (at a dose corresponding to a plasma level of 50–100 µg/mL) **Duration of trial:** 12 weeks + 24 weeks follow-up **Country:** Italy **Setting:** outpatient
Participants	**Methods of recruitment of patients:** patients with BPD attending the conducting clinic **Overall sample size:** 43 **Diagnosis of borderline personality disorder:** DSM-IV-TR **Means of assessment:** clinical expert; SCID-I and SCID-II **Mean age:** 25.2 years (SD 6.4; range = no information) **Sex:** 76.47% women **Comorbidity:** no comorbid axis I or II disorders **Inclusion criteria** 1. Aged 18 to 50 years 2. Diagnosis of BPD based on DSM-IV-TR **Exclusion criteria** 1. Diagnosis of dementia or other cognitive disorders 2. Schizophrenia or other psychotic disorders 3. Diagnosis of bipolar disorders 4. Co-occurring major depressive episode and/or substance abuse disorder 5. Administration of psychotropic medications and/or psychotherapy in the 2 months preceding the beginning of the trial
Interventions	**Experimental group** **Treatment name:** omega-3 fatty acids: eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) + valproic acid **Number randomised to group:** 23 **Duration:** 12 weeks **Control/comparison group**

Bellino 2014 *(Continued)*

Comparison name: valproic acid
Number randomised to group: 20
Duration: 12 weeks

Both groups
Concomitant psychotherapy: not allowed
Concomitant pharmacotherapy: not allowed
Proportions of participants taking standing medication during trial observation period: none

Outcomes

Primary outcomes

1. BPD severity, measured by the BPDSI. Assessed at baseline and at 12 weeks (EOT)
2. Self-harm, measured by SHI. Assessed at baseline and at 12 weeks (EOT)
3. Suicide-related outcomes, measured by BPDSI subscale. Assessed at baseline and at 12 weeks (EOT)
4. Mental health status (functioning), measured by CGI-S. Assessed at baseline and at 12 weeks (EOT)

Secondary outcomes

1. Anger, measured by MOAS and BPDSI subscale. Assessed at baseline and at 12 weeks (EOT)
2. Affective instability, measured by BPDSI subscale. Assessed at baseline and at 12 weeks (EOT)
3. Chronic feelings of emptiness, measured by subscales of Zan-BPD, CGI-BPD or BPDSI-IV Rating and BPDSI subscale. Assessed at baseline and at 12 weeks (EOT)
4. Impulsivity, measured by BIS and BPDSI subscale. Assessed at baseline and at 12 weeks (EOT)
5. Interpersonal problems, measured by BPDSI subscale. Assessed at baseline and at 12 weeks (EOT)
6. Abandonment, measured by BPDSI subscale. Assessed at baseline and at 12 weeks (EOT)
7. Identity disturbance, measured by BPDSI subscale. Assessed at baseline and at 12 weeks (EOT)
8. Dissociation and psychotic-like symptoms, measured by BPDSI subscale. Assessed at baseline and at 12 weeks (EOT)
9. Depression, measured by HAM-D. Assessed at baseline and at 12 weeks (EOT)
10. Attrition, measured in terms of participants lost after randomisation in each group
11. Adverse effects, measured by Dosage Record and Treatment Emergent Symptom Scale (DOTES)

Notes

Sample calculation: no information

Ethics approval: yes

Funding source: no funding received

Conflicts of interest: No conflicts of interests reported

Comments from trial authors (limitations): "The present study suffers from some limitations that should be considered: (a) the small sample size; (b) the lack of a placebo controlled group; and (c) the exclusion of patients with an Axis I co-diagnosis" (Bellino 2014, p. 131).

Comments from review authors: supplemental information received through personal email correspondence with the authors in January 2019 (Bellino 2019 [pers comm])

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** ”Research Randomizer (Urbaniak and Plous, Social Psychology Network Wesleyan University, Middletown, CT), a free web-based service for randomization” (Bellino 2019 [pers comm])
Allocation concealment (selection bias)	High risk	**Quote:** ”Allocation was not concealed as the study was not blind” (Bellino 2019 [pers comm]).

Bellino 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	**Quote:** ”(...) the study was not blind” (Bellino 2019 [pers comm]).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "In this study, assessment was performed by an investigator who received a training session on psychometric instruments, prior to starting the investigation" (Bellino 2014, p. 127). **Quote:** ”Only the investigator who performed patients' assessment was blind to the treatment they received” (Bellino 2019 [pers comm]).
Incomplete outcome data (attrition bias) All outcomes	High risk	**Quote:** "We had a rather high rate of dropouts (almost 20%) in our study" (Bellino 2014 p. 130). **Quote:** "We used statistical analysis to evaluate patients completing the 12-week trial" (Bellino 2014 p. 127). **Comment:** High dropout rate. Efficacy analysis on completers only
Selective reporting (reporting bias)	Low risk	**Comment:** no deviations from protocol
Vested Interest (funding and/or author affiliations)	Low risk	**Comment:** The author declared that there was no conflict of interest.
Other bias	Low risk	**Comment:** no indication of other bias

Black 2014

Study characteristics	
Methods	8-week trial with 3 arms: 1. moderate-dosage quetiapine 2. low-dosage quetiapine 3. placebo **Duration of trial:** 8 weeks **Country:** USA **Setting:** outpatient
Participants	**Methods of recruitment of patients:** referral, advertisements and word of mouth **Overall sample size:** 95 **Diagnosis of borderline personality disorder:** DSM (no information on version) **Means of assessment:** SCID (no information on version) **Mean age:** 29.5 years (SD no information; range = 18-45) **Sex:** 70.53% women **Comorbidity:** mood disorders, anxiety disorders, substance abuse, axis I disorders **Inclusion criteria**

Black 2014 *(Continued)*

1. Aged 18–45 years, with moodiness, impulsivity, distrustfulness and difficult relationships
2. Diagnosis of BPD based on DSM-IV
3. Participants had to meet Revised Diagnostic Interview for Borderlines criteria for borderline personality disorder
4. Required to have a total score ≥ 9 on the Zan-BPD at visit 2

Exclusion criteria

1. Ever having met criteria for a psychotic disorder
2. Primary neurological condition or cognitive impairment
3. Current substance dependence or recent opiate abuse
4. Amphetamine, barbiturates, cocaine or hallucinogens
5. Medically unstable
6. History of lack of response to atypical antipsychotics
7. Pregnancy or lactation
8. Acute suicidality

Interventions	**Experimental group** **Treatment name:** quetiapine 300 mg/day (moderate dosage) **Number randomised to group:** 33 **Duration:** 8 weeks **Comparison group** **Comparison name:** quetiapine 150 mg/day (low dosage) **Number randomised to group:** 33 **Duration:** 8 weeks **Control group** **Control name:** placebo **Number randomised to group:** 29 **Duration:** 8 weeks **All groups** **Concomitant psychotherapy:** Participants entering the trial could not begin any type of psychotherapy during the trial. **Concomitant pharmacotherapy:** No other psychotropic medication than benzodiazepines and anticholinergics was permitted. **Proportions of participants taking standing medication during trial observation period:** Only one participant (in the placebo group) took benzodiazepines during the trial.
Outcomes	**Primary outcomes** 1. BPD severity, measured by Zan-BPD. Assessed at baseline and once weekly for 8 weeks 2. Mental health status (functioning), measured by Zan-BPD. Assessed at baseline and once weekly for 8 weeks **Secondary outcomes** 1. Anger, measured by Zan-BPD. Assessed at baseline and once weekly for 8 weeks 2. Affective instability, measured by Zan-BPD. Assessed at baseline and once weekly for 8 weeks 3. Impulsivity, measured by Zan-BPD. Assessed at baseline and once weekly for 8 weeks 4. Interpersonal problems, measured by Zan-BPD. Assessed at baseline and once weekly for 8 weeks 5. Depression, measured by Zan-BPD. Assessed at baseline and once weekly for 8 weeks 6. Attrition 7. Adverse events. Spontaneous reporting
Notes	**Sample calculation**: yes **Ethics approval:** yes

Black 2014 *(Continued)*

Funding source: funded or partially funded by pharmaceutical industry

Conflicts of interest: Dr Schulz has served as a consultant to Eli Lilly, Forum, Genentech, and Teva.

Comments from trial authors (limitations)

1. "The non completion rate was 33%. While this rate is not unusual for trials of borderline personality disorder, investigators need to address the issue of attrition" (Black 2014, p. 1180).
2. "Stringent criteria excluded people with current major depression, post-traumatic stress disorder, panic disorder, obsessive-compulsive disorder, and substance dependence, to ensure a greater focus on changes in borderline symptoms rather than in comorbid disorders. For that reason, the results may not generalize to borderline patients with these disorders" (Black 2014, p. 1180).
3. "While quetiapine was effective in treating many symptoms of borderline personality disorder, its adverse effects must be taken into consideration. We believe the results should generalize to the use of immediate-release quetiapine because the active ingredient is identical to that in extended-release quetiapine" (Black 2014, p. 1180).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** insufficient information on how random sequence was generated to permit a judgement of low or high risk of bias
Allocation concealment (selection bias)	Unclear risk	**Comment**: Insufficient information on concealment of random sequence generation to permit a judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "Participants, site personnel, and investigators were blind to treatment group assignment." **Quote**: "To preserve blinding, all participants received one bottle of 150 mg quetiapine (or placebo) tablets initially, and then after 4 weeks received two bottles; the second bottle contained either 150 mg quetiapine tablets (for the moderate-dosage group) or placebo tablets (for the low-dosage and placebo groups)."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote:** "Participants, site personnel, and investigators were blind to treatment group assignment." **Comment:** The article provided inadequate information on who assessed the outcomes and whether blinding was maintained to permit a judgement of low or high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** Dropout was 33%. ITT analysis was performed. Adverse events predicted dropout.
Selective reporting (reporting bias)	High risk	**Comment:** All outcomes from 1-9 were defined beforehand as primary outcomes. However, in the trial, only Zan-BPD was stated as the primary outcome.
Vested Interest (funding and/or author affiliations)	High risk	**Quote:** “Supported by a grant from AstraZeneca to Dr. Schulz, with subcontracts to Drs. Black and Zanarini**”** (Black 2014, p. 1181).
Other bias	Low risk	**Comment:** no indication of other bias

Bogenschutz 2004

Study characteristics	
Methods	12-week trial with 2 arms: 1. olanzapine (2.5-20 mg/d), most 5-10 mg/d, mean at endpoint 6.9 mg/d (SD 3.2) 2. placebo **Duration of trial:** 12 weeks (patients had to be free of mood stabilisers, antipsychotics, benzodiazepines, and antidepressants for at least 2 weeks prior to participation) **Country:** no information **Setting:** outpatient
Participants	**Methods of recruitment of patients:** Patients were recruited from the community and from outpatient clinics at a university psychiatric hospital. **Overall sample size:** 40 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** SCID-II **Mean age:** 32.6 years (SD 10.3; range = 18-54) **Sex:** 62.50% women **Comorbidity:** "Patients met criteria for a mean of 2.9 SCID-II personality disorders (including BPD) and a mean of 2.2 Axis I diagnoses from the MINI" (Bogenschutz 2004, p. 106). **Inclusion criteria:** no information **Exclusion criteria** 1. Schizophrenia 2. Schizoaffective disorder 3. Bipolar affective disorder 4. Current major depressive episode 5. Psychotic disorder due to substance or general medical condition 6. Substance dependence not in full or partial remission 7. Suicide attempts in past 6 months 8. Having current suicidal intent or definite plan 9. Pregnancy 10. Neurologic impairment
Interventions	**Experimental group** **Treatment name:** olanzapine **Number randomised to group:** 20 **Duration:** no information **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 20 **Duration:** no information **Both groups** **Concomitant psychotherapy:** "Patients were allowed to continue ongoing psychotherapy (if initiated more than 3 months prior to randomisation)" (Bogenschutz 2004, p. 105). **Concomitant pharmacotherapy:** medication for stable, chronic medical conditions such as hypertension

Bogenschutz 2004 *(Continued)*

	Proportions of participants taking standing medication during trial observation period: no information
Outcomes	**Primary outcomes** 1. Suicidal ideation, measured by CGI-BPD-recurrent suicidal ideation. Assessed at baseline and at 2, 4, 8 and 12 weeks (EOT) 2. Mental health status (functioning), measured by CGI. Assessed at baseline and at 2, 4, 8 and 12 weeks (EOT) **Secondary outcomes** 1. Anger, measured by CGI-BPD (inappropriate anger) and AIAQ. Assessed at baseline and at 2, 4, 8 and 12 weeks (EOT) 2. Affective instability measured by CGI-BPD (affective instability). Assessed at baseline and at 2, 4, 8 and 12 weeks (EOT) 3. Feelings of emptiness, measured by CGI-BPD (chronic feelings of emptiness). Assessed at baseline and at 2, 4, 8 and 12 weeks (EOT) 4. Impulsivity, measured by CGI-BPD (impulsivity) and OAS-M (aggression). Assessed at baseline and at 2, 4, 8 and 12 weeks (EOT) 5. Interpersonal problems, measured by CGI-BPD (unstable interpersonal relationship). Assessed at baseline and at 2, 4, 8 and 12 weeks (EOT) 6. Avoidance of abandonment, measured by CGI-BPD (abandonment). Assessed at baseline and at 2, 4, 8 and 12 weeks (EOT) 7. Identity disturbance, measured by CGI-BPD (identity disturbance). Assessed at baseline and at 2, 4, 8 and 12 weeks (EOT) 8. Dissociative symptoms, measured by CGI-BPD (transient paranoia or dissociation). Assessed at baseline and at 2, 4, 8 and 12 weeks (EOT) 9. Attrition 10. Adverse effects, measured by weight. Recorded at each visit
Notes	**Sample calculation**: no information **Ethics approval:** no information **Funding source:** funded or partially funded by pharmaceutical industry **Conflicts of interest:** No other conflicts of interest were reported besides funding from the pharmaceutical industry. **Comments from trial authors (limitations)** 1. Based on the relatively small sample size and the large variance for the scales (OAS-M, ASI, AIMS, Simson-Angus Scale), the trial may not have had adequate power to consistently detect differences on these scales. 2. There was a discrepancy between the SCL-90 scores in this trial and a previous trial. There was no clear explanation for this; however, it could be due to demographic factors. This trial sample included men, was more ethnically diverse and possibly lower in socioeconomic status and education than the sample in the referred previous trial (Zanarini 2001).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** The article referred to the trial as being randomised, however inadequate information on random sequence generation was provided to permit a judgement of low or high risk of bias.

Bogenschutz 2004 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	**Comment:** no information on allocation concealment to permit a judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote**: "double-blind trial", "pseudo-dose [...] for patients receiving placebo" (Bogenschutz 2004, p. 105).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** The article referred to the trial being double-blind, however, there was insufficient information on how blinding of outcome assessors was carried out and maintained to permit a judgement of low or high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** "evaluable patients" refers to all patients remaining at least 2 weeks in the study, i.e. who attended both baseline and preliminary assessment after two weeks; reasons for early termination specified (Bogenschutz 2004, p. 106). However, 2 patients dropped out of the olanzapine group due to "violation of protocol" (Bogenschutz 2004, p. 106). Of the 40 patients enrolled, 23 completed the full 12 weeks of the trial (10 in olanzapine group, 13 in placebo group). Reasons for early termination: Lost to follow-up: 2 in the olanzapine group, 5 in the placebo group Lack of efficacy: 2/2 Weight gain: 2/0 Sedation: 2/0 Violation of protocol: 2/0 Continuous data based on LOCF of patients remaining at least 2 weeks in the trial Dichotomous data based on ITT sample
Selective reporting (reporting bias)	Unclear risk	**Comment:** No protocol available
Vested Interest (funding and/or author affiliations)	High risk	**Quote:** "Supported by a grant from Eli Lilly and Co, Indianalpolis, Ind." (Bogenschutz 2004, p. 104)
Other bias	Low risk	**Comment:** No other apparent sources of bias were found.

Bozzatello 2017

Study characteristics	
Methods	51 participants; 12-week open-label trial with 2 arms: 1. asenapine 2. olanzapine **Duration of trial**: 12 weeks **Country:** Italy **Setting:** outpatient
Participants	**Methods of recruitment of patients:** "Patients attended the Centre for Personality Disorders of the Psychiatric Clinic, Department of Neuroscience, University of Turin, Italy." (Bozzatello 2017, p. 6) **Overall sample size:** 51

Bozzatello 2017 *(Continued)*

Diagnosis of borderline personality disorder: DSM-V

Means of assessment: SCID-I and SCID-II

Mean age: 24.7 years (SD 5.3; range = no information)

Sex: 62.5% women

Comorbidity: no information

Inclusion criteria

1. Age 18-50 years
2. Diagnosis of BPD based on DSM-5 criteria

Exclusion criteria

1. A diagnosis of dementia or other cognitive disorders, schizophrenia or other psychotic disorders, or bipolar disorders
2. Co-occurring major depressive episode or substance abuse (or both)
3. Administration of psychotropic medications or psychotherapy (or both) in the two months preceding the beginning of the trial
4. Female patients who did not use an adequate birth control

Interventions	**Experimental group** **Treatment name:** asenapine 5-10 mg/day (dose range = 5-10 mg/day) **Number randomised to group:** 25 **Duration:** 12 weeks **Control/comparison group** **Comparison name:** olanzapine 5-10 mg/day **Number randomised to group:** 26 **Duration:** 12 weeks **Both groups** **Concomitant psychotherapy:** Psychotherapy was not allowed during the trial (exclusion criterion). **Concomitant pharmacotherapy:** Psychothropics were not allowed during the trial (exclusion criterion). **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary outcomes** 1. BPD severity, measured by the BPDSI 2. Self-harm, measured by SHI and the BPDSI subscale 'Parasuicidal behaviour'. Assessed at baseline and at 12 weeks (EOT) 3. Mental health status (psychosocial functioning), measured by the Social Occupational Functioning Assessment Scale (SOFAS) and CGI-S. Assessed at baseline and at 12 weeks (EOT) **Secondary outcomes** 1. Anger, assessed by MOAS and BPDSI subscale 'outbursts of anger'. Assessed at baseline and at 12 weeks (EOT) 2. Affective instability, assessed by BPDSI subscale 'affective instability'. Assessed at baseline and at 12 weeks (EOT) 3. Chronic feelings of emptiness, assessed by BPDSI subscale 'emptiness'. Assessed at baseline and at 12 weeks (EOT) 4. Impulsivity, assessed by BIS and BPDSI subscale 'impulsivity'. Assessed at baseline and at 12 weeks (EOT) 5. Interpersonal problems, assessed by BPDSI subscale 'interpersonal relationships'. Assessed at baseline and at 12 weeks (EOT)

Bozzatello 2017 *(Continued)*

6. Abandonment, assessed by BPDSI subscale 'abandonment'. Assessed at baseline and at 12 weeks (EOT)
7. Identity disturbance, assessed by BPDSI subscale 'identity'. Assessed at baseline and at 12 weeks (EOT)
8. Dissociation and psychotic-like symptoms, assessed by BPDSI subscale 'Dissociation/paranoid ideation'. Assessed at baseline and at 12 weeks (EOT)
9. Depression, assessed by Ham-D. Assessed at baseline and at 12 weeks (EOT)
10. Attrition, assessed by number of patients lost after randomisation in each group
11. Adverse effects, measured by Dosage Record and Treatment Emergent Symptoms Scale (DOTES). Assessed at baseline and at 12 weeks (EOT)

Notes

Sample calculation: no information. Post hoc power calculations were performed.

Ethics approval: yes, "Approval was obtained from the ethics committee of the University Hospital "Città della Salute e della Scienza – Ospedale dell'Ordine Mauriziano" of Turin." (Bozzatello 2017, p. 811)

Funding source: no funding received

Conflicts of interest: No conflicts of interests were reported.

Comments from trial authors (limitations)

1. "The open label study design, lack of a placebo group, and small sample size constituted major limitations of this trial." (Bozzatello 2017, p. 16)
2. "Another limitation was that the study was not powered to detect a difference between the drugs on the dissociation/paranoid ideation item of the BPDSI." (Bozzatello 2017, p. 16)

Comments from review authors: dropouts due to "lack of compliance" (Bozzatello 2017, p. 809), i.e. n = 4 in asenapine group and n = 3 in olanzapine group; this introduces risk of bias. Unclear how "lack of compliance" was defined

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Research Randomizer (Urbaniak and Plous, Social Psychology Network Wesleyan University, Middletown, CT), a free web-based service for randomization, was used". (Bozzatello 2017, p. 811)
Allocation concealment (selection bias)	High risk	**Comment:** no mention of allocation concealment. Unlikely that sequence generation was concealed due to open-label design
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Comment:** open-label trial. Participants and personnel were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	**Comment:** open-label trial. Outcome assessor was not blinded. **Quote:** "Assessment was performed by an investigator (P.B.) who had received a training session on psychometric instruments prior to the study." (Bozzatello 2017, p. 812)
Incomplete outcome data (attrition bias) All outcomes	High risk	**Quote:** "Statistical analysis were performed both in the group of patients who completed the trial and in the whole group of patients who were randomized including drop-outs. In the second group, intention to treat (ITT) analysis was performed with the last observation carried forward (LOCF)." (Bozzatello 2017, p. 812)

Bozzatello 2017 *(Continued)*

		Quote: “The ITT-LOCF analysis was performed on the entire sample of 51 patients recruited." (Bozzatello 2017, p. 812) **Quote:** “We had a rather high drop-out rate in our study (21.7%) […] intention to treat analysis with last observation carried forward was performed to analyze data in the whole group of patients who entered the trial, and the significant effects of the two drugs found with the ANOVA were the same obtained in the group of completers.” (Bozzatello 2017, p. 817) **Quote:** "Drop-outs due to “lack of compliance” " (Bozzatello 2017, p. 809), i.e. n = 4 in asenapine group and n = 3 in olanzapine group; this introduces risk of bias. Unclear how “lack of compliance” was defined
Selective reporting (reporting bias)	Low risk	**Comment:** reporting according to protocol
Vested Interest (funding and/or author affiliations)	Low risk	**Quote:** “This research received no sources of funding to assist with conducting the study and preparing the manuscript”. (Bozzatello 2017, p. 817)
Other bias	Low risk	**Comment:** no apparent other biases detected

Cowdry 1988

Study characteristics	
Methods	A 6-week trial with 5 arms: 1. Placebo 2. Alprazolam 3. Carbamazepine 4. Trifluoperazine hydrochloride 5. Tranylcypromine sulfate **Duration of trial:** 6 weeks x 5 **Country:** USA **Setting:** outpatient
Participants	**Methods of recruitment of patients:** referral by private psychotherapist **Overall sample size:** 16 **Diagnosis of borderline personality disorder:** DSM-III **Means of assessment:** DIB **Mean age:** 31.6 years (range = 23-42) **Sex:** 100% women **Comorbidity:** other DSM-III Axis II diagnoses: dependent personality = 15 (94%); avoidant personality = 13 (81%), histrionic personality = 10 (63%), schizotypal personality = 6 (37%), narcissistic personality = 3 (19%), paranoid personality = 2 (12%); DSM-III Axis I affective disorder diagnoses of previous episodes: atypical bipolar disorder = 1 (6%), major depressive episode with melancholia = 4 (25%), major depressive episode without melancholia = 3 (19%), dysthymic disorder only = 5 (31%) **Inclusion criteria** 1. Met at least five of the eight DSM-III criteria for BPD

Cowdry 1988 *(Continued)*

2. Had a score of at least 7 of 10 on Gunderson's DIB203
3. Had a history of extensive behavioural dyscontrol, such as multiple overdoses, self-mutilation (wrist cuts or cigarette burns), or physical violence
4. Met Liebowitz and Klein's 14 criteria for hysteroid (rejection-sensitive) dysphoria
5. Had a duration of illness of at least two years since age 18 years
6. Had no current DSM-III diagnosis of schizophrenia, major affective disorder, alcoholism, or substance abuse
7. Had no serious cardiovascular, renal, hepatic, or neurological disorder
8. Were able to be medication-free for at least two weeks before the baseline biomedical studies
9. Had a firm commitment to remain in psychotherapy with the referring professional for the duration of the study
10. Were willing to use a satisfactory method of birth control during the medication trial

Exclusion criteria: none mentioned

Interventions	**Experimental group** **Treatment name:** alprazolam **Number randomised to group:** 16 **Duration:** 6 weeks (a two-week dosage adjustment period, four weeks of constant dosage, a week of tapering the medication, and at least one medication-free week before beginning the next drug trial (intervention)) **Experimental group** **Treatment name:** carbamazepine **Number randomised to group:** 16 **Duration:** 6 weeks (a two-week dosage adjustment period, four weeks of constant dosage, a week of tapering the medication, and at least one medication-free week before beginning the next drug trial (intervention)) **Experimental group** **Treatment name:** trifluoperazine hydrochloride **Number randomised to group:** 16 **Duration:** 6 weeks (a two-week dosage adjustment period, four weeks of constant dosage, a week of tapering the medication, and at least one medication-free week before beginning the next drug trial (intervention)) **Experimental group** **Treatment name:** tranylcypromine sulfate **Number randomised to group:** 16 **Duration:** 6 weeks (a two-week dosage adjustment period, four weeks of constant dosage, a week of tapering the medication, and at least one medication-free week before beginning the next drug trial (intervention)) **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 16 **Duration:** 6 weeks (a two-week dosage adjustment period, four weeks of constant dosage, a week of tapering the medication, and at least one medication-free week before beginning the next drug trial (intervention)) **Both groups** **Concomitant psychotherapy:** no information **Concomitant pharmacotherapy:** no information **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary** 1. BPD severity measured, “At the end of each trial, we obtained ratings of clinical change on seven point scales similar in concept to the Clinical Global Improvement scale, on which the patient or physi-

Cowdry 1988 *(Continued)*

cian was asked to rate change on each scale "compared to a usual month prior to the start of the study." (Cowdry 1988, p. 11). Assessed at time points: baseline and weekly until week 6 (EOT) for each medication trial

2. Suicide-related outcomes, assessed by an adapted CGI scale (see primary outcome 1). Assessed at time points: baseline and weekly until week 6 (EOT) for each medication trial

Secondary

1. Anger, assessed by either an adapted CGI scale (see primary outcome 1) or the modified Bunney-Hamburg rating scale. Assessed at time points: unclear from reporting
2. Impulsivity, assessed by an adapted CGI scale (see primary outcome 1). Assessed at time points: baseline and weekly until week 6 (EOT) for each medication trial
3. Depression, assessed by either an adapted CGI scale (see primary outcome 1) or the modified Bunney-Hamburg rating scale. Assessed at time points: unclear from reporting
4. Attrition in terms of patients lost after randomisation in each group (not included in the quantitative analysis due to unclear reporting)

Notes

Sample calculation: no information

Ethics approval: no information

Funding source: no information

Conflicts of interest: no information

Comments from trial authors (limitations): The number of patients was small, the medication trials were brief, and the outcome measures had to be adapted to the special needs of this population and therefore were not well validated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** The study was referred to as randomised; however, the method used to generate the allocation sequence was not described in sufficient detail to allow an assessment of whether it produced comparable groups.
Allocation concealment (selection bias)	Unclear risk	**Comment:** Allocation concealment and the method used to conceal the allocation sequence was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quotes:** "The laboratory results were examined by the non-blinded physician, and, regardless of whether the patient was actually receiving carbamazepine, a new "target dosage" was provided to the blinded physician, to be reached if side effects did not prevent dosage increases. During the final two randomized trials (trifluoperazine and tranylcypromine), the patient adhered to the MAOI diet; an initial target dosage of four capsules was established, adjusted by the blinded physician at the end of the first week (based largely on side effects), and thereafter was held constant unless major side effects necessitated a dosage decrease." (Cowdry 1988, p. 112)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** The article referred to the trial being double-blind, however, there was insufficient information on how blinding of outcome assessors was carried out and maintained to permit a judgement of low or high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** large attrition rates and carry-over effects (11 out of 16 participants dropped out). Patients who dropped out of one trial were unavailable for the following trials.
Selective reporting (reporting bias)	High risk	**Comments:** Several outcomes were not reported e.g. adverse events, which was mentioned to have been assessed by "a 36-item checklist during the fi-

Cowdry 1988 *(Continued)*

		nal week of each medication trial" (Cowdry 1988, p. 188, 113), spontaneous reporting of self-harm is not reported. Subscales of adapted CGI scale and modified Bunney-Hamburg scales were not reported. Unclear reporting of which scale was used for each outcome and at which time point each outcome was assessed.
Vested Interest (funding and/or author affiliations)	Unclear risk	**Comment:** insufficient information on funding and conflict of interest to permit judgement of high or low risk of bias
Other bias	Unclear risk	**Comment**: There was obvious carry-over effects despite washout periods between each medication trial.

Crawford 2018

Study characteristics	
Methods	52-weeks trial with 2 arms: 1. lamotrigine with usual care 2. inert placebo with usual care **Duration of trial:** 52 weeks **Country:** UK **Setting:** inpatient and outpatient
Participants	**Methods of recruitment of patients:** "Potential participants were initially approached about the trial by any healthcare professional who was involved in their care, providing that the consultant psychiatrist for the team had agreed in principle to patients under their care taking part in the study. If a psychiatrist or other healthcare professional had a patient under their care who they believed met the eligibility criteria, they then introduced the patient to the trial and provided them with an information sheet. When the patient provided verbal agreement to discuss their eligibility and possible enrolment into the trial with a member of the research team, a screening number was assigned and contact details passed on to the research team to discuss consent." (Crawford 2018, p. 6) **Overall sample size:** 276 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** IPDE and SCID-I **Mean age:** 36.1 years (SD 11.0; range = no information) **Sex:** 75.36% women **Comorbidity:** no information; however, patients with a coexisting diagnosis of bipolar, psychotic disorders were excluded. **Inclusion criteria** 1. Aged ≥ 18 years 2. Meet DSM-IV diagnostic criteria for BPD 3. Willingness and ability to provide written informed consent to take part in the trial **Exclusion criteria** 1. Coexisting diagnosis of bipolar affective disorder (type I and II) or psychotic disorder (schizophrenia, schizoaffective disorder or mood disorder with psychotic features)

Crawford 2018 *(Continued)*

2. Already being prescribed a mood stabiliser (lithium, carbamazepine or valproate) or had had one within the past 4 weeks
3. Known medical history of liver or kidney impairment
4. Cognitive or language difficulties preventing informed consent

Interventions	**Experimental group** **Treatment name:** lamotrigine + usual care **Number randomised to group:** 137 **Duration:** 52 weeks **Control/comparison group** **Comparison name:** inert placebo + usual care **Number randomised to group:** 139 **Duration:** 52 weeks **Both groups** **Concomitant psychotherapy:** no information **Concomitant pharmacotherapy:** no information. Patients were excluded if they already were prescribed a mood stabiliser within the past 4 weeks. Both groups received usual care. **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary outcomes** 1. BPD severity, measured by Zan-BPD. Assessed at baseline, 12, 24 and 52 weeks (EOT) 2. Self-harm, measured in terms of proportion of participants with self-harming behaviour and by the Deliberate Self-harm Inventory (DSHI) Assessed at baseline, 12, 24 and 52 weeks (EOT) 3. Suicide-related outcomes, measured by DSHI and in terms of proportion of participants committing suicide. Assessed at baseline, 12, 24 and 52 weeks (EOT) **Secondary outcomes** 1. Affective instability, measured by affective disturbance subscale of Zan-BPD; mean, SD, adjusted difference in mean (95% CI). Assessed at baseline, 12, 24 and 52 weeks (EOT) 2. Impulsivity, measured by impulsivity subscale of Zan-BPD. Assessed at baseline, 12, 24 and 52 weeks (EOT) 3. Interpersonal problems measured by disturbed relationship subscale of Zan-BPD and the Social Functioning Questionnaire (SFQ). Assessed at baseline, 12, 24 and 52 weeks (EOT) 4. Depression, measured by BDI. Assessed at baseline, 12, 24 and 52 weeks (EOT) 5. Attrition, measured in terms of patients lost after randomisation in each group 6. Adverse effects, measured by use of a pro forma designed to cover the possible effects listed in the British National Formulary entry for lamotrigine. Assessed at baseline, 12, 24 and 52 weeks (EOT)
Notes	**Sample calculation:** yes **Ethics approval:** "The trial was approved by the London-Central Research Ethics Committee (reference number 2/LO/1514)". (Crawford 2018, p. 12) **Funding source:** funded by grants from universities, authorities or research foundations **Conflicts of interest:** No conflicts of interest were reported. **Comments from trial authors (limitations):** "Levels of adherence in this pragmatic trial were low, but greater adherence was not associated with better mental health". (Crawford 2018, p. viii) **Comments from review authors:** Supplemental information regarding data received through personal email correspondence with the authors in November 2020 (Crawford 2020 [pers comm])

Risk of bias

Crawford 2018 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** ”Study participants were then randomised centrally by the Nottingham Clinical Trials Unit using a remote web-based system. We used permuted stacked blocks stratified by study centre, severity of personality disorder and extent of hypomanic symptoms. The block size was randomly assigned between 4 and 6.” (Crawford 2018, p. xx)
Allocation concealment (selection bias)	Low risk	**Quote:** "Site pharmacies were unblinded to trial arm allocation and were provided with a list of the randomisation codes and corresponding trial arm allocation for that site. The trial medication was produced with tear-off labels that identified it as being lamotrigine or placebo in a coded format, so that pharmacy staff could dispense the appropriate medication for a participant. Pharmacy procedures required that the tear-off label was removed during dispensing and added to trial documents for accountability. The need to maintain the blinding of researchers and other individuals at the site was made clear to those delegated to work on the trial within the pharmacy." (Crawford 2018 p. 5-6)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "The trial medication was produced with tear-off labels that identified it as being lamotrigine or placebo in a coded format, so that pharmacy staff could dispense the appropriate medication for a participant. Pharmacy procedures required that the tear-off label was removed during dispensing and added to trial documents for accountability. The need to maintain the blinding of researchers and other individuals at the site was made clear to those delegated to work on the trial within the pharmacy." (Crawford 2018 p. 5-6) **Quote:** “All patients, carers and referring psychiatrists were blinded to treatment assignment until the participant had left the trial or until 52 weeks post-randomisation (whichever was the longer).” (Crawford 2018, p. 5)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** “Blinding of investigators, researchers, the trial manager and the trial statistician was maintained until all data were entered, the database was locked and initial analyses of trial data were complete. The exception to this was for participants whose referring psychiatrist was also the principal investigator, in which case the allocation for that particular participant was revealed following the final assessment.” (Crawford 2018, p. 5)
Incomplete outcome data (attrition bias) All outcomes	High risk	**Quote:** ”The primary analysis was performed according to the intention-to-treat principle, without imputation of missing data.” (Crawford 2018, p. 4) "For the main analysis, complete-case analysis was used in which participants with missing data were excluded." (Crawford 2018, HTA-report, p. 10)
Selective reporting (reporting bias)	Low risk	**Comment:** The published protocol matched with the full report.
Vested Interest (funding and/or author affiliations)	Low risk	**Quote:** "Funding for this trial was provided by the Health Technology Assessment programme of the National Institute for Health Research (NIHR) and will be published in full in Health Technology Assessment ;Vol. 22, No. 17. See the NIHR Journals Library website for further project information. The Imperial Biomedical Research Centre Facility, which is funded by NIHR, also provided support that has contributed to the research results reported within this paper. Part of Richard Morris’ salary during the project was paid by NIHR Collaboration for Leadership in Applied Health Research and Care East Midlands". (Crawford 2018, p. viii)
Other bias	Low risk	**Comment:** no indication of other bias

De la Fuente 1994

Study characteristics	
Methods	32-day trial with 2 arms: 1. carbamazepine (CBZ) 2. placebo (PLC) **Duration of trial:** 32 days (after at least 10 days psychotropic drug washout, 15 days for TCAs and MAOIs; no patient had taken neuroleptics in the 2-month period before the trial) **Country:** Belgium **Setting:** inpatient
Participants	**Methods of recruitment of patients:** no information **Overall sample size:** 20 **Diagnosis of borderline personality disorder:** DSM-III-R **Means of assessment:** DIB **Mean age:** 32.7 years (SD = no information; range = 22-45) **Sex:** 70% women **Comorbidity:** no information **Inclusion criteria** 1. Fulfilling the DSM-III-R criteria for BPD 2. Score of at least 7 in the Gunderson and Kolb DIB **Exclusion criteria** 1. Standard physical or neurological examinations abnormal 2. Perturbed standard biological blood tests 3. Perturbed electrocardiogram 4. DSM-III-R axis I disturbances 5. Positive history for epilepsy or standard EEG traits of epilepsy 6. Antecedents of encephalitis or cranial trauma 7. Inability to stop alcohol or psychoactive substances 8. Suspected poor treatment compliance 9. Meeting the criteria for major depression on DSM-III-R (however, patients depressed for less than 2 weeks were not excluded)
Interventions	**Experimental group** **Treatment name:** carbamazepine **Number randomised to group:** 10 **Duration:** 32 days **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 10 **Duration:** 32 days **Both groups** **Concomitant psychotherapy:** Supportive atheoretical psychotherapy was administered to all patients.

De la Fuente 1994 *(Continued)*

	Concomitant pharmacotherapy: There was a 10-day psychotropic drug washout prior to the trial and a 15-day drug washout for TCAs and MAOIs. "No patient had taken neuroleptics in the 2-month period before the study." (De la Fuente 1994, p. 480) **Proportions of participants taking standing medication during trial observation period:** no further details
Outcomes	**Primary outcomes:** none **Secondary outcomes** 1. Anger, measured by SCL-90-HOS. Assessed at baseline, day 8 and day 32 (EOT) 2. Impulsivity, measured by Acting-out scale. Recorded with day-by-day events 3. Interpersonal problems, measured by SCL-90-INT. Assessed at baseline, day 8 and day 32 (EOT) 4. Psychotic symptoms, measured by BPRS, SCL-90-PSY and SCL-90-PAR. Assessed at baseline, day 8 and day 32 (EOT) 5. Depression, measured by HDRS-24. Assessed at baseline, day 8 and day 32 (EOT) 6. Attrition 7. Adverse effects, asked for by a non-blind clinician at baseline, day 8, day 16, and day 32 (EOT)
Notes	**Sample calculation:** no information **Ethics approval:** no information **Funding source:** unclear funding **Conflicts of interest:** No conflicts of interest were reported. **Comments from trial authors (limitations)** 1. "The number of BPD patients that achieved the CBZ treatment period was small (only eight for the whole study)." (De la Fuente 1994, p. 484) 2. "In the present work, CBZ was given only for 32 days. Maybe the positive trends observed in the CBZ group could have been significant with a more prolonged administration." (De la Fuente 1994, p. 484)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** Insufficient information on the method used for random sequence generation to permit a judgement of low or high risk of bias
Allocation concealment (selection bias)	Unclear risk	**Comment:** Insufficient information to permit judgement of high or low risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment**: Insufficient information on how blinding of patients was carried out and maintained to permit a judgement of low or high risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "The study was carried out by two clinicians. One of them [...] was blind to the drug treatment and performed all the clinical and psychometric assessments. [...] We instructed the patients to not communicate side effects to the blind clinician." (De la Fuente 1994, p. 480)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Quote:** "Of the 20 patients enrolled in the trial, we randomized 10 into the CBZ group and 10 received PLC. [...] Two patients receiving CBZ dropped out. [...] No patient on PLC dropped out." (De la Fuente 1994, p. 481) **Comment:** Reasons for early termination specified (De la Fuente 1994, p. 481):

De la Fuente 1994 *(Continued)*

		dramatic increase in frequency and intensity of aggression (against self and others): 2 in carbamazepine group, 0 in placebo group However, it remained unclear if the reported continuous outcomes were measured by LOCF analyses. We decided to use the same numbers of patients for which dichotomous outcomes were reported. For dichotomous outcomes, lacking numbers of patients were imputed as having the unfavourable results.
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol found
Vested Interest (funding and/or author affiliations)	Unclear risk	**Comment:** authors affiliated with Department of Psychiatry, Erasme Hospital, Free University, Brussels. No details about funding or sponsoring provided
Other bias	Low risk	**Comment:** No apparent other sources of bias found

Frankenburg 2002

Study characteristics	
Methods	24-week trial with 2 arms: 1. valproate semisodium 2. placebo **Duration of trial:** 24 weeks **Country:** USA **Setting:** outpatient
Participants	**Methods of recruitment of patients:** advertisement in newspapers in Boston **Overall sample size:** 30 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV borderline module) **Mean age:** 26.85 years (SD = no information; range = no information) **Sex:** 100% women **Comorbidity:** bipolar II disorder **Inclusion criteria** 1. Females 2. 18-40 years 3. Disturbed by mood changes, distrustfulness, impulsivity and stormy relationships **Exclusion criteria** 1. Acutely suicidal patients (i.e. having clear-cut and pressing intent to commit suicide in near future) 2. Actively abusing alcohol or drugs 3. Meet current criteria for major depressive episode or hypomanic episode 4. Current or lifetime schizophrenia, schizoaffective disorder, psychotic disorder not otherwise specified 5. Bipolar I disorder

Frankenburg 2002 *(Continued)*

6. Patients formerly been treated with valproate semisodium
7. Patients who were pregnant, breastfeeding or not using reliable forms of contraception
8. Medically ill
9. Seizure disorder

Interventions	**Experimental group** **Treatment name:** valproate semisodium **Number randomised to group:** 20 **Duration:** 6 months **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 10 **Duration:** 6 months **Both groups** **Concomitant psychotherapy:** no other psychotropic medication allowed **Concomitant pharmacotherapy:** no patient was in psychotherapy **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary outcomes:** none **Secondary outcomes** 1. Anger, measured by SCL-90-HOS. Assessed at baseline week 1, 2, 3, 4 and at 2, 3, 4, 5 and 6 months (EOT) 2. Impulsivity, measured by MOAS. Assessed at baseline week 1, 2, 3, 4 and at 2, 3, 4, 5 and 6 months (EOT) 3. Interpersonal problems, measured by SCL-90-INT. Assessed at baseline week 1, 2, 3, 4 and at 2, 3, 4, 5 and 6 months (EOT) 4. Depression, measured by SCL-90-DEP. Assessed at baseline week 1, 2, 3, 4 and at 2, 3, 4, 5 and 6 months (EOT) 5. Attrition 6. Adverse effects, measured by weight, menstrual changes, tremors, diarrhoea, hair loss, increase in hepatic transaminases and thrombocytopenia. Assessed at baseline week 1, 2, 3, 4 and at 2, 3, 4, 5 and 6 months (EOT)
Notes	**Sample calculation:** no information **Ethics approval:** no information **Funding source:** funded or partially funded by pharmaceutical industry **Conflicts of interest:** No other conflicts of interest were reported besides funding from the pharmaceutical industry. **Comments from trial authors (limitations)** 1. "[...] sample size was small". (Frankenburg 2002, p. 445) 2. "[...the sample consisted only of women with borderline personality disorder. Whether the results can also be applied to men meeting criteria for borderline personality disorder is unknown." Frankenburg 2002, p. 445-6) 3. "the sample comprised of moderately ill outpatients who were not suffering from a concurrent major depressive episode, abusing substances or taking concurrent medications. It is unknown if similar results would be obtained in a more severely impaired sample of borderline patients, particularly those who are inpatients at the time that their participation in a controlled trial of divalproex sodium begins". (Frankenburg 2002, p. 446) 4. "the retention rate throughout the first 3 months of the study was good. However, only 4 participants (40%) in the placebo condition and 7 participants (35%) in the valproate semisodium condition completed the entire 6-month trial." (Frankenburg 2002, p. 446)

Frankenburg 2002 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Prearranged random number sequence" (Frankenburg 2002, p. 443)
Allocation concealment (selection bias)	Low risk	**Quote:** "Tablets were supplied in numbered bottles containing drug or placebo as determined by a prearranged random number sequence". (Frankenburg 2002, p. 443) **Comment:** Participants and investigators enrolling participants could not foresee assignment because of sequentially numbered drug containers of identical appearance.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "Tablets were supplied in numbered bottles [...] Each tablet contained either 250 mg of valproate semisodium or matching inert placebo. [...] One of the investigators [...] was given either the real or a sham level (if the subject was receiving placebo). This same investigator met with the subjects for [...] medication checks and adjusted the dose according to perceived response, reported or sham level, and side effects." (Frankenburg 2002, p. 443)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** no information given on who exactly assessed outcomes, or how outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Quote:** "Endpoint values [...] are based on last observation carried forward." (Frankenburg 2002, p. 444) **Comments:** reasons for early termination specified (Frankenburg 2002, p. 444): Lost to follow-up: 9 in the valproate semisodium group, 3 in the placebo group Moved out of the area: 1/0 Inability to use reliable forms of contraception: 1/0 Withdrawal of consent: 1/0 Diarrhoea and tremors: 1/0 Development of a major depressive episode: 0/2 Hair loss: 0/1 For dichotomous outcomes, lacking numbers of patients were imputed as having the unfavourable result. Of the 30 patients enrolled, 11 completed the full 24 weeks of the trial (7 in valproate semisodium group, 4 in placebo group).
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol found
Vested Interest (funding and/or author affiliations)	High risk	**Quote:** "Supported by a grant from Abbott Laboratories, Chicago, Ill." (Frankenburg 2002, p. 442)
Other bias	Low risk	**Comment:** No apparent other sources of bias found

Goldberg 1986

Study characteristics

Methods	12-week trial with 2 arms:

Goldberg 1986 *(Continued)*

1. thiothixene
2. placebo

Duration of trial: 12 weeks (after 1 week placebo washout)

Country: USA

Setting: outpatient

Participants	**Methods of recruitment of patients:** "A short version of the SIB was placed as an advertisement in the local newspaper to recruit patients". (Goldberg 1986, p. 681) **Overall sample size:** 40 **Diagnosis of borderline personality disorder:** DSM-III **Means of assessment:** Schedule of Interviewing Schizotypal Personalities (SIB) **Mean age:** 32 years (SD = no information; range = no information) **Sex:** 58% women **Comorbidity:** schizotypal personality disorder and having at least one psychotic symptom **Inclusion criteria:** no information **Exclusion criteria** 1. Current alcoholism or drug addiction 2. Schizophrenia 3. Mania 4. Melancholia 5. Severe hepatic, renal, or cardiovascular disease 6. Organic brain syndrome 7. Mental retardation 8. History of epilepsy or seizures 9. Glaucoma 10. Severe hypertensive or hypotensive cardiovascular disease 11. Severe metabolic disorders
Interventions	**Experimental group** **Treatment name:** thiothixene **Number randomised to group:** 24 **Duration:** 12 weeks **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 26 **Duration:** 12 weeks **Both groups** **Concomitant psychotherapy:** no information **Concomitant pharmacotherapy:** participants had to pass one week placebo washout, no further details **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary outcomes** 1. BPD severity, measured by SIB-borderline score assessed at baseline and 12 weeks (EOT) 2. Mental health status (functioning), measured by GAS. Assessed at baseline and 12 weeks (EOT)

Goldberg 1986 *(Continued)*

Secondary outcomes

1. Anger, measured by HSCL-HOS. Assessed at baseline and 12 weeks (EOT)
2. Interpersonal problems, measured by HSCL-INT. Assessed at baseline and 12 weeks (EOT)
3. Psychotic symptoms, measured by SIB-psychotic. Assessed at baseline and 12 weeks (EOT)
4. Depression, measured by HSCL-DEP. Assessed at baseline and 12 weeks (EOT)
5. Attrition
6. Adverse effects. Measured by spontaneous reporting

Notes

Sample calculation: no information

Ethics approval: no information

Funding source: unclear funding

Conflicts of interest: No conflicts of interest were reported.

Comments from trial authors (limitations)

1. "If one were to ask whether our results indicate that patients with BPD and/or SPD can be treated effectively with thiothixene, our answer would have to be "not as these diagnoses are currently defined in DSM-III," because we found no drug effect on the total borderline score, schizotypal score, or on the Global Assessment Scale"."However, we would go on to say that there are some patients with these diagnoses who do respond to thiothixene and they are the ones who were more severely ill at baseline with regard to illusions, ideas of reference, psychoticism, phobic anxiety, and obsessive-compulsivity." (Goldberg 1986, p. 685)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** Insufficient information on the method used for random sequence generation to permit a judgement of low or high risk of bias
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information given on allocation concealment to permit a judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "Both agents were provided in identical-appearing capsules containing 5 mg of thiothixene hydrochloride or an equivalent amount of lactose for placebo. The initial dose for all patients was one capsule [...] and on each succeeding visit the dose was increased by one capsule unless side-effects or marked improvement intervened. A maximum dose of 40 mg, or eight capsules, was to be allowed [...]." (Goldberg 1986, p. 682)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** The article referred to the trial being double-blind, however, there was insufficient information on how blinding of outcome assessors was carried out and maintained to permit a judgement of low or high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Quote:** "Patients who terminated their participation early were assessed at that point and those assessments were taken as their endpoints." (Goldberg 1986, p. 682) **Comment:** Of the 50 patients enrolled, 40 completed treatment (17 in thiothixene group, 23 in placebo group). Reasons for early termination: Adverse effects: 7 in thiothixene group, 0 in placebo group Lack of efficacy: 0/3 Continuous data based on LOCF

Goldberg 1986 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol found
Vested Interest (funding and/or author affiliations)	Unclear risk	**Comment:** no details on sponsoring or funding. Authors affiliated with the Department of Psychiatry, Medical College of Virginia/Virginia Commonwealth University, Richmond
Other bias	Low risk	**Comment:** No apparent other sources of bias found

Grant 2022

Study characteristics	
Methods	A 12-week parallel trial with 2 arms: 1. Brexpiprazole 2. Placebo **Duration of trial**: 12 weeks + a 13th week of tapering/safety **Country:** US **Setting:** Outpatient
Participants	**Method of recruitment of participants:** Recruitment from clinics and local advertisements **Overall sample size:** 80 **Diagnosis of borderline personality disorder:** DSM-5 **Means of assessment:** Zan-BPD **Mean age:** mean age 39.7 ± 11.6 (range: 19-61) **Sex:** 56.3% women **Comorbidity:** Brexpiprazole group: N = 25 (62.5%), including anxiety disorder (N = 19), mood disorder (N = 15), ADHD (N = 4), and eating disorder (N = 4). Placebo group: N = 25 (65%), including anxiety disorder (N = 19), mood disorder (N = 13), ADHD (N = 1), and eating disorder (N = 3). **Inclusion criteria** 1. Aged 18–65 years 2. Primary diagnosis of BPD 3. A total score of at least 9 on the clinician-rated ZAN-BPD at study entry 4. Ability to understand and sign the consent form. **Exclusion criteria** 1. Unstable medical illness 2. Schizophrenia or bipolar disorder 3. An active substance use disorder 4. Current pregnancy or lactation, or inadequate contraception in women of childbearing potential 5. A suicide attempt within the 6 months before the baseline visit or significant risk of suicide (in the opinion of the investigator, defined as a 'yes' to suicidal ideation questions 4 or 5, or answering 'yes' to suicidal behaviour on the Columbia Suicide Severity Rating Scale within the past 6 months) 6. Illicit substance use based on urine toxicology screening (excluding marijuana) 7. Initiation of psychological interventions within 3 months of screening 8. Use of any new psychotropic medication started within the past 3 months before study initiation 9. Previous treatment with brexpiprazole 10. Cognitive impairment that might interfere with the capacity to understand and self-administer medication or provide written informed consent

Grant 2022 *(Continued)*

Interventions	**Experimental group** **Treatment name:** Brexpiporazole 1 mg/day for 1 week, then 2 mg/day for 10 weeks, then 1 mg/day for 1 week (taper period) **Number randomised to group:** 40 **Duration:** 12 weeks + 1 tapering week **Control/comparison group** **Comparison name:** Placebo in the same administration scheme as the experimental group **Number randomised to group:** 40 **Duration:** 12 weeks + 1 tapering week **Both groups** **Concomitant psychotherapy:** No information **Concomitant pharmacotherapy:** In the brexpiprazole group, eight were on antidepressants, five were on antiepileptics and three were on stimulants. In the placebo group, ten were on antidepressants, seven were on antiepileptics and three were on stimulants. **Proportions of participants taking standing medication during trial observation period:** 12 out of 40 (30%) in the brexipiprazole group took psychotropics and 14 out of 40 (35%) in the placebo group took psychotropics.
Outcomes	**Primary outcomes** 1. BPD severity assessed by Zan-BPD at baseline, week 1, 2, 4, 6, 8, 10 and 12 and BEST assessed at week 1 and 8. 2. Suicidality, assessed by CSSRS at baseline, week 1, 2, 4, 6, 8, 10 and 12 (data published only at https://clinicaltrials.gov/ct2/show/study/NCT03418675). 3. Self-harm: Number of patients with episodes of self-harm during treatment 4. Psychosocial functioning, assessed by Sheehan Disability Score-Self-Rating, at baseline, week 1, 2, 4, 6, 8, 10 and 12 (data published only at https://clinicaltrials.gov/ct2/show/study/NCT03418675). **Secondary outcomes** 1. Impulsivity, assessed by BIS at baseline and week 12 (data published only at https://clinicaltrials.gov/ct2/show/study/NCT03418675) 2. Depression, assessed by, 24-item Hamilton Rating Scale for Depression assessed at baseline, week 1, 2, 4, 6, 8, 10 and 12 (data published only at https://clinicaltrials.gov/ct2/show/study/NCT03418675) 3. Attrition in terms of patients lost after randomisation in each group 4. Adverse effects measured at baseline, week 1, 2, 4, 6, 8, 10, 12 and 13
Notes	**Sample size calculation:** Yes. It was determined that 35 participants were needed in each treatment group to detect a difference with an overall 5% type I error risk. **Ethics approval:** Yes. Approval by the University of Chicago Institutional Review Board **Funding source:** Funded or partially funded by pharmaceutical industry **Conflicts of interest:** The first author has received grants from pharmaceutical industry; last author has worked as a consultant in pharmaceutical industry. **Comments from trial authors (limitations)** 1. “There were some missing data, largely because of switching to an online platform given restrictions from COVID-19.” (Grant 2022 p. 62) 2. “The relatively small sample size as a result of dropout in the early weeks of the study may further call into question whether some of the secondary measures may have been significant if adequately powered.” (Grant 2022 p. 62-63)

Grant 2022 *(Continued)*

3. "Although well-tolerated, the activating side effect of brexpiprazole may have jeopardised the blind potentially, although this seems unlikely given that participants were more likely to report side effects with placebo." (Grant 2022 p. 63)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "The University of Chicago's investigational pharmacy, which was independent of the research team, randomised all participants (block sizes of eight, using computer-generated randomisation with no clinical information) to either the brexpiprazole or matching placebo in a 1:1 fashion". (Grant 2022 p. 59)
Allocation concealment (selection bias)	Low risk	**Quote:** "The University of Chicago's investigational pharmacy, which was independent of the research team, randomised all participants." (Grant 2022 p. 59) **Comment:** trial medication was handled by an independent pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote: "**The study blind was maintained by having placebo and active treatments of identical size, weight, shape and colour, as confirmed by the independent pharmacy." (Grant 2022 p. 59)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** No information given on who performed the outcome assessment and how their blinding was maintained
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** Participants were included in efficacy analyses if they completed at least one post-randomisation visit. Imputation was not undertaken for missing data. Of the 80 patients enrolled, 55 completed the full 12 weeks of the trial (30 in the brexpiprazole group and 25 in placebo group). 69 completed at least one post-randomisation visit (35 in the brexpiprazole group and 34 in placebo group). Reasons for early termination: Discontinued post-randomisation but before first visit: 5 in the brexpiprazole group, 3 in the placebo group Lost to follow-up: 5 in the brexpiprazole group, 3 in the placebo group
Selective reporting (reporting bias)	Unclear risk	**Comment:** Data have been posted in full (with the exception of two scales but a reasonable explanation for this has been given). However, this posting lacks a thorough quality control as of yet, and it is unclear why these data have not been included in the full paper.
Vested Interest (funding and/or author affiliations)	High risk	**Quote:** "This study was funded by an investigator initiated grant from Otsuka Pharmaceuticals. S.R.C.'s role in this study was funded by a Wellcome Trust Clinical Fellowship (110049/Z/15/Z and 110049/Z/15/A)." (Grant 2022 p. 63)
Other bias	Low risk	**Comment:** No other apparent sources of bias found

Hallahan 2007

Study characteristics	
Methods	12-week trial with 2 arms: 1. omega-3 fatty acid 2. placebo **Duration of trial:** 12 weeks **Country:** Ireland **Setting:** outpatient
Participants	**Methods of recruitment of patients:** "All patients were recruited from the Accident and Emergency (A&E) Department of Beaumont Hospital, an academic teaching hospital in Dublin, Ireland." (Hallahan 2007, p. 118) **Overall sample size:** 49 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** SCID-II **Mean age:** 30.6 years (SD = no information; range = no information) **Sex:** 65.31% women **Comorbidity:** recurrent self-harm **Inclusion criteria:** no information **Exclusion criteria** 1. Current addiction 2. Substance misuse 3. Psychosis 4. Eating disorder 5. Dyslipidaemia 6. Treatment, diet or illness known to interfere with trial drug 7. Weight loss > 10% during previous 3 months 8. Taking supplements containing omega-3 fatty acids of consuming fish more than once per week 9. Changes to or introduction of psychotropic medication during previous 6 weeks 10. Pregnancy
Interventions	**Experimental group** **Treatment name:** omega-3 fatty acid **Number randomised to group:** 22 **Duration:** 12 weeks **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 27 **Duration:** 12 weeks **Both groups** **Concomitant psychotherapy:** "During the course of the study patients continued to receive standard psychiatric care and had changes to their psychotropic medication as prescribed." (Hallahan 2007, p. 118). Patients with changes to or introduction of psychotropic medication during the 6 weeks prior to screening were not eligible. **Concomitant pharmacotherapy:** not allowed

Hallahan 2007 *(Continued)*

	Proportions of participants taking standing medication during trial observation period: 53.1% of participants continued to receive standard psychiatric care and had changes to their psychotropic medication as prescribed.
Outcomes	**Primary outcomes** 1. Suicidal behaviour, measured by OAS-M suicidality subscale. Assessed at baseline and 12 weeks (EOT) 2. Self-harm: Number of patients with episodes of self-harm during treatment **Secondary outcomes** 1. Anger, measured by OAS-M irritability subscale. Assessed at baseline and 12 weeks (EOT) 2. Impulsivity, measured by OAS-M aggression subscale. Assessed at baseline and 12 weeks (EOT) 3. Depression, measured by BDI and HRSD. Assessed at baseline and 12 weeks (EOT) 4. Attrition in terms of non-completers
Notes	**Sample calculation:** yes **Ethics approval:** yes **Funding source:** funded by grants from universities, authorities or research foundations **Conflicts of interest:** Trial medication was provided by a pharmaceutical company. **Comments from trial authors (limitations):** "Although 14 patients reported episodes of self-harm during the study, it was known a priori that the study was insufficiently powered to detect significant differences between groups". (Hallahan 2007, p. 122)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "computer-generated list" (Hallahan 2007, p. 119)
Allocation concealment (selection bias)	Low risk	**Quote:** "An independent colleague dispensed either active or placebo capsules according to a computer-generated list. The code was only revealed to the researchers once data collection was complete". (Hallahan 2007, p. 119) **Comment:** Participants and investigators enrolling participants could not foresee assignment because of central allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote**: "Participants were prescribed four identical capsules of either active agent or placebo [...] Placebo ensured a degree of equality in the incidence of 'fishy breath', the most frequent side-effect of taking active treatment." (Hallahan 2007, p. 119)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "identical capsules [...] Placebo ensured a degree of equality in the incidence of 'fishy breath' [...] An independent colleague dispensed [...] capsules according to a computer-generated list. The code was only revealed to the researchers once data collection was complete." (Hallahan 2007, p. 119)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comments:** LOCF used, reasons for early termination specified (Hallahan 2007 p. 120): Left district: 1 in active group, 2 in placebo group Lost to follow-up: 2 in active group, 2 in placebo group Admitted to psychiatric hospital: 0 in active group, 2 in placebo group Refused to continue treatment: 0 in active group, 1 in placebo group Dichotomous outcomes calculated on basis of the ITT sample

Hallahan 2007 *(Continued)*

		Of the 49 patients enrolled, 39 completed treatment (19 of the 22 allocated to active treatment, 20 of the 27 allocated to placebo).
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol found
Vested Interest (funding and/or author affiliations)	Low risk	**Quotes:** "Pronova (now Epax) AS, Lysaker, Norway, provided the active preparation and placebo but were not otherwise involved in the study." (Hallahan 2007, p. 118) "B.H. [i.e. first author] received salary support from the Department of Psychiatry, University of Illinois at Chicago, USA." (Hallahan 2007, p. 122)
Other bias	Low risk	**Comment:** No apparent other sources of bias found

Hollander 2001

Study characteristics	
Methods	10-week trial with 2 arms: 1. valproate semisodium 2. placebo **Duration:** 10 weeks **Country:** USA **Setting:** outpatient
Participants	**Methods of recruitment of patients:** "[...] referral from private psychiatrists and mental health professionals in the community, self-help groups, outpatient clinics at Mount Sinai Medical Center and the Bronx Veterans Affairs medical Center (New York, N.Y.), advertisement, and the media." (Hollander 2001, p. 200) **Overall sample size:** 21 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** SCID-II **Mean age:** 38.6 years (SD 10.37; range = 18-62) **Sex:** 52.38% women **Comorbidity:** no information **Inclusion criteria:** no information **Exclusion criteria** 1. Current suicidal ideation 2. Current substance abuse 3. Current major depression 4. Bipolar disorder type I or II 5. Psychotic disorders 6. Medical or neurologic illness 7. Pregnancy

Hollander 2001 *(Continued)*

Interventions	**Experimental group** **Treatment name:** valproate semisodium **Number randomised to group:** 12* **Duration:** 10 weeks **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 4* **Duration:** 10 weeks **Both groups** **Concomitant psychotherapy:** no information **Concomitant pharmacotherapy:** no information **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary outcomes** 1. Suicidal behaviour, measured by OAS-M suicidality subscale. Assessed at baseline and 10 weeks (EOT) 2. Mental health status, measured by non-responders (functioning) (CGI-I score of 3 or more). Assessed at baseline and 10 weeks (EOT) **Secondary outcomes** 1. Anger, measured by OAS-M irritability subscale. Assessed at baseline and 10 weeks (EOT) 2. Impulsivity, measured by the Aggression Questionnaire and OAS-M aggression subscale. Assessed at baseline and 10 weeks (EOT) 3. Depression, measured by BDI. Assessed at baseline and 10 weeks (EOT) 4. Attrition
Notes	**Sample calculation:** no information **Ethics approval:** no information **Funding source:** funded or partially funded by pharmaceutical industry **Conflicts of interests:** No conflicts of interest were reported besides partial funding from the pharmaceutical industry. **Comments from trial authors (limitations)** 1. "The study is limited by the small sample size and high dropout rate". (Hollander 2001, p. 202) 2. "Although the planned patient assignment ratio was 2:1 (divalproex sodium: placebo), the ratio was actually 3:1." (Hollander 2001, p. 202) 3. "All findings are in the hypothesised direction, but the small sample size, high variability of the measures, imbalance in the number of patients in the 2 conditions, and high dropout rate contributed to the limited significant findings." (Hollander 2001, p. 202) **Comments from review authors** 1. Small sample size. *Initially 21 participants entered the trial; only 16 were randomised to a treatment group without giving reason. 2. Continuous outcomes based on ITT (LOCF). Of the 16 patients randomised, 6 completed treatment (6 in valproate semisodium group, 0 in placebo group). 3. High dropout rate. Reason for early termination: all patients dropped out owing to either lack of efficacy or impulsive decisions; none dropped out due to side effects.

Risk of bias

Bias	Authors' judgement	Support for judgement

Hollander 2001 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	**Comment:** Insufficient information on method for random sequence generation provided to permit a judgement of low or high risk of bias
Allocation concealment (selection bias)	Unclear risk	**Comment:** insufficient information to permit judgement of high or low risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Quote:** "The treating psychiatrist was kept blind to patient medication; blood valproate levels were read and dose adjustments to both valproate semisodium and placebo were determined by a psychiatrist not seeing patients for this study." (Hollander 2001, p. 201) **Comment:** no information given if opaque capsules were used, and if the placebo pseudo-dose was also "adjusted"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "clinician-rated outcome measures [...] based on the average of the ratings of the treating psychiatrist and independent evaluator (a psychologist blind to side effects as well as to medication group)" (Hollander 2001, p. 201)
Incomplete outcome data (attrition bias) All outcomes	High risk	**Quote:** "Patients taking valproate semisodium had a 50% dropout rate [...] versus 100% dropout in the placebo group. [...] No patients dropped out owing to side effects; all dropped out owing to either lack of efficacy or impulsive decisions. [...]" (Hollander 2001, p. 201) **Comments:** LOCF used (Hollander 2001, p. 202) Initially 21 participants entered the trial; only 16 were randomised to a treatment group without giving reasons. Of the 16 patients randomised, 6 completed treatment (6 in divalproex group, 0 in placebo group). Reasons for early termination: "No patients dropped out owing to side effects; all dropped out owing to either lack of efficacy or impulsive decisions. [...]" (Hollander 2001, p. 201)
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol found
Vested Interest (funding and/or author affiliations)	High risk	**Quote:** "Supported in part by grants from the National Institute of Mental Health (1 RO3 MH58168-01A1), Richville, Md. (Dr. Hollander); Abbott Laboratories, Abbott Park, Ill. (Dr. Hollander); the National Center for Research Resources, National Institutes of Health (5 MO1 RR00071), Rockville, Md., for the Mount Sinai General Clinical Research Center; and the Seaver Foundation and the PBO Foundation, New York, N.Y." (Hollander 2001, p. 199)
Other bias	Low risk	**Comment**: no indication of other bias

Jariani 2010

Study characteristics	
Methods	12-week trial with 2 arms: 1. olanzapine 2. sertraline **Duration of trial:** 12 weeks **Country:** Iran

Jariani 2010 *(Continued)*

	Setting: outpatient
Participants	**Methods of recruitment of patients:** no information other than patients on methadone maintenance treatment with BPD diagnosis **Overall sample size:** 120 **Diagnosis of borderline personality disorder:** DSM-IV-TR **Means of assessment:** clinical interview **Mean age:** 27 years (SD = no information; range = no information) **Sex:** no information on percentage for overall sample size **Comorbidity:** 100% had a substance use disorder. **Inclusion criteria:** no information **Exclusion criteria:** no information; however, stated that patients did not suffer from any axis I disorders or other somatic disorders such as hepatitis or AIDS
Interventions	**Experimental group** **Treatment name:** olanzapine (5-10 mg/d, exact mean final dose unclear) **Number randomised to group:** no information* **Duration:** 12 weeks **Control/comparison group** **Comparison name:** sertraline (50-100 mg/d, exact mean final dose unclear) **Number randomised to group:** no information* **Duration:** 12 weeks **Both groups** **Concomitant psychotherapy:** no information **Concomitant pharmacotherapy:** methadone **Proportions of participants taking standing medication during trial observation period:** 100% of participants were concomitantly treated with methadone.
Outcomes	**Primary outcomes** 1. Self-harm (not further specified); not reported in trial, but reported a significant difference. Assessed at baseline, and at week 4, 8 and 12 (EOT) 2. Mental health status (functioning), measured by SCL-90-R. Assessed at baseline, and at week 4, 8 and 12 (EOT) **Secondary outcomes** 1. Anger, measured by SCL-90-R. Assessed at baseline, and at week 4, 8 and 12 (EOT) 2. Interpersonal problems, measured by SCl-90-R. Assessed at baseline, and at week 4, 8 and 12 (EOT) 3. Dissociation and psychotic-like symptoms, measured by SCl-90-R. Assessed at baseline, and at week 4, 8 and 12 (EOT) 4. Depression, measured by SCL-90-R. Assessed at baseline, and at week 4, 8 and 12 (EOT)
Notes	**Sample calculation:** yes **Ethics approval:** yes, "This clinical trial was granted an approval from Medical Ethics Committee at Lorestan Medical University on 12/04/2007". (Jariani 2010, p. 545) **Funding source:** unclear funding **Conflicts of interest:** No conflicts of interest were reported. **Comments from trial authors (limitations):** none mentioned

Jariani 2010 *(Continued)*

	Comments from review authors: *No information provided for the number of participants in each group and not possible to contact the authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** According to the sample size formula, 120 males and females on MMT with a diagnosis of BPD were chosen and randomly placed in two groups in which they received either olanzapine (5-10 mg daily) or sertraline (50-100 mg daily) (Jariani 2010, p. 545).
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information on allocation concealment reported to permit a judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** no information on blinding reported to permit a judgement of low or high risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** no information on blinding reported to permit a judgement of low or high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** The complete numbers of participants in each group were not provided for analysis results. No details given about patient flow after randomisation
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol found
Vested Interest (funding and/or author affiliations)	Unclear risk	**Comment:** no information
Other bias	Low risk	**Comment:** no other sources found

Kulkarni 2018

Study characteristics

Methods	8-week trial with 2 arms: 1. memantine hydrochloride + treatment-as-usual 2. placebo + treatment-as-usual **Duration of trial:** 8 weeks + 4 weeks for washout **Country:** Australia **Setting:** outpatient
Participants	**Methods of recruitment of patients: "**Participants were recruited primarily via doctor referral, and via printed and electronic advertisements on noticeboards at various sites of The Alfred Hospital (Melbourne, VIC, Australia), and were primarily from Alfred Psychiatry outpatient units and community clinics". (Kulkarni 2018, p. 182) **Overall sample size:** 34

Kulkarni 2018 *(Continued)*

Diagnosis of borderline personality disorder: DSM-IV

Means of assessment: Zan-BPD

Mean age: 34.4 years (SD = no information; range = no information)

Sex: 85.29% women

Comorbidity: bipolar II disorder

Inclusion criteria

1. Both genders
2. Aged 16-65 years
3. Diagnosis of BPD according to Zan-BPD
4. Proficiency in reading and writing English

Exclusion criteria

1. Clinical evidence of CNS pathology, neurological disorder, head injury, epileptic seizures or convulsions
2. Currently pregnant or breastfeeding
3. A current DSM-IV-TR diagnosis of substance abuse or dependence disorder, or another axis I disorder including a past or current diagnosis of schizophrenia, delusional (paranoid) disorder, schizoaffective disorder, bipolar I (mixed, manic, depressed or euthymic) or psychotic depression. Individuals with bipolar II were included.
4. Clinically significant and active evidence of liver or kidney disease, or haematological, respiratory, endocrine or cardiovascular disease
5. Use of prescription drugs that may cause relevant drug interactions with the trial drug according to the summary of product characteristics: NMDAR antagonist (amantadine, ketamine, dextromethorphan), L-dopa, dopamine agonist and cholinergic agonist
6. Commencing new psychotherapy or new medication during trial period
7. History of mental retardation or documented IQ below 75

Interventions

Experimental group
Treatment name: memantine-hydrochloride + treatment-as-usual
Number randomised to group: 17
Duration: 8 weeks

Control/comparison group
Comparison name: placebo + treatment-as-usual
Number randomised to group: 17
Duration: 8 weeks

Both groups
Concomitant psychotherapy: psychotherapy and other psychosocial interventions as usual treatment
Concomitant pharmacotherapy: Treatment-as-usual consisted of medications of antidepressants (selective serotonin reuptake inhibitors, tricyclics, monoamine oxidase inhibitors noradrenergic and specific serotonin antagonist and serotonin noradrenaline reuptake inhibitors), mood stabilisers and antipsychotics, as well as psychotherapy and other psychosocial interventions.
Proportions of participants taking standing medication during trial observation period: no information

Outcomes

Primary outcomes:

1. BPD severity, measured by Zan-BPD. Assessed at baseline and at week 2, 4, 6 and 8 (EOT)

Secondary outcomes

1. Attrition, measured in terms of patients lost after randomisation in each group

Kulkarni 2018 *(Continued)*

2. Adverse effects, measured by "An adverse effects questionnaire, administered fortnightly to assess adverse effects known to be related to memantine use" (Kulkarni 2018, p. 4).

Notes

Sample calculation: yes

Ethics approval: yes

Funding source: funded by grants from universities, authorities or research foundations

Conflicts of interest: No conflicts of interest were reported.

Comments from trial authors (limitations)

1. Exploratory study
2. "[...] small sample size with inherent potential for statistical error (type I/type II)" (Kulkarni 2018, p. 185)
3. "[...] plateau of total scores was not reached in either active or placebo groups." (Kulkarni 2018, p. 185)
4. [...] blood plasma levels of memantine were not analysed in the study, which could confirm adherence to the medication and expose any potential individual variability in drug pharmacokinetics." (Kulkarni 2018, p. 185)

Comments from review authors: supplemental information provided by trial author through email correspondence (Kulkarni 2020 [pers comm])

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "All participants were individually randomized by The Alfred Clinical Trials Pharmacy to receive either a 10 mg "run-in dose" for 7 days followed by oral daily memantine hydrochloride 20 mg, or oral placebo according to a computer-generated randomization list". (Kulkarni 2018, p. 182)
Allocation concealment (selection bias)	Low risk	**Comment:** central allocation by pharmacy-controlled randomisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Quote:** "All study personnel and participants remained blinded to treatment assignment for the duration of the study". (Kulkarni 2018, p. 182) **Comment:** The article referred to the trial as being double-blind but did not provide information on how blinding was secured.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** The article referred to the trial being double-blind, however, there was insufficient information on how blinding of outcome assessors was carried out and maintained to permit a judgement of low or high risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** Intent-to-treat imputation method mentioned in abstract. 26.5% discontinued the intervention. From the flow diagram – 8 discontinued from 34 - still 33 analysed
Selective reporting (reporting bias)	High risk	**Comment:** NCT02097706 - Two secondary outcomes (Cogstate (cognitive assessment) & Borderline Evaluation of Severity over Time) were mentioned in the protocol but not included in the full report. No mention of adverse effects as a secondary outcome in protocol
Vested Interest (funding and/or author affiliations)	Low risk	**Comment:** reported no conflicts of interest
Other bias	Low risk	**Comment:** no others sources found

Leone 1982

Study characteristics	
Methods	6-week trial with 2 arms: 1. loxapine 2. chlorpromazine **Duration**: 6 weeks **Country:** USA **Setting:** outpatient
Participants	**Methods of recruitment of patients:** no information **Overall sample size:** 80 **Diagnosis of borderline personality disorder:** DSM-III **Means of assessment:** no information **Mean age:** 30.75 years (SD = no information; range = 16-59) **Sex:** 60% women **Comorbidity:** no information **Inclusion criteria:** no information **Exclusion criteria** 1. Using sedatives or tranquillisers 2. Having been treated with psychotropic drugs within 48 hours of beginning treatment with trial drugs 3. Allergy/hypersensitivity to trial drugs 4. Organic brain syndrome 5. Mental retardation 6. Severe medical disease
Interventions	**Experimental group** **Treatment name:** loxapine **Number randomised to group:** 40 (as randomised) **Duration:** 6 weeks **Control/comparison group** **Comparison name:** chlorpromazine **Number randomised to group:** 40 (as randomised) **Duration:** 6 weeks **Both groups** **Concomitant psychotherapy:** no information **Concomitant pharmacotherapy:** "Patients did not receive any other psychotropic medication during the study. Night-time sedatives were limited to flurazepam and chloral hydrate." (Leone 1982, p. 148) **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary outcomes** 1. BPD severity measured by CGI. Assessed at baseline, 48 hours, and week 1, 2, 4 and 6 (EOT) 2. Mental health status, measured by CGI and Systematic Nurses' Observation of Psychopathology (SNOOP). Assessed at baseline, 48 hours, and week 1, 2, 4 and 6 (EOT)

Leone 1982 *(Continued)*

Secondary outcomes

1. Affective instability, measured by The Profile of Mood States (POMS). Assessed at baseline, 48 hours, and week 1, 2, 4 and 6 (EOT)
2. Psychotic symptoms, measured by BPRS. Assessed at baseline, 48 hours, and week 1, 2, 4 and 6 (EOT)
3. Attrition
4. Adverse effects, recorded upon appearance in terms of data of onset, intensity, duration, and any remedial action

Notes

Sample calculation: no information

Ethics approval: no information

Funding source: funded or partially funded by pharmaceutical industry

Conflicts of interest: No conflicts of interest were reported besides from funding from the pharmaceutical industry.

Comments from trial authors (limitations): "Controlled studies are needed which use competing diagnostic schemes and which systematically evaluate drug response over longer periods of time". (Leone 1982, p. 159)

Comments from review authors: unable to use outcome data (except for attrition)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Matched groups [...] Subjects [...] were selected randomly to receive loxapine or chlorpromazine. [...] There were 24 women and 16 men in each treatment group." (Leone 1982, p. 148) **Comment:** probably matching procedure used
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information given on allocation concealment to permit a judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "drugs were supplied in identical opaque capsules". (Leone 1982, p. 148)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** no information given. Within this review, only the outcomes of attrition and adverse effects, that were "recorded upon appearance" (Leone 1982, p. 148), were used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comments:** continuous outcomes based on available cases: of the 80 patients enrolled, 69 completed at least 3 weeks of treatment and were included (34 in loxapine group, 35 in placebo group) Reasons for early termination: Did not follow trial procedures: 4 in loxapine group, 4 in chlorpromazine group Had to be admitted to hospital within 3 days: 2 in loxapine group, 1 in chlorpromazine group Only dichotomous outcomes used here, for which patients who had dropped out were imputed as having the negative outcome.
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol found

Leone 1982 *(Continued)*

Vested Interest (funding and/or author affiliations)	High risk	**Quote:** "This study was supported by a grant from Lederle Laboratories, Pear River, New York." (Leone 1982, p. 148)
Other bias	Low risk	**Comment:** no indication of other bias

Linehan 2008

Study characteristics	
Methods	24-week trial with 2 arms: 1. DBT + olanzapine 2. DBT + placebo **Duration:** 24 weeks **Country:** USA **Setting:** outpatient
Participants	**Methods of recruitment of patients:** no information **Overall sample size:** 24 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** SCID-II **Mean age:** 36.8 years (SD 9.0; range = no information) **Sex:** 100% women **Comorbidity:** no information **Inclusion criteria** 1. BPD according to DSM-IV (SCID-II, IPDE) 2. BPD criterion for inappropriate anger met 3. Score of 6 or higher on the irritability scale of the Overt Agression Scale Modified (OAS-M) **Exclusion criteria** 1. Episode of self-inflicted self-injury, including suicide attempts during 8 weeks prior to screening 2. Current diagnosis of schizophrenia, bipolar I disorder, schizoaffective disorder, major depressive disorder with psychotic features or other psychotic disorder 3. Substance dependence during last 6 months 4. Mental retardation 5. Seizure disorder 6. Pregnant women or women planning to become pregnant 7. Breastfeeding
Interventions	**Experimental group** **Treatment name:** olanzapine (2.5-15 mg/d, mean final dose 4.46, SD 1.16) **Number randomised to group:** 12 **Duration:** 6 months **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 12

Linehan 2008 *(Continued)*

	Duration: 6 months **Both groups** **Concomitant psychotherapy:** All participants received DBT. **Concomitant pharmacotherapy:** no information **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary outcomes** 1. Suicidal ideation, measured in terms of number of patients with a high suicidality score on the OAS-M Suicidality subscale. Assessed at baseline, week 7, 14 and 21 (EOT) 2. Self-mutilating behaviour, measured in terms of number of patients with self-injury **Secondary outcomes** 1. Depression, measured by Ham-D. Assessed at baseline, week 7, 14 and 21 (EOT) 2. Attrition 3. Adverse effects, measured by weight gain (lb); remaining data on adverse effects not usable
Notes	**Sample calculation:** no information **Ethics approval:** no information **Funding source:** funded or partially funded by pharmaceutical industry **Conflicts of interest:** Dr Linehan is a consultant for Eli Lilly and is a member of their speakers/advisory board. **Comments from trial authors (limitations):** "A limitation to this study is the small sample size". (Linehan 2008, p. 1004) **Comments from review authors:** data refer to the intention-to-treat sample.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "random number sequence" (Linehan 2008, p. e2)
Allocation concealment (selection bias)	Unclear risk	**Comment:** Insufficient information on allocation concealment to permit judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** Insufficient information on how blinding of participants and personnel was secured and maintained (e.g. packaging of trial medication) to permit judgement of low or high risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "Patients, psychotherapists, pharmacotherapist, and assessment interviewers were kept naive to medication assignment. At the end of the study, the pharmacotherapist and interviewers were unable to guess group assignment above chance." (Linehan 2008, p. e2)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Quote:** "Outcomes were intent-to-treat analyses". (Linehan 2008, p. e3) **Comment:** Reasons for early termination specified (Linehan 2008, p. e4); patients who had dropped out were imputed as having the negative outcome.

Linehan 2008 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol found
Vested Interest (funding and/or author affiliations)	High risk	**Quote:** "This research was supported by a grant from Eli Lilly and Co., Protocol F1D-US-X173, to Dr. Linehan; by Remind Rx Medication Compliance Systems; and by a contribution of electronic pill bottles from IBV Technologies, Seattle, Wash. [...]. Dr. Linehan is a consultant for, has received grant/research support and honoraria from, and is a member of the speakers/advisory board for Eli Lilly. Drs. McDavid, Brown, Sayrs, and Gallop report no additional financial or other relationships relevant to the subject of this article." (Linehan 2008, p. 999)
Other bias	Low risk	**Comment:** no indication of other bias

Loew 2006

Study characteristics	
Methods	10-week trial with 2 arms: 1. topiramate 2. placebo **Duration of trial:** 10 weeks **Country:** Germany **Setting:** outpatient
Participants	**Methods of recruitment of patients:** Patients were primarily recruited through advertisements. **Overall sample size:** 56 **Diagnosis of borderline personality disorder:** DSM (edition not mentioned) **Means of assessment:** SCID-II **Mean age:** 25.25 years (SD = no information; range = no information) **Sex:** 100% women **Comorbidity:** no information **Inclusion criteria:** no information **Exclusion criteria** 1. Currently suicidal patients 2. Abusing alcohol or drugs 3. Schizophrenia 4. Severe somatic illness 5. Current use of topiramate or other psychotropic medication or psychotherapy
Interventions	**Experimental group** **Treatment name:** topiramate **Number randomised to group:** 28* **Duration:** 10 weeks **Control/comparison group**

Loew 2006 *(Continued)*

Comparison name: placebo
Number randomised to group: 28*
Duration: 10 weeks

Both groups
Concomitant psychotherapy: not allowed
Concomitant pharmacotherapy: any other psychotropic medication not allowed
Proportions of participants taking standing medication during trial observation period: no information

Outcomes

Primary outcomes: general psychiatric pathology, measured by SCL-90-R-GSI

Secondary outcomes

1. Anger, measured by SCL-90-R-HOS. Assessed at baseline and every week for 10 weeks (EOT)
2. Interpersonal problems, measured by SCL-90-R-INT. Assessed at baseline and every week for 10 weeks (EOT)
3. Psychotic symptoms, measured by SCL-90-R-PAR and SCL-90-R-PSY. Assessed at baseline and every week for 10 weeks (EOT)
4. Depression, measured by SCL-90-R-DEP. Assessed at baseline and every week for 10 weeks (EOT)
5. Attrition
6. Adverse effects, measured by non-structured questionnaire. No information on time of assessment

Notes

Sample calculation: yes

Ethics approval: yes

Funding source: no funding received

Conflicts of interest: No conflicts of interest were reported

Comments from trial authors (limitations): "This analysis is limited, in part, because the sample size was (despite a valid power analysis) relatively small and consisted only of moderately ill women with BPD." (Loew 2006, p. 65). "The placebo effect proved to be relatively small between the first and last evaluations. Whether these results could also be replicated to men meeting the criteria for BPD, and/or with severe cases of BPD, and/or with patients abusing substances or taking concurrent medications is unknown". (Loew 2006, p. 65). "The length of this trial was only 10 weeks, which possibly reduced the dropout rate." (Loew 2006, p. 65)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** Trial was referred to as randomised, however, there was not sufficient information on how randomisation was carried out to permit a judgement of low or high risk of bias.
Allocation concealment (selection bias)	Unclear risk	**Quote:** "Randomization was carried out confidentially by the clinic administration". (Loew 2006, p. 63) **Comment:** unclear which measures were taken to assure confidentiality throughout the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Quote:** "Subjects received blinded medication daily, which constituted either topiramate or a matching placebo.[…]Tablets were supplied in numbered boxes. Both subjects and clinicians were blinded regarding topiramate/placebo assignment." (Loew 2006, p. 63)
Blinding of outcome assessment (detection bias)	Unclear risk	**Quote:** "Subjects received blinded medication daily, which constituted either topiramate or a matching placebo.[…]Tablets were supplied in numbered box-

Loew 2006 *(Continued)*

All outcomes		es. Both subjects and clinicians were blinded regarding topiramate/placebo assignment." (Loew 2006, p. 63) **Comment:** Unclear if 'clinicians' also applied to outcome assessors, therefore, insufficient information to permit a judgement of low or high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Quote:** "Fifty-nine subjects were eligible to take part in the study [...] 56 patients were required [...] randomization was carried out [...] with a 1:1 assignment to the active drug (N = 28) and placebo (N = 28)". (Loew 2006, p. 63) **Comments:** Of the 56 patients enrolled, 52 completed treatment (27 in topiramate group, 25 in placebo group). Reasons for early termination: Absent more than twice for weekly evaluation: 1 in the topiramate group, 3 in the placebo group LOCF used; reasons for early termination specified (Loew 2006, p. 63) Not clear why or how the 56 participants were finally chosen out of the 59 potential participants
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol found
Vested Interest (funding and/or author affiliations)	Unclear risk	**Quote:** "The study was planned and conducted independent[ly] of any institutional influence and approved by the clinic's ethics committee in accordance with the Declaration of Helsinki and ethical laws pertaining to the medical professions." (Loew 2006, p. 63)
Other bias	Low risk	**Comment:** No apparent other sources of bias found

Markovitz 1995a

Study characteristics	
Methods	A 14-week trial with 2 arms: 1. fluoxetine 2. placebo **Duration of trial:** 14 weeks **Country:** USA **Setting:** inpatient
Participants	**Methods of recruitment of patients:** no information **Overall sample size:** 17 **Diagnosis of borderline personality disorder:** DSM-III-R **Means of assessment:** SCID-II and Gunderson's DIB20 **Mean age:** no information **Sex:** no information **Comorbidity:** Axis I: Each patient had on average 3.0 current Axis I diagnoses and 4.7 lifetime diagnoses at the time of the study. Axis II: 100% borderline, 82% self-defeating, 82% paranoid, 71% compulsive, 65% avoidant, 65% dependent, 59% histrionic, 59% passive-aggressive, 53% schizotypal, 35%

Markovitz 1995a *(Continued)*

	narcissistic, 35% antisocial. Axis III: 92% premenstrual syndrome, 47% headaches/migraines, 41% IBS, 35% fibrocytis, 29% neurodermatitis, 29% sleep apnoea **Inclusion criteria:** no information **Exclusion criteria:** no information
Interventions	**Experimental group** **Treatment name:** fluoxetine **Number randomised to group:** 9 **Duration:** 14 weeks **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 8 **Duration:** 14 weeks **Both groups** **Concomitant psychotherapy:** no information **Concomitant pharmacotherapy:** no information **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary** 1. Psychosocial functioning, assessed by the Global Assesment Scale at baseline and every other week until week 14 (EOT) **Secondary** 1. Depression, assessed by Becks Depression Inventory and Hamilton's Depression Scale at baseline and every other week until week 14 (EOT) 2. Attrition in terms of patients lost after randomisation in each group at EOT
Notes	**Sample calculation:** no information **Ethics approval:** no information **Funding source:** no information **Conflicts of interest:** no information **Comments from trial authors (limitations):** "All of the rating instruments were continuing to show increasing improvement at 14 weeks in patients on fluoxetine, suggesting the trial may not have been long enough". (Markovitz 1995a, p. 271) **Comment from review authors:** This trial was not included in quantitative analyses due to data unavailability for effect size calculations.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** The study was referred to as randomised; however, the method used to generate the allocation sequence was not described in sufficient detail to allow an assessment of whether it produced comparable groups.
Allocation concealment (selection bias)	Unclear risk	**Comment:** Allocation concealment and the method used to conceal the allocation sequence was not described.

Markovitz 1995a *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** The study was referred to as being double-blind but there was no information on method or if the blinding was successful.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** The study was referred to as being double-blind but there was no information on method or if the blinding was successful.
Incomplete outcome data (attrition bias) All outcomes	High risk	**Quote:** "Dropout after 3 weeks but prior to 14 weeks and their final rating scores carried through for each subsequent time point. Seven of nine patients on fluoxetine completed the entire study, and seven of eight patients on placebo completed all 14 weeks of the trial". (Markovitz 1995a, p. 271) **Comment:** last-observation-carried-forward
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol available. Insufficient information to permit judgement of high or low risk of bias
Vested Interest (funding and/or author affiliations)	Unclear risk	**Comment:** insufficient information on funding and conflict of interest to permit judgement of high or low risk of bias
Other bias	Low risk	**Comment**: The study appeared to be free of other sources of bias.

Moen 2012

Study characteristics	
Methods	16-week trial with 2 arms: 1. divalproex (valproate) 2. placebo **Duration of trial:** 16 weeks (a 4-week selection phase and a 12-week experimental phase) **Country:** USA **Setting:** inpatient
Participants	**Methods of recruitment of patients:** "[...] newspaper and radio advertisements in the Minneapolis area. Local psychiatric clinics and mental health centers also were notified of the study, although no clinical referrals were made". (Moen 2012, p. 256-7) **Overall sample size:** 15 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** SCID-I, SCID-II and past clinical records to screen for other mental illnesses, and SCL-90 **Mean age:** 35.5 years (SD = no information; range = 22-51) **Sex:** 80% women **Comorbidity:** "Although current diagnosis of major depression was an exclusion criterion, a history of major depression was allowed provided it had been 12 weeks since the last major depressive episode." (Moen 2012, p. 257). No further information **Inclusion criteria:** BPD diagnosis

Moen 2012 *(Continued)*

Exclusion criteria

1. Current or past history of bipolar disorder, schizophrenia, or major depression with psychotic features (although current diagnosis of major depression was an exclusion criterion, a history of major depression was allowed provided it had been 12 weeks since the last major depressive episode)
2. Current prescription of any psychotropic medication
3. Acutely suicidal (i.e. had a clear-cut and pressing intent to commit suicide in the near future)
4. Current alcohol or illicit substance dependency
5. Seizure disorder or anticonvulsant medications or both
6. Pregnant, breastfeeding, planning to become pregnant, or not using a reliable form of contraception (women of childbearing potential were given a pregnancy test at the beginning of the trial)

Interventions	**Experimental group** **Treatment name:** divalproex **Number randomised to group:** 10 **Duration:** 12 weeks **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 5 **Duration:** 12 weeks **Both groups** **Concomitant psychotherapy:** condensed 4 weeks of Dialectical Behaviour Therapy (DBT) prior to medication **Concomitant pharmacotherapy:** no information; however, there was a washout before trial initiation and each potential research patient had to be medication-free for 2 to 4 weeks. **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary outcomes** 1. BPD severity measured by BEST. Assessed at baseline, week 4, 8 and 12 (EOT) 2. Mental health status (functioning), measured by SCL-90 total score. Assessed at baseline, week 4, 8 and 12 (EOT) **Secondary outcomes** 1. Impulsivity, measured by BIS and BIS-Motor Score. Assessed at baseline, week 4, 8 and 12 (EOT) 2. Depression, measured by the HAM-D. Assessed at baseline, week 4, 8 and 12 (EOT) 3. Attrition 4. Adverse effects, measured by spontaneous reporting and laboratory values. "To study the possibility of medication side effects, all physical and psychiatric symptoms were recorded. Patients' weight and height were measured at entry to double-blind study (to calculate body mass index) and at completion of the trial". (Moen 2012, p. 259) Laboratory testing and ECG at weeks 3, 6, 11 and 13
Notes	**Sample calculation:** no information **Ethics approval:** approved by institutional review board for Texas University Health Science Centre – Houston, USA **Funding source:** funded or partially funded by pharmaceutical industry **Conflicts of interest:** Dr Schulz is a consultant to Eli Lilly and company and Genetech. **Comments from trial authors (limitations):** "[...] the small sample size limited our statistical power to investigate significant treatment group differences as well as our ability to generalize from our sample". (Moen 2012, p. 259)

Risk of bias

Moen 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** insufficient information on methods used to generate random sequence to permit a judgement of low or high risk of bias
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information on allocation concealment to permit judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Quote**: "Blood samples were obtained to measure blood concentration of divalproex ER at weeks 4, 8, and 16. A study physician then adjusted the dose to maintain the medication at the therapeutic range. The study physician changed the dosing of the study medicine and placebo at pre-determined dose-escalation steps so as not to reveal medication assignment". (Moen 2012, p. 258) **Comment:** Personnel appeared to have been blinded, but there was no information regarding how participants were blinded (e.g. on concealment of medication type)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "All raters were kept blind of the serum divalproex level results. Only one study physician (A.A.), who did not participate in the ratings, was privy to the results of serum divalproex levels." (Moen 2012, p. 257)
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** last-observation-carried-forward (LOCF) used. Low numbers overall
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol found
Vested Interest (funding and/or author affiliations)	High risk	**Quote:** "This study was sponsored by a research grant from Abbott Pharmaceuticals to the principal investigator, S. Charles Schulz, MD. Dr. Schulz receives grant or research support from AstraZeneca, Myriad RBM, and Otsuka and is a consultant to Eli Lilly and Company and Genetech. Drs. Moen, Freitag, Miller, Lee, and Adityanjee and Ms. Romine and Ms. Song report no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products". (Moen 2012, p. 260)
Other bias	Low risk	**Comment:** no other sources found

Montgomery 1982a

Study characteristics	
Methods	6-month trial with 2 arms: 1. flupenthixol 2. placebo **Duration:** 24 weeks **Country:** UK **Setting:** outpatient

Montgomery 1982a *(Continued)*

Participants	**Methods of recruitment of patients:** "[...] endogenously depressed patients who were taking part in a comparative antidepressant efficacy study of zimelidine and maprotiline were recruited". (Montgomery 1982a, p. 292) **Overall sample size:** 30 **Diagnosis of borderline personality disorder:** DSM-III **Means of assessment:** clinical interview **Mean age:** 35.05 years (SD = no information; range = no information) **Sex:** 70% women **Comorbidity:** no information **Inclusion criteria** 1. Patients admitted following a suicidal act 2. Having a history of 2 or more previous documented suicidal acts 3. More than 75% BPD (23 out of 30* by DSM-III and clinical interview) **Exclusion criteria** 1. Overt schizophrenia or depression 2. Organic illness
Interventions	**Experimental group** **Treatment name:** flupenthixol **Number randomised to group:** 14 **Duration:** 6 months **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 16 **Duration:** 6 months **Both groups** **Concomitant psychotherapy:** All patients attended the special crisis intervention clinic within two weeks of the index suicidal act. **Concomitant pharmacotherapy:** no information **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary outcomes:** 1. Suicidal behaviour, measured by the number of participants in each group with/without suicidal act within the 6 months of treatment. Assessed at week 4, 8, 12, 16, 20 and 24 (EOT) **Secondary outcomes:** adverse effects, measured by standard reporting form
Notes	**Sample calculation:** no information **Ethics approval:** no information **Funding source:** unclear funding **Conflicts of interest:** No conflicts of interest were reported. **Comments from trial authors (limitations):** none mentioned
Risk of bias	

Montgomery 1982a *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** insufficient information on methods used to generate random sequence to permit a judgement of low or high risk of bias
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information provided on allocation concealment to permit a judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote**: "intramuscular flupenthixol decanoate or placebo drawn from identical matching ampoules" (Montgomery 1979, p. 227)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote:** "intramuscular flupenthixol decanoate or placebo drawn from identical matching ampoules" (Montgomery 1979, p. 227)
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Quote:** "To preserve blindness patients with significant Parkinsonian side effects were removed from the trial and counted as dropouts." (Montgomery 1979, p. 227) **Comments:** reported dichotomous outcomes based on the completer sample (no further details on dropout patients concerning diagnosis, sex, and age) Of the 37 patients enrolled, 30 completed treatment (4 dropouts in the active group leaving 14 completers, 3 dropouts in the placebo group leaving 16 completers) Reasons for early termination: Parkinsonian side effects: 2 in flupenthixol group/0 in placebo group No reason given: 2/3 Only dichotomous data used in this review; dropouts were imputed as having the negative outcome.
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol found
Vested Interest (funding and/or author affiliations)	Unclear risk	**Comment:** no details about funding/sponsoring provided
Other bias	Low risk	**Comment:** no indication of other bias

Montgomery 1982b

Study characteristics	
Methods	38 participants; 6-month trial with 2 arms: 1. mianserin 2. placebo **Duration of trial:** 24 weeks **Country:** UK **Setting:** outpatient

Montgomery 1982b *(Continued)*

Participants	**Methods of recruitment of patients:** "[...] endogenously depressed patients who were taking part in a comparative antidepressant efficacy study of zimelidine and maprotiline were recruited". (Montgomery 1982a, p. 292) **Overall sample size:** 38 **Diagnosis of borderline personality disorder:** DSM-III **Means of assessment:** clinical interview **Mean age:** 35.65 years (SD = no information; range = no information) **Sex:** 68.42% women **Comorbidity:** no information **Inclusion criteria** 1. Patients admitted following a suicidal act 2. Having a history of 2 or more previous documented suicidal acts 3. More than 75% BPD (23 out of 30* by DSM-III and clinical interview) **Exclusion criteria** 1. Overt schizophrenia or depression 2. Organic illness
Interventions	**Experimental group** **Treatment name:** mianserin **Number randomised to group:** 29 **Duration:** 6 months **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 29 **Duration:** 6 months **Both groups** **Concomitant psychotherapy:** Patients were followed up in a clinic, with back-up from social workers, community nurses and a crisis intervention team. **Concomitant pharmacotherapy:** no information **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary outcomes:** suicidal behaviour, measured by the number of participants in each group with/without act of self-harm within the 6 months of treatment. Assessed at week 4, 8, 12, 16, 20 and 24 (EOT) **Secondary outcomes:** attrition in terms of participants lost after randomisation
Notes	**Sample calculation:** no information **Ethics approval:** no information **Funding source:** unclear funding **Conflicts of interest:** No conflicts of interest were reported. **Comments from trial authors (limitations):** none mentioned
Risk of bias	

Montgomery 1982b *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** insufficient information on methods used to generate random sequence to permit a judgement of low or high risk of bias
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information provided on allocation concealment to permit a judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** The trial was referred to as being double-blind, however, insufficient information was given on how blinding of participants and personnel was carried out (packaging of trial medication etc.) and maintained, to permit a judgement of low or high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** The trial was referred to as being double-blind, however, insufficient information was given on how blinding of outcome assessors was carried out and maintained, to permit a judgement of low or high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** dichotomous outcomes used here were based on the ITT sample; patients who had dropped out were imputed as having the negative outcome. High dropout rate (20 out of 58; Montgomery 1983, p. 787), but reasons not specified, nor to which treatment group the lost patients belonged. Therefore, dropouts could not be imputed in categorical outcomes as having the negative outcome.
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol found
Vested Interest (funding and/or author affiliations)	Unclear risk	**Comment:** no details about funding/sponsoring provided
Other bias	Low risk	**Comment:** no indication of other bias

NCT00533117

Study characteristics	
Methods	12-month trial with 4 arms: 1. DBT + fluoxetine 2. DBT + placebo 3. supportive therapy + fluoxetine 4. supportive therapy + placebo **Duration of trial:** 12 months **Country:** USA **Setting:** inpatient
Participants	**Method of recruitment of participants:** "Participants were recruited from the emergency department, clinician referrals and advertisements. The recruitment period ended 6 months prior to the study end date." (NCT00533117) **Overall sample size:** 75 (86 participants were randomised but 11 dropped out prior to the start of treatment)

NCT00533117 *(Continued)*

Diagnosis of borderline personality disorder: DSM-IV

Means of assessment: no information

Mean age: 30.2 years (SD 8.7; range = no information)

Sex: 77.3% women

Comorbidity: no information

Inclusion criteria

1. Meets criteria for a diagnosis of borderline personality disorder
2. History of at least one suicide attempt or self-mutilation episode 12 months prior to trial entry
3. Experiences continued urges to self-mutilate or attempt suicide
4. Stable living situation
5. Use of effective birth control if sexually active
6. Clinically stable enough to tolerate placebo condition
7. Not participating in other forms of treatment during the trial

Exclusion criteria

1. Any current organic mental syndromes, lifetime schizophrenic or bipolar disorders, psychotic disorders, or mental retardation
2. Inability to complete psychiatric interview due to lack of cooperation or lack of comprehension
3. Unable to tolerate fluoxetine or DBT
4. Currently receiving treatment for an acute medical illness or other debilitating problem, including substance abuse or anorexia nervosa
5. History of major depression lasting more than 3 months
6. Current Hamilton Depression score above 22 and not receiving treatment
7. Pregnant or breastfeeding

Interventions

Experimental group 1
Treatment name: dialectic behaviour therapy (DBT) + fluoxetine
Number randomised to group: 18
Duration: 12 months

Control/comparison group 1
Comparison name: DBT + placebo
Number randomised to group: 19
Duration: 12 months

Experimental group 2
Treatment name: supportive therapy + fluoxetine
Number randomised to group: 20
Duration: 12 months

Control/comparison group 2
Comparison name: supportive therapy + placebo
Number randomised to group: 18
Duration: 12 months

All groups
Concomitant psychotherapy: DBT or supportive therapy
Concomitant pharmacotherapy: Benzodiazepines were permitted for sleep.
Proportions of participants taking standing medication during trial observation period: no information

Outcomes

Primary outcomes

NCT00533117 *(Continued)*

1. Self-harm, measured in terms of proportion of patients with non-suicidal self-injury, and suicide attempt and NSSI count total over the course of the 12-month treatment period (sum of 6 bimonthly assessments during the treatment phase)
2. Suicide-related outcomes, measured by proportion of patients with suicidal acts, and suicide attempts total count over the course of the 12-month treatment period (sum of 6 bimonthly assessments during the treatment phase)

Secondary outcomes

1. Attrition, measured in terms of patients lost after randomisation in each group
2. Adverse effects, measured by spontaneous reporting

Notes

Sample calculation: no information

Ethics approval: no information

Funding source: funded by grants from universities, authorities or research foundations

Conflicts of interest: No conflicts of interest were reported.

Comments from trial authors (limitations): none mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** insufficient information on methods used to generate random sequence to permit a judgement of low or high risk of bias.
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information provided on allocation concealment to permit a judgement of low or high risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** Trial registration stated that the study had triple-blinding (participant, investigator and outcome assessor), however, there was no information on how the blinding was secured or if it was adequately maintained throughout the study to permit a judgement of low or high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** Trial registration stated that the study had triple-blinding (participant, investigator and outcome assessor), however, there was no information on how the blinding was secured or if it was adequately maintained throughout the study to permit a judgement of low or high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment**: even dropout rates, total rates around ¼ of participants, no information on ITT, but all randomised participants were analysed.
Selective reporting (reporting bias)	Low risk	**Comment**: only a trial registry. All data reported
Vested Interest (funding and/or author affiliations)	Low risk	**Comment**: Sponsored by New York State Psychiatric Institute; Collaboration with National Institute of Mental Health
Other bias	Low risk	**Comment:** no indication of other bias

Nickel 2004

Study characteristics

Nickel 2004 *(Continued)*

Methods	8-week trial with 2 arms: 1. topiramate 2. placebo **Duration of trial:** 8 weeks **Country:** Germany **Setting:** outpatient
Participants	**Method of recruitment of participants:** no information **Overall sample size:** 31 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** SCID-II **Mean age:** 26.05 years (SD = no information; range = no information) **Sex:** 100% women **Comorbidity:** no information **Inclusion criteria** 1. Women 2. Age between 20 and 35 years 3. Disturbed by moodiness, distrustfulness, impulsivity, and painful and difficult relationships 4. Subjective feelings of constantly increasing anger caused by participants life situation **Exclusion criteria** 1. Actively suicidal patients 2. Abusing alcohol or drugs 3. Major depression 4. Schizophrenia 5. Bipolar disorder 6. Current use of topiramate or other psychotropic medication 7. Psychotherapy 8. Somatically ill 9. Pregnant or planning to become pregnant
Interventions	**Experimental group** **Treatment name:** topiramate **Number randomised to group:** 21 **Duration:** 8 weeks **Control/ comparison group** **Comparison name:** placebo **Number randomised to group:** 10 **Duration:** 8 weeks **Both groups** **Concomitant psychotherapy:** not allowed **Concomitant pharmacotherapy:** not allowed **Proportions of participants taking standing medication during trial observation period:** no information; however, concomitant medication was not allowed.
Outcomes	**Primary outcomes:** none

Nickel 2004 *(Continued)*

Secondary outcomes

1. Anger, measured by STAXI trait anger subscale. Assessed at baseline and every week for 8 weeks (EOT)
2. Impulsivity, measured by STAXI anger-out subscale. Assessed at baseline and every week for 8 weeks (EOT)
3. Attrition
4. Adverse effects, measured by non-structured questionnaire. Assessed every week for 8 weeks

Notes

Sample calculation: yes, "According to a power analysis, 21 patients were required for a topiramate trial." (Nickel 2004, p. 1516)

Ethics approval: yes, "[The trial design] was approved by the clinic's "Ethikkomision" (the German equivalent of the Committee on Human Subjects". (Nickel 2004, p. 1516)

Funding source: unclear funding

Conflicts of interest: No conflicts of interest were reported.

Comments from trial authors (limitations)

1. "The sample size was (in spite of a valid power analysis) relatively small". (Nickel 2004, p. 1518)
2. "[...] the sample consisted only of women with borderline personality disorder. Whether these results could also be replicated with men meeting the criteria for borderline personality disorder is unknown". (Nickel 2004, p. 1518)
3. "[...] the sample was composed of moderately ill outpatients who were not suffering from a concurrent major depressive episode and were not abusing substances or taking concurrent medications." (Nickel 2004, p. 1518-9)
4. "[...] the length of this trial was only 2 months, which may have reduced the dropout rate". (Nickel 2004, p. 1519)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** The article mentioned that the trial was randomised, however, there was insufficient information on how the randomisation procedure was carried out to permit a judgement of low or high risk of bias.
Allocation concealment (selection bias)	Unclear risk	**Quote:** "Randomization was carried out confidentially by the clinic administration." (Nickel 2004, p. 1516) **Comment:** Allocation sequence appeared to have been confidential, however, there was insufficient information on how this confidentiality was maintained to permit a judgement of low or high risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "Tablets were supplied in numbered boxes. Both subjects and clinicians were blinded regarding topiramate/placebo assignment." (Nickel 2004, p. 1516).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote:** "Tablets were supplied in numbered boxes. Both subjects and clinicians were blinded regarding topiramate/placebo assignment." (Nickel 2004, p. 1516). **Comment:** Unclear if clinicians were also outcome assessors, therefore insufficient information to permit judgement of low or high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Quote:** "Two subjects, who failed to appear 2 to 3 times for the weekly evaluations, dropped out of the study, and their data were not further analysed. Finally, data from 29 women [...] were evaluated." (Nickel 2004, p. 1516)

Nickel 2004 *(Continued)*

		Comment: continuous outcomes based on available case analysis. Of the 31 patients enrolled, 29 completed treatment. Reasons for early termination: Failed to appear at least 2 times for weekly evaluation, no further details: 2 in topiramate group/0 in placebo group
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol found
Vested Interest (funding and/or author affiliations)	Unclear risk	**Quote:** "The authors report no financial affiliation or other relationship relevant to the subject matter of this article." (Nickel 2004, p. 1515)
Other bias	Low risk	**Comment:** No apparent other sources of bias found

Nickel 2005

Study characteristics	
Methods	8-week trial with 2 arms: 1. topiramate 2. placebo **Duration of trial:** 8 weeks **Country:** Germany **Setting:** outpatient
Participants	**Method of recruitment of participants:** Patients were recruited with the assistance of colleagues in their practices and the clinic outpatient department, as well as through advertisements in the local and regional press. **Overall sample size:** 44 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** SCID-II **Mean age:** 29.1 years (SD = no information; range = no information) **Sex:** 100% men **Comorbidity:** Comorbid mood disorders, somatoform disorders, anxiety disorders and eating disorders were ascertained in the trial sample. **Inclusion criteria** 1. At least 18 years of age 2. Had subjectively perceived that the excessive burdens caused by their life situations had produced feelings of constantly increasing anger **Exclusion criteria** 1. Actively suicidal 2. Currently fulfilling criteria for an addictive illness 3. Severe major depression 4. Acute psychosis 5. Bipolar disorder 6. Current use of topiramate or other psychotropic medication

Nickel 2005 *(Continued)*

7. Current psychotherapy
8. Somatically ill

Interventions	**Experimental group** **Treatment name:** topiramate **Number randomised to group:** 22 **Duration**: 8 weeks **Control/comparison group** **Medication name:** placebo **Number randomised to group:** 22 **Duration:** 8 weeks **Both groups** **Concomitant psychotherapy:** not allowed **Concomitant pharmacotherapy:** psychotropic medication not allowed **Proportions of participants taking standing medication during trial observation period:** no information; however, concomitant psychotropic medication was not allowed.
Outcomes	**Primary outcomes:** none **Secondary outcomes** 1. Anger, measured by STAXI trait-anger subscale. Assessed at baseline and every week for 8 weeks (EOT) 2. Impulsivity, measured by STAXI anger-out subscale. Assessed at baseline and every week for 8 weeks (EOT) 3. Attrition 4. Adverse effects, measured by weight and a non-structured questionnaire. Assessed every week for 8 weeks (EOT)
Notes	**Sample calculation:** no information **Ethics approval:** design approved by Ethikkommission der ROMED Kliniken KG **Funding source:** no funding received **Conflicts of interest:** No conflicts of interest were reported. **Comments from trial authors (limitations)** 1. "[...] the sample size was (in spite of valid power analysis) relatively small." (Nickel 2005, p. 498) 2. "[...] the sample was composed of moderately ill outpatients who were not suffering from a concurrent major depressive episode, abusing substances, or taking concurrent medications". (Nickel 2005, p. 498) 3. "[...] the length of this trial was only 2 months, which may have reduced the dropout rate, particularly in the placebo group". (Nickel 2005, p. 498)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** The article mentioned that the trial was randomised, however, there was insufficient information on how the randomisation procedure was carried out to permit a judgement of low or high risk of bias.
Allocation concealment (selection bias)	Unclear risk	**Quote:** "Randomization was carried out confidentially by the clinic administration." (Nickel 2005, p. 496)

Nickel 2005 *(Continued)*

		Comment: Allocation sequence appeared to have been confidential, however, there was insufficient information on how this confidentiality was maintained to permit a judgement of low or high risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "Subjects received blinded medication daily, which at the beginning amounted to either 50 mg of topiramate or of a matching placebo. [...]Tablets were supplied in numbered boxes. Both subjects and clinicians were blinded regarding topiramate or placebo assignment." (Nickel 2005, p. 496)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote:** "Subjects received blinded medication daily, which at the beginning amounted to either 50 mg of topiramate or of a matching placebo. [...]Tablets were supplied in numbered boxes. Both subjects and clinicians were blinded regarding topiramate or placebo assignment." (Nickel 2005, p. 496) **Comment:** Unclear if clinicians were also outcome assessors, therefore insufficient information to permit judgement of low or high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Quotes**: "Forty-eight subjects were eligible to take part in the study [...] 44 patients were required [...] randomization was carried out confidentially by the clinical administration [...] 1:1 randomisation ratio for topiramate (TG, N = 22) versus placebo treatment (N = 22)". (Nickel 2005, p. 496) "Two subjects from the placebo group failed to appear more than twice for the weekly evaluations and dropped out of the study; their data were not further analysed. Thus, data from 42 men (42 out of 44) were evaluated." (Nickel 2004, p. 1516). **Comments**: unclear, why or how the 44 participants were finally chosen out of the 47 potential participants Of the 44 patients enrolled, 42 completed treatment (22 in the active group, 20 in the placebo group) Reasons for early termination: Failed to appear more than twice for weekly evaluation, no further reasons given: 0 in the active group, 2 in the placebo group Reasons for early termination not further specified. Continuous outcomes based on available case analysis. For dichotomous data, dropouts were imputed as having the negative outcome.
Selective reporting (reporting bias)	Unclear risk	**Comment**: no protocol found
Vested Interest (funding and/or author affiliations)	Unclear risk	**Quote:** "The study was planned and conducted in accordance with the Declaration of Helsinki and ethical laws pertaining to the medical professions and its design approved by Ethikkommission der ROMED Kliniken KG. All subjects gave written informed consent. The study was conducted independent of any institutional influence and was not funded, and there were no conflicts of interest." (Nickel 2004, p. 496)
Other bias	Low risk	**Comment:** No apparent other sources of bias found

Nickel 2006

Study characteristics	
Methods	8-week trial with 2 arms: 1. aripiprazole

Nickel 2006 *(Continued)*

	2. placebo **Duration of trial:** 8 weeks **Country:** Germany **Setting:** outpatient
Participants	**Method of recruitment of participants:** Participants were recruited through advertisements. **Overall sample size**: 52 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** SCID-II **Mean age:** 21.65 years (SD 3.4; range = no information) **Sex:** 82.69% women, 17.3% men **Comorbidity**: Comorbidity included depressive disorders, anxiety disorders, obsessive-compulsive disorders and somatoform disorders. **Inclusion criteria:** meeting criteria for borderline personality disorder **Exclusion criteria** 1. Current suicidal ideation 2. Schizophrenia 3. Current use of aripiprazole or another psychotropic medication 4. Current psychotherapy 5. Pregnancy, planned pregnancy or sexual activity without contraception 6. Severe somatic illness
Interventions	**Experimental group** **Treatment name:** aripiprazole **Number randomised to group:** 26 **Duration:** 8 weeks **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 26 **Duration:** 8 weeks **Both groups** **Concomitant psychotherapy:** not allowed **Concomitant pharmacotherapy:** not allowed **Proportions of participants taking standing medication during trial observation period:** no information; however, concomitant medication was not allowed.
Outcomes	**Primary outcomes** 1. Self-mutilating behaviour, measured by the number of patients with/without self-injury during the 8-week treatment 2. Psychosocial functioning, measured by SCL-90-R GSI. Assessed at baseline and every week for 8 weeks (EOT) **Secondary outcomes** 1. Anger, measured by SCL-90-R-HOS and STAXI-trait anger subscale. Assessed at baseline and every week for 8 weeks (EOT) 2. Impulsivity, measured by STAXI-anger out subscale. Assessed at baseline and every week for 8 weeks (EOT)

Nickel 2006 *(Continued)*

3. Interpersonal problems, measured by SCL-90-R-INT. Assessed at baseline and every week for 8 weeks (EOT)
4. Psychotic symptoms, measured by SCL-90-R-PAR and SCL-90-R-PSY. Assessed at baseline and every week for 8 weeks (EOT)
5. Depression, measured by SCL-90-R-DEP and Ham-D. Assessed at baseline and every week for 8 weeks (EOT)
6. Adverse effects, measured by a non-validated questionnaire, serious side effects and suicidal acts. Assessed every week for 8 weeks (EOT)

Notes	**Sample calculation:** no information **Ethics approval:** Yes, "The study was planned and conducted in accordance with the Declaration of Helsinki and ethical laws pertaining to the medical profession, and its design was approved by the clinic's ethics committee". (Nickel 2006, p. 835) **Funding source:** no funding received **Conflicts of interest:** No conflicts of interest were reported **Comments from trial authors (limitations)** 1. "Despite a valid power analysis, the group was small". (Nickel 2006, p. 836) 2. "The length of this trial was only 8 weeks, which possibly reduced the failure rate". (Nickel 2006, p. 836) 3. "The effects of aripiprazole on the fourth dimension—disturbed relationships—were not evaluated". (Nickel 2006, p. 837) 4. "the Zanarini Rating Scale for Borderline Personality Disorder, a new clinician-rated outcome measure specifically designed for borderline personality disorder, was not available in the German language when we began the study." (Nickel 2006, p. 837)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** The article mentioned that the trial was randomised, however, there was insufficient information on how the randomisation procedure was carried out to permit a judgement of low or high risk of bias.
Allocation concealment (selection bias)	Unclear risk	**Quote**: "The random assignment was carried out confidentially by the clinic administration and arranged so that the same number of patients would be treated with the active drug (N = 26, 21 women and 5 men) as with a placebo (N = 26, 22 women and 4 men)". (Nickel 2006, p. 835) **Comment:** Allocation sequence appeared to have been confidential, however, there was insufficient information on how this confidentiality was maintained to permit a judgement of low or high risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote**: "the subjects received medication in a blinded manner, […] The dosage remained constant. Tablets were supplied in numbered boxes. Both the subjects and the clinicians were blinded regarding the assignment of aripiprazole or placebo." (Nickel 2006, p. 835)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote**: "the subjects received medication in a blinded manner, […] The dosage remained constant. Tablets were supplied in numbered boxes. Both the subjects and the clinicians were blinded regarding the assignment of aripiprazole or placebo." (Nickel 2006, p. 835) **Comment:** Unclear if clinicians were also outcome assessors, therefore insufficient information to permit judgement of low or high risk of bias

Nickel 2006 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	**Quotes:** "Five subjects who missed more than two weekly evaluations dropped out." (Nickel 2006, p. 835) "according to the intent-to-treat principle performed with the last-observation-carried-forward" (Nickel 2007, p. 1025) **Comments:** Of the 52 patients enrolled, 47 completed treatment. Reasons for dropout not further specified. Reasons for early termination: Failed to appear more than twice for weekly evaluation, no further reasons given: 5 participants, no further details Continuous outcomes based on ITT sample (LOCF); dichotomous outcomes based on ITT sample
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol found
Vested Interest (funding and/or author affiliations)	Unclear risk	**Quote:** "The study was planned and conducted in accordance with the Declaration of Helsinki and ethical laws pertaining to the medical profession, and its design was approved by the clinic's ethics committee. The study was conducted independently of any institutional influence and was not funded." (Nickel 2006, p. 835)
Other bias	Low risk	**Comment:** No apparent other sources of bias found

Pascual 2008

Study characteristics	
Methods	12-week trial with 2 arms: 1. ziprasidone 2. placebo **Duration of trial:** 12 weeks, following a 2-week baseline period **Country:** Spain **Setting:** outpatient
Participants	**Method of recruitment of participants:** "[...] referred from clinical service (outpatient and psychiatrics emergency services)" (Pascual 2008, p. e2) **Overall sample size:** 60 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** SCID-II and DIB-R **Mean age:** 29.2 years (SD = no information; range = no information) **Sex:** 81.67% women **Comorbidity:** no information **Inclusion criteria** 1. Meeting the DSM-IV diagnostic criteria for borderline personality disorder, assessed by 2 semi-structured diagnostic interviews: SCID-II and DIB-R 2. Aged between 18 and 45 years

Pascual 2008 *(Continued)*

3. No comorbidity with schizophrenia, drug-induced psychosis, organic brain syndrome, alcohol or other substance dependence, bipolar disorder, mental retardation and major depressive episode in course
4. CGI-S scores ≥ 4
5. Current use of medically accepted contraception in the case of female patients

Exclusion criteria

1. Schizophrenia
2. Alcohol or other substance dependence
3. Current major depressive episode
4. Bipolar disorder
5. Drug-induced psychosis
6. Organic brain syndrome
7. Mental retardation

Interventions

Experimental group
Treatment name: ziprasidone
Number randomised to group: 30
Duration: 12 weeks

Control/comparison group
Comparison name: placebo
Number randomised to group: 30
Duration: 12 weeks

Both groups
Concomitant psychotherapy: Patients participated in weekly, 2-hour, non-specific group psychotherapy sessions.
Concomitant pharmacotherapy: allowed to continue with benzodiazepine (maximum of 40 mg/day), antidepressants, and mood stabilisers if initiated prior to inclusion; doses could not be modified.
Proportions of participants taking standing medication during trial observation period: In the ziprasidone condition, 76.7% of patients were taking benzodiazepines, 70% were taking antidepressants and 40% were taking mood stabilisers. In the placebo condition, the proportions were 83.3% benzodiazepines, 73.3% antidepressants and 40% mood stabilisers.

Outcomes

Primary outcomes

1. BPD severity, measured by CGI-BPD-global. Assessed at baseline and at weeks 2, 4, 6, 8, 0, 12 (EOT) and 14
2. Suicidal ideation, measured by CGI-BPD-suicide. Assessed at baseline and at weeks 2, 4, 6, 8, 0, 12 (EOT) and 14
3. Psychosocial functioning, measured by SCL-90-R-GSI. Assessed at baseline and at weeks 2, 4, 6, 8, 0, 12 (EOT) and 14

Secondary outcomes

1. Anger, measured by CGI-BPD-anger. Assessed at baseline and at weeks 2, 4, 6, 8, 0, 12 (EOT) and 14
2. Affective instability, measured by CGI-BPD-affect instability. Assessed at baseline and at weeks 2, 4, 6, 8, 0, 12 (EOT) and 14
3. Feelings of emptiness, measured by CGI-BPD-emptiness. Assessed at baseline and at weeks 2, 4, 6, 8, 0, 12 (EOT) and 14
4. Impulsivity, measured by CGI-BPD-impulsivity and BIS. Assessed at baseline and at weeks 2, 4, 6, 8, 0, 12 (EOT) and 14
5. Interpersonal problems, measured by CGI-BPD-unstable relations. Assessed at baseline and at weeks 2, 4, 6, 8, 0, 12 (EOT) and 14
6. Avoidance of abandonment, measured by CGI-BPD-abandonment. Assessed at baseline and at weeks 2, 4, 6, 8, 0, 12 (EOT) and 14

Pascal 2008 *(Continued)*

7. Identity disturbance, measured by CGI-BPD-identity. Assessed at baseline and at weeks 2, 4, 6, 8, 0, 12 (EOT) and 14
8. Psychotic paranoid symptoms, measured by CGI-BPD-paranoid ideation and BPRS. Assessed at baseline and at weeks 2, 4, 6, 8, 0, 12 (EOT) and 14
9. Depression, measured by Ham-D-17 and BDI. Assessed at baseline and at week 2, 4, 6, 8, 0, 12 (EOT) and 14
10. Attrition
11. Adverse effects, measured by treatment-emergent adverse events, EKG, laboratory assessment, UKU Side Effect Rating Scale for extrapyramidal side effects. Assessed at baseline and at weeks 2, 4, 6, 8, 0, 12 (EOT) and 14

Notes

Sample calculation: no information

Ethics approval: yes

Funding source: funded or partially funded by pharmaceutical industry

Conflicts of interest: No conflicts of interest were reported besides partial funding from the pharmaceutical industry.

Comments from trial authors (limitations)

1. "[...] due the characteristics of the sample size, the results cannot be extrapolated to inpatients, patients with less clinically severe disorders or patients with active comorbid Axis I disorders." (Pascual 2008, p. e5)
2. "[...] the majority of patients included in our sample were receiving concomitant treatment with benzodiazepines and/or antidepressants. Despite the fact that stable doses were maintained we cannot rule out possible drug-drug interactions". (Pascual 2008, p. e5)
3. "In spite of randomisation, the placebo group showed greater severity." (Pascual 2008, p. e5)
4. "Another limitation [...] is the high dropout rate [...].By including a psychosocial intervention we pretended to improve compliance and lower dropout rates, but [were] unsuccessful." (Pascual 2008, p. e5)
5. "[...] the psychosocial interventions may have masked the differences between ziprasidone and placebo." (Pascual 2008,p. e5)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "Randomization was performed by blocks of 4 generated using the SPSS software package". (Pascual 2008, p. 604)
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information provided on allocation concealment to permit a judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** The trial was referred to as being double-blind, however, no information was provided on how blinding was carried out or maintained.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** The trial was referred to as being double-blind, however, no information was provided on how blinding was carried out or maintained.
Incomplete outcome data (attrition bias) All outcomes	High risk	**Quote:** "All analyses were conducted on an intent-to-treat basis. [...] Patients were included in the analyses only if they had a baseline measure and at least 1 post-baseline measure. [...] The end point was based on a last-observation-carried-forward (LOCF) strategy." (Pascual 2008, p. 604 et seq.)

Pascal 2008 *(Continued)*

		Comment: intent-to-treat data referred to all participants that were randomly assigned and who initiated the experimental phase (Pascal 2008, p. 605). However, it remained unclear why 5 out of the 65 eligible participants "dropped out during the selection phase". (Pascal 2008, p. 605) Reasons for dropout specified and balanced across the two groups, including withdrawal due to "clinician decision/insufficient treatment effect" (Pascal 2008, p. 605 et seq.) Of the 60 patients enrolled, 29 completed the full 12 weeks of the trial (13 in ziprasidone group, 16 in placebo group). Reasons for early termination: Need of psychiatric hospitalisation: 4 in ziprasidone group/3 in placebo group Adverse events/patient decision: 9/4 Clinician decision/insufficient treatment effect: 3/7 Other reasons: 1/0 Continuous data based on LOCF data of the ITT sample; dichotomous data based on ITT sample
Selective reporting (reporting bias)	Low risk	**Comment:** The trial protocol was available and all of the prespecified primary and secondary outcomes that were of interest in the review were reported in the prespecified way.
Vested Interest (funding and/or author affiliations)	High risk	**Quote:** "This study was supported by grants from the Fondo de Investigación Sanitaria (Ministry of Health, Spain), the REM-TAP Network, and Pfizer, Madrid, Spain. The authors report no additional financial or other relationships relevant to the subject of this article." (Pascal 2008, p. 603)
Other bias	Low risk	**Comment:** no indication of other bias

Reich 2009

Study characteristics	
Methods	12-week trial with 2 arms: 1. lamotrigine 2. placebo **Duration:** 12 weeks **Country:** USA **Setting:** outpatient
Participants	**Method of recruitment of participants:** Patients were recruited through websites and advertising on local radio and television stations. **Overall sample size:** 27 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** DIB-R score > 8 **Mean age:** 31.2 years (SD = no information; range = no information) **Sex:** 88.89% women, 11.11% men **Comorbidity:** Cormobid diagnoses included in the trial were major depression, PTSD, OCD, GAD, panic disorder, social phobia and specific phobia. Major depression was the most common comorbid diagno-

Reich 2009 *(Continued)*

sis in both groups. Comorbid anxiety disorders were also common in both groups. For the lamotrigine group, panic disorder was the second most common comorbid diagnosis, followed by post-traumatic stress disorder; for the placebo group, panic disorder was the second most common comorbid diagnosis, followed by social phobia. There were no significant differences in comorbidity between the two groups.

Inclusion criteria

1. Between 18 and 64 years of age
2. Had to meet DSM-IV criteria for BPD using the Borderline module of the Diagnostic Interview for DSM-IV Personality Disorders and have a score on the DIB-R of 8 or greater
3. Had to score 'serious' on the affective instability item of Zan-BPD
4. Had to achieve a total score of 4 on nine items measuring lability of anger on the Affective Lability Scale (ALS)

Exclusion criteria

1. Diagnosis of dementia
2. Psychiatric disorder secondary to a general medical condition
3. Bipolar disorder or psychotic disorder (schizophrenia, schizoaffective disorder, or mood disorder with psychotic features)
4. Diagnosis of substance dependence (active within last 60 days)
5. Hospitalised
6. Unstable general medical condition
7. Previous treatment with lamotrigine for 1 week or more
8. Enrolment in a drug trial within last 60 days
9. Enrolment in psychotherapy in the last 30 days
10. Active suicidal or homicidal ideation
11. Pregnancy or nursing

Interventions	**Experimental group** **Treatment name:** lamotrigine **Number randomised to group:** 15 **Duration**: 12 weeks **Control/comparison group** **Medication name:** placebo **Number randomised to group:** 12 (one of the 13 patients assigned to placebo was disqualified because of failure to adhere to the trial protocol and was not included in analyses) **Duration**: 12 weeks **Both groups** **Concomitant psychotherapy:** Patients enrolled in psychotherapy in the last 30 days were not eligible. **Concomitant pharmacotherapy:** Patients could be taking one antidepressant, but had to have been on a stable dose of that medication for 1 month. **Proportions of participants taking standing medication during trial observation period:** "Significantly more patients in the placebo group than in the lamotrigine took antidepressants during the study (week 2: 4.73, df = 1, P = 0.03). In the placebo group, one patient was taking doxepin, one patient was taking bupropion, one patient was taking citalopram, and two patients were taking escitalopram. In the lamotrigine group, one patient was taking paroxetine." (Reich 2009, p. 272)
Outcomes	**Primary outcomes:** BPD severity, measured by ZAN-BPD total score. Assessed at baseline and every week for 12 weeks (EOT) **Secondary outcomes** 1. Affective instability, measured by ZAN-BPD-affective instability score and ALS. Assessed at baseline and every week for 12 weeks (EOT) 2. Impulsivity, measured by ZAN-BPD-impulsivity score Assessed at baseline and every week for 12 weeks (EOT)

Reich 2009 *(Continued)*

3. Attrition
4. Adverse effects: measured by laboratory values and physical examination. Assessed at baseline and week 12 (EOT)

Notes

Sample calculation: no information

Ethics approval: no information

Funding source: funded or partially funded by pharmaceutical industry

Conflicts of interest: No conflicts of interest were reported besides funding from the pharmaceutical industry.

Comments from trial authors (limitations)

1. "[...] the study involved only small sample size". (Reich 2009, p. 274)
2. "[...] although 14 (52%) of the patients in our study had been hospitalised at one point, all of them were outpatients at the time of the study, and none was actively suicidal. Thus, the study may have excluded many more severely ill borderline patients." (Reich 2009, p. 274)
3. "[...] patients in our study were predominantly female. Although both male patients receiving lamotrigine in our study had improvements in the primary outcome measures, it is not clear to what extent our results would generalize to male patients with BPD." (Reich 2009, p. 274)
4. "[...] our study was of only 12 weeks duration, a short period for an illness in which improvement unfolds slowly." (Reich 2009, p. 274)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "patients were randomized [...] in a 1:1 manner. This was determined by a prearranged random number sequence." (Reich 2009, p. e-3)
Allocation concealment (selection bias)	Unclear risk	**Comment:** insufficient information to permit judgement (unclear, if the number sequence was kept confidentially or if enrolling investigators could possibly foresee assignment)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Quote:** "The prescribing psychiatrist (D.B.R.) prescribed one tablet of study medication, 25 mg of lamotrigine, or matching inert placebo". (Reich 2009, p. 2) **Comment:** The study was described as being double-blind, however, there was insufficient information on how the blinding was secured or if it was adequately maintained throughout the study to permit a judgement of low or high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote**: "double-distinction between "prescribing psychiatrist (D.B.R.)" who fixed the dose and "study staff" who made assessments" (Reich 2009, p. 3)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Quote:** "One patient in the placebo group was disqualified because of failure to adhere to the study protocol." (Reich 2009, p. e-3) **Comment:** not clear if the reported mean changes were based on the ITT sample or completers only
Selective reporting (reporting bias)	Low risk	**Comment:** The trial protocol was available and all of the prespecified primary and secondary outcomes that were of interest in the review that were prespecified in the protocol were reported in the text.

Reich 2009 *(Continued)*

Vested Interest (funding and/or author affiliations)	High risk	**Quote:** "The study was supported by a grant from GlaxoSmithKline." (Reich 2009, p. e-5)
Other bias	Low risk	**Comment:** no indication of other bias

Rinne 2002

Study characteristics	
Methods	6-week trial with 2 arms: 1. fluvoxamine 2. placebo **Duration**: 6 weeks, patients had to be medication-free for at least 2 weeks before entering the trial **Country**: Holland **Setting:** outpatients
Participants	**Method of recruitment of participants:** "[Patients were] recruited from psychiatric outpatient clinics, from community mental health centres, and through advertisement in newspapers and on the Internet." (Rinne 2002, p. 2049) **Overall sample size:** 38 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** SCID-II + a score of 110 or more on the Borderline Trait and Distress scale of a self-report screener for personality disorders (ADP-IV) + score of 20 or more on BPDSI **Mean age:** 29.2 years (SD 7.6 years; range = no information) **Sex**: 100% women **Comorbidity**: depression (28.95%), dysthymia (21.05%), generalised anxiety disorder (7.89%) and PTSD (31.58%) **Inclusion criteria** 1. A score of 110 or more on the Borderline Trait and Distress Scale of a self-report screener for personality disorders, the Assessment of DSM-IV Personality Disorder 2. Meet five or more of the criteria on a semi-structured diagnostic interview, the Structured Interview for DSM-IV Personality Disorders 3. A score of 20 or more on a fully structured interview, the BPDSI **Exclusion criteria:** no information
Interventions	**Experimental group** **Treatment name:** fluvoxamine **Number randomised to group:** 20 **Duration:** 6 weeks; patients had to be medication-free for at least 2 weeks prior to entering trial **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 18 **Duration:** 6 weeks; patients had to be medication-free for at least 2 weeks prior to entering trial **Both groups**

Rinne 2002 *(Continued)*

Concomitant psychotherapy: Two patients who began psychotherapy dropped out of the trial; thus, psychotherapeutic treatment was likely not to have been allowed.
Concomitant pharmacotherapy: Patients had to stop taking all psychoactive drugs and be medication-free for at least 2 weeks before entering the trial (6 weeks for fluoxetine).
Proportions of participants taking standing medication during trial observation period: Patients had to be free of medication 2-6 weeks prior to entering trial; however, no further information was stated.

Outcomes

Primary outcomes: none

Secondary outcomes

1. Anger, measured by BPDSI-anger. Assessed at baseline and week 6 (EOT)
2. Affective instability, measured by BPDSI-rapid mood shifts. Assessed at baseline and week 6 (EOT)
3. Impulsivity, measured by BPDSI-impulsivity. Assessed at baseline and week 6 (EOT)
4. Attrition
5. Adverse effects: any, measured by number of participants experiencing specific adverse events (not used here as data referred to intermediate assessment, whereas post-treatment data were not available)

Notes

Sample calculation: no information

Ethics approval: no information

Funding source: funded by grants from universities, authorities or research foundations

Conflicts of interest: No conflicts of interest were reported.

Comments from trial authors (limitations)

1. "[...] the dose of fluvoxamine, 150 mg/day, may have been too low for the treatment of impulsive and aggressive behaviour. However, this dose was chosen because it is fairly high and is sufficient for most indications but is low enough to restrict side effects." (Rinne 2002, p. 2052)
2. "[...] It cannot be ruled out completely that the power of the study was too small to detect smaller differences in reductions of anger and impulsivity and interactions with depression." (Rinne 2002, p. 2052)
3. "The lack of an effect of fluvoxamine on impulsivity might also be related to the relatively low internal consistency of the impulsivity subscale of the Borderline Personality Disorder Severity Index (alpha = 0.48)." (Rinne 2002, p. 2053)

Comments from review authors: This is an RCT followed by a single-blind half cross-over and an open treatment phase; only the first RCT phase was regarded in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** Insufficient information on methods used to generate random sequence to permit a judgement of low or high risk of bias
Allocation concealment (selection bias)	Unclear risk	**Comment:** Insufficient information provided on allocation concealment to permit a judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** The trial was referred to as being double-blind, however, no information was provided on how blinding was carried out or maintained.
Blinding of outcome assessment (detection bias)	Unclear risk	**Comment:** The trial was referred to as being double-blind, however, no information was provided on how blinding was carried out or maintained.

Rinne 2002 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	**Quotes:** "The final study group comprised the 38 subjects eligible for participation". (Rinne 2002, p. 2049), "an intent-to-treat analysis was performed" (Rinne 2002, p. 2050) **Comments:** Of the 38 patients enrolled, 35 completed the RCT phase (19 in active drug group, 16 in placebo group). Reasons for early termination: Serious aggravation of self-damaging behaviours: 0 in the fluvoxamine group, 2 in the placebo group Severe side effects: 1/0 Continuous outcomes based on ITT; BMDP imputation technique used for dropouts
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol found
Vested Interest (funding and/or author affiliations)	High risk	**Quote:** "Supported by the De Geestgronden Institute of Mental Health Care, by Stichting tot Steun of Vereiniging Bennekom, by national Fund for Mental Health grant 4820, and by Solvay Pharma." (Rinne 2002, p. 2053)
Other bias	Low risk	**Comment:** No apparent other sources of bias found

Salzman 1995

Study characteristics	
Methods	12-week trial with 2 arms: 1. fluoxetine 2. placebo **Duration of trial:** 12 weeks **Country**: USA **Setting**: outpatient
Participants	**Method of recruitment of participants:** Patients were recruited through newspaper advertisement. **Overall sample size:** 22 **Diagnosis of borderline personality disorder:** DSM-III-R **Means of assessment:** DIB-R, SCID-II and clinical interview **Mean age:** 36.3 years (SD = no information; range = no information) **Sex:** 63.64% women* **Comorbidity**: Patients were excluded if they had current axis I disorders, as determined by clinical interview, or concurrent secondary axis II disorder. No further information **Inclusioncriteria:** no information **Exclusion criteria** 1. Self-mutilating behaviours during the past 4 years 2. Recent suicidal behaviour

Salzman 1995 *(Continued)*

3. Current suicidal or aggressive behaviour
4. Current substance abuse or excessive daily alcohol use (> 2 drinks/day)
5. History of psychiatric hospitalisation
6. Concurrent secondary axis II disorder, major depression or other axis I disorder

Interventions	**Experimental group** **Treatment name:** fluoxetine **Number randomised to group:** 13 **Duration:** 12 weeks with 1 week of placebo run-in **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 9 **Duration:** 13 weeks, including 1 week of placebo run-in **Both groups** **Concomitant psychotherapy:** Two patients were receiving psychotherapy; however, they did not differ in demographic variables, in entry criteria, or in response to treatment from the remaining participants. **Concomitant pharmacotherapy:** Other psychotropic medication was an exclusion criterion. **Proportions of participants taking standing medication during trial observation period:** Other psychotropic medication was an exclusion criterion. No further information provided
Outcomes	**Primary outcomes:** mental health status (functioning), measured by GAS. Assessed at baseline and every week after for 13 weeks (EOT). Analyses for pre and post-treatments only **Secondary outcomes** 1. Anger, measured by PDRS-anger, POMS-anger, and OAS-M-anger against objects. Assessed at baseline and every week after for 13 weeks (EOT). Analyses for pre and post-treatments only 2. Depression, measured by Ham-D, PDRS-depression and POMS-depression. Assessed at baseline and every week after for 13 weeks (EOT). Analyses for pre and post-treatments only
Notes	**Sample calculation:** no information **Ethics approval:** no information **Funding source:** unclear funding **Conflicts of interest:** No conflicts of interest were reported. **Comments from trial authors (limitations)** 1. "In order to place these findings in a meaningful clinical context, it is necessary to emphasize the small sample size and also the relative high functioning of the participants studied." (Salzman 1995, p. 27) 2. "The findings reported here may not necessarily be generalized to other BPD patients who are more severely impaired, either functionally or affectively, or who show significant self-abuse or suicidal or psychotic features." (Salzman 1995, p. 27) **Comments from review authors:** *reported on completers only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "random-assignment comparison" (Salzman 1995, p. 24) **Comment:** Trial was referred to as randomised, however, there was not sufficient information on how randomisation was carried out to permit a judgement of low or high risk of bias.

Salzman 1995 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	**Comment:** Insufficient information provided on allocation concealment to permit a judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Quote:** "All subjects began with a single, 20 mg capsule or identical placebo, and doses were titrated up to a maximum of 60 mg/day according to the needs of the patient and in accordance with package insert guidelines." (Salzman 1995, p. 24) **Comment:** Participants appeared to have been blinded as medication and placebo were identical, however, there was no information about whether personnel were blind to allocation sequence.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote**: "Subjects were evaluated by independent observers". (Salzman 1995, p. 24)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Quote:** "Thirty-one subjects met criteria for this study; four decided not to enroll and were lost to follow-up. Of 27 subjects who enrolled in the study, 22 completed the trial. One subject dropped out because she wanted assurance that she would be in the medication group; four others dropped out without explanation and were lost to follow-up." (Salzman 1995, p. 24) **Comment:** Of the 27 patients enrolled, 22 completed treatment. Reasons for early termination: Wanted assurance to be in the active drug group: 1 (not specified, which group) Dropped out without explanation: 4 (not specified, which group) Continuous outcomes based on completer analysis
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol found
Vested Interest (funding and/or author affiliations)	Unclear risk	**Comment:** no details provided
Other bias	Low risk	**Comment:** No apparent other sources of bias found

Schmahl 2012a

Study characteristics	
Methods	6-week trial with 2 arms: 1. naltrexone (dosed at 50 mg) 2. placebo **Duration of trial:** 8 weeks. In both Schmahl 2012a and Schmahl 2012b, the first week ('week 0') was without pharmaceutical intervention and served to assess a baseline level. Therapeutic interventions were carried out during the following 6 weeks ('weeks 1–6'), split into two phases: (a) 3 weeks of treatment with naltrexone and (b) 3 weeks of treatment with placebo (cross-over design). The sequence of the two treatment phases was randomised and concealed from both the patients and the trial personnel. In both trials, the last week ('week 7') was without pharmacological intervention. **Country:** Germany **Setting:** inpatient

Schmahl 2012a *(Continued)*

Participants	**Methods of recruitment of patients:** "Patients were recruited and treated from August 1998 to June 2001 at the Department of Psychiatry and Psychotherapy, University of Freiburg." (Schmahl 2012a, p. 63) **Overall sample size:** 13 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** IPDE **Mean age:** 28.3 years (SD 8.0; range = 18–44) **Sex:** 100% women **Comorbidity:** no information **Inclusion criteria** 1. Score of at least 18 on Dissociation Experiences Scale (DES) 2. Female gender 3. Aged between 18 and 50 years **Exclusion criteria** 1. Lifetime diagnosis of schizophrenia assessed using the SCID I 2. Psychotic or delusional disorder, current major depressive episode, lifetime diagnosis of opioid dependence, current diagnosis of opioid abuse, liver insufficiency or hepatitis, or other major medical or neurological medical condition (as assessed by complete medical and neurological examination) 3. Pregnancy or lactating 4. Psychotropic medication two weeks before and during the trial (fluoxetine = 4 weeks; lithium = 8 weeks) 5. Concomitant treatment with opioid analgesics 6. Hypersensitivity to naltrexone
Interventions	**Experimental group** **Treatment name:** naltrexone **Number randomised to group:** 13 **Duration:** 3 weeks **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 13 (cross-over) **Duration:** 3 weeks **Both groups** **Concomitant psychotherapy:** non-specific therapeutic intervention **Concomitant pharmacotherapy:** Some pharmacotherapies were not allowed: no psychotropic medication permitted two weeks before and during the trial (fluoxetine = 4 weeks; lithium = 8 weeks). Concomitant treatment with opioid analgesics was an exclusion criterion. **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary outcomes:** none **Secondary outcomes** 1. Dissociation and psychotic-like symptoms, measured by Dissociative States Scale (DSS). Assessed at week 1, 2 and 3 (EOT) 2. Adverse effects, measured by UKU (udvalg for kliniske undersogelser) side effect scale. Adverse events were recorded by staff during trials such as physical side effects to medication.

Schmahl 2012a *(Continued)*

Notes	**Sample calculation:** no information **Ethics approval:** yes **Funding source:** unclear funding **Conflicts of interest:** No conflicts of interest were reported. **Comments from trial authors (limitations):** "the relatively small sample size is a major limitation, especially as the non-significant results preclude any firm conclusions and as the possibilities of subgroup and predictor analyses are quite limited in small samples". (Schmahl 2012a, p. 67)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** A computer-generated randomisation list was used to carry out block randomisation (Schmahl 2012a, p. 62).
Allocation concealment (selection bias)	Low risk	**Quote:** "The sequence of the two treatment phases was randomized and concealed from both the patients and the study personnel". (Schmahl 2012a, p. 62).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment**: The study was described as being double-blind, however, there was no information on how the blinding was secured or if it was adequately maintained throughout the study to permit a judgement of low or high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** The study was described as being double-blind, however, there was no information on how the blinding was secured or if it was adequately maintained throughout the study to permit a judgement of low or high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Quote:** "We carried out both intent-to-treat (ITT) analyses (using the LOCF method) and analyses according to protocol (ATP). The results were very similar when using either strategy, and we decided to report the results from ATP analyses only if the results from ITT analyses were markedly different. As we found little support for assuming that the dropouts might be related to treatment, effect size estimates from ATP analyses might be less biased than ITT effect-size estimates and were used accordingly. The pattern of dropouts was balanced across treatment condition; in both studies one patient dropped out in both treatment conditions". (Schmahl 2012a, p. 63)
Selective reporting (reporting bias)	Unclear risk	**Comment:** secondary outcome in protocol did not state mild-moderate-intense adverse events as did the full report. Lack of definition of serious adverse events and non-serious adverse events
Vested Interest (funding and/or author affiliations)	Low risk	**Quote: "**There were no conflicts of interest" (Schmahl 2012a, p. 67).
Other bias	Low risk	**Comment:** no other apparent source of bias

Schmahl 2012b

Study characteristics

Methods	6-week trial with 4 arms:

Schmahl 2012b *(Continued)*

1. naltrexone (50 mg)
2. naltrexone (200 mg)
3. placebo 1
4. placebo 2

Duration of trial: 8 weeks. In both Schmahl 2012a and Schmahl 2012b, the first week ('week 0') was without pharmaceutical intervention and served to assess a baseline level. Therapeutic interventions were carried out during the following 6 weeks ('weeks 1–6'), split into two phases: (a) 3 weeks of treatment with naltrexone and (b) 3 weeks of treatment with placebo (cross-over design). The sequence of the two treatment phases was randomised and concealed from both the patients and the trial personnel. In both trials, the last week ('week 7') was without pharmacological intervention.

Country: Germany

Setting: inpatient and outpatient

Participants

Methods of recruitment of patients: Patients were recruited from January 2006 to September 2007 at the Department of Psychosomatic Medicine and Psychotherapy, Central Institute of Mental Health, Mannheim; the Department of Psychiatry and Psychotherapy, University of Rostock; and the Center for Psychosomatic Medicine, Bad Wiessee.

Overall sample size: 16

Diagnosis of borderline personality disorder: DSM-IV

Means of assessment: IPDE

Mean age: 29.2 years (SD 8.9; range = 18–42)

Sex: 100% women

Comorbidity: pre-existing substance misuse

Inclusion criteria

1. Score of at least 18 on the Dissociation Experiences Scale (DES)
2. Female gender
3. Aged between 18 and 50 years

Exclusion criteria

1. Lifetime diagnosis of schizophrenia assessed using the SCID-I
2. Psychotic or delusional disorder, current major depressive episode, lifetime diagnosis of opioid dependence, current diagnosis of opioid abuse, liver insufficiency or hepatitis, other major medical or neurological medical condition (as assessed by complete medical and neurological examination)
3. Pregnancy or lactating
4. Psychotropic medication two weeks before and during the trial (fluoxetine = 4 weeks; lithium = 8 weeks)
5. Concomitant treatment with opioid analgesics
6. Hypersensitivity to naltrexone
7. Any liver-related disorder

Interventions

Experimental groups
Treatment name: naltrexone (50 + 200 mg naltrexone and blood plasma levels)
Number randomised to group: 16 (cross-over)
Duration: 3 weeks

Control/comparison groups
Comparison name: placebo
Number randomised to group: 16 (cross-over)
Duration: 3 weeks

Schmahl 2012b *(Continued)*

	Both groups **Concomitant psychotherapy:** non-specific therapeutic intervention **Concomitant pharmacotherapy:** Some pharmacotherapies were not allowed: no psychotropic medication permitted two weeks before and during the trial (fluoxetine = 4 weeks; lithium = 8 weeks). Concomitant treatment with opioid analgesics was an exclusion criterion. **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary outcomes** 1. BPD severity, measured the Borderline Symptom scale (BSL-95) Assessed at weeks 1, 2 and 3 (EOT) 2. Self-injury, measured by non-suicidal self-injurious acts, as well as the number and duration of flashbacks; all were retrospectively assessed at the end of each week at weeks 1, 2 and 3 (EOT). **Secondary outcomes** 1. Dissociation and psychotic-like symptoms, measured by Dissociative States Scale (DSS) Assessed at weeks 1, 2 and 3 (EOT) 2. Depression, measured by BDI and Ham-D. Assessed at weeks 1, 2 and 3 (EOT) 3. Adverse effects, measured by UKU (udvalg for kliniske undersogelser) side effect scale. Adverse events were recorded by staff during trials such as physical side effects to medication.
Notes	See Schmahl 2012a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** A computer-generated randomisation list was used to carry out block randomisation (Schmahl 2012b, p. 62).
Allocation concealment (selection bias)	Low risk	**Quote:** "The sequence of the two treatment phases was randomized and concealed from both the patients and the study personnel". (Schmahl 2012b, p. 62).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment**: The study was described as being double-blind, however, there was no information on how the blinding was secured or if it was adequately maintained throughout the study to permit a judgement of low or high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment**: The study was described as being double-blind, however, there was no information on how the blinding was secured or if it was adequately maintained throughout the study to permit a judgement of low or high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Quote:** "We carried out both intent-to-treat (ITT) analyses (using the LOCF method) and analyses according to protocol (ATP). The results were very similar when using either strategy, and we decided to report the results from ATP analyses only if the results from ITT analyses were markedly different. As we found little support for assuming that the dropouts might be related to treatment, effect size estimates from ATP analyses might be less biased than ITT effect size estimates and were used accordingly. The pattern of dropouts was balanced across treatment condition; in both studies one patient dropped out in both treatment conditions". (Schmahl 2012b, p. 63)
Selective reporting (reporting bias)	Unclear risk	**Comment:** secondary outcome in protocol did not state mild-moderate-intense adverse events as did the full report. Lack of definition of serious adverse events and non-serious adverse events

Schmahl 2012b *(Continued)*

Vested Interest (funding and/or author affiliations)	Low risk	**Quote: "**There were no conflicts of interest" (Schmahl 2012b, p. 67).
Other bias	Low risk	**Comment:** no apparent other source of bias

Schulz 2007

Study characteristics	
Methods	12-week trial with 2 arms: 1. olanzapine 2. placebo **Duration:** 12 weeks (after screening period of 2-14 days) **Country:** Belgium, France, Germany, Norway, Portugal, Spain, Sweden, UK and USA **Setting:** outpatient
Participants	**Method of recruitment of participants:** no information **Overall sample size:** 314 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV) and Zan-BPD total score of 9 or higher **Mean age:** 31.81 years (SD = no information; range = no information) **Sex:** 71.02% women **Comorbidity**: no information; however, many psychiatric disorders were excluded. **Inclusion criteria** 1. Outpatients of any gender 2. Aged 18–65 years 3. Meet all of the DSM–IV general diagnostic criteria for a personality disorder and DSM–IV criteria for borderline personality disorder as determined by the DIPD–IV 4. ZAN–BPD total score of 9 at the time of randomisation **Exclusion criteria** 1. Bipolar disorder, schizophrenia, major depressive disorder or substance dependence within last 3 months 2. Current PTSD, panic disorder or obsessive-compulsive disorder
Interventions	**Experimental group** **Treatment name:** olanzapine (2.5-20 mg/d, mean final dose 7.09 mg/d, SD 5.11) **Number randomised to group:** 150 **Duration:** 12 weeks **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 155 **Duration:** 12 weeks **Both groups**

Schulz 2007 *(Continued)*

Concomitant psychotherapy: no information
Concomitant pharmacotherapy: no medications with primarily CNS activity (except for protocol-specified benzodiazepines and hypnotics)
Proportions of participants taking standing medication during trial observation period: no information

Outcomes

Primary outcomes

1. BPD severity, measured by number of patients in each group with response/no response, i.e. 50% reduction, at least, in Zan-BPD total score. Assessed at week 1, 2, 4, 6, 8, 10, and 12 (EOT)
2. Suicidal behaviour, measured by Zan-BPD-suicidal or self-mutilating behaviour. Assessed at week 1, 2, 4, 6, 8, 10, and 12 (EOT)
3. Suicidal ideation, measured by OAS-M-suicidal ideation. Assessed at week 1, 2, 4, 6, 8, 10, and 12 (EOT)
4. Mental health status (functioning), measured by Sheehan Disability Scale-total and GAF. Assessed at week 1, 2, 4, 6, 8, 10, and 12 (EOT)

Secondary outcomes

1. Anger, measured by Zan-BPD-intense anger, OAS-M-irritability and SCL-90-R-HOS. Assessed at weeks 1, 2, 4, 6, 8, 10, and 12 (EOT)
2. Affective instability, measured by Zan-BPD-affective instability. Assessed at weeks 1, 2, 4, 6, 8, 10, and 12 (EOT)
3. Feelings of emptiness, measured by Zan-BPD-chronic feelings of emptiness. Assessed at weeks 1, 2, 4, 6, 8, 10, and 12 (EOT)
4. Impulsivity, measured by Zan-BPD-impulsivity and OAS-M-aggression. Assessed at weeks 1, 2, 4, 6, 8, 10, and 12 (EOT)
5. Interpersonal problems, measured by Zan-BPD-unstable interpersonal relationships. Assessed at weeks 1, 2, 4, 6, 8, 10, and 12 (EOT)
6. Avoidance of abandonment, measured by Zan-BPD-frantic efforts to avoid abandonment. Assessed at weeks 1, 2,4, 6, 8, 10, and 12 (EOT)
7. Identity disturbance, measured by Zan-BPD-identity disturbance. Assessed at weeks 1, 2, 4, 6, 8, 10, and 12 (EOT)
8. Dissociative symptoms, measured by Zan-BPD-paranoid ideation of disassociation. Assessed at weeks 1, 2, 4, 6, 8, 10, and 12 (EOT)
9. Depression, measured by MADRS. Assessed at weeks 1, 2, 4, 6, 8, 10, and 12 (EOT)
10. Attrition
11. Adverse effects: measured by weight, laboratory values, vitals and ECG as well as the Simpson-Angus Scale, BARS and IMS. Assessed at weeks 2, 4, 8 and 12 (EOT)

Notes

Sample calculation: no information

Ethics approval: yes

Funding source: funded or partially funded by pharmaceutical industry

Conflicts of interest: Dr Schulz has consulted for Eli Lilly, AstraZeneca and Vanda. Authors HCD, QT, YT, DL and SC are employed by Lilly Research Laboratories.

Comments from trial authors (limitations): none mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "patients [...] were randomly assigned to treatment". (Eli Lilly 2008, p. 15), **Comment:** Randomisation conducted centrally

Schulz 2007 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	**Quote:** "All participants, study site personnel and investigators were masked to randomisation codes." (Schulz 2008, p. e1) **Comment:** Insufficient information on how allocation sequence was concealed and maintained until randomised trial phase started to permit a judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** Participants and personnel were described as being masked to randomisation codes, however, there was insufficient information about how blinding in the randomised phase was carried out and maintained (e.g. identical capsules of trial medication).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** Participants and personnel were described as being masked to randomisation codes, however, there was Insufficient information about how blinding in the randomised phase was carried out and maintained (e.g. blind to adverse events etc.).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Quote:** "Analyses were done on an intent-to-treat basis [...] In general, LOCF mean change analyses". (Eli Lilly 2008, p. 5) **Quote:** "Of the 314 randomized patients, 305 had both a baseline and a non-missing post-baseline observation and were thus qualified for the primary efficacy analysis." (Eli Lilly 2008, p. 16) **Comment:** Unclear, what "non-missing post-baseline observation" exactly means. However, discontinuing participants were included in the 305 participants whose results were analysed using LOCF. Continuous outcomes based on LOCF/ITT 314 patients were enrolled and randomly allocated. Outcomes referred partly to all of them, partly to 310 or 305 patients. No further details given
Selective reporting (reporting bias)	High risk	**Comment:** Several outcome measures (secondary and adverse events) were reported that were not prespecified according to the trial protocol.
Vested Interest (funding and/or author affiliations)	High risk	**Quote:** "This study was sponsored by Eli Lilly. S.C.S. has received honorarium from Eli Lilly, AstraZeneca and Bristol-Meyers Squibb; grant fees from Eli Lilly, AstraZeneca, Abbott, MIND Institute and the NIMH; and consultation fees from Eli Lilly, AstraZeneca and Vanda. H.C.D., Q.T., Y.T., D.L. and S.C. are employed by Lilly Research Laboratories." (Schulz 2008 p. e1)
Other bias	Low risk	**Comment:** No indication of other bias

Shafti 2010

Study characteristics	
Methods	8-week trial with 2 arms: 1. olanzapine 2. haloperidol **Duration of trial:** 8 weeks **Country:** Iran **Setting:** inpatient

Shafti 2010 *(Continued)*

Participants	**Method of recruitment of participants:** The participants were inpatients. Not otherwise specified **Overall sample size:** 28 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** no information **Mean age**: 29.49 years (SD = no information; range = no information) **Sex**: 100% women **Comorbidity**: none **Inclusion criteria:** female gender **Exclusion criteria:** any prominent comorbid mental disorder
Interventions	**Experimental group** **Treatment name:** olanzapine **Number randomised to group**: 14 **Duration**: 8 weeks **Control/comparison group** **Comparison name:** haloperidol **Number randomised to group:** 14 **Duration:** 8 weeks **Both groups** **Concomitant psychotherapy:** not allowed **Concomitant pharmacotherapy:** not allowed **Proportions of participants taking standing medication during trial observation period:** no other concurrent psychotropic medication during testing
Outcomes	**Primary outcomes:** mental health status (functioning), measured by CGI-S and BPRS. Assessed at baseline and at week 8 (EOT) **Secondary outcomes** 1. Anger, measured by Buss-Durkee Hostility Inventory (BDHI). Assessed at baseline and at week 8 (EOT) 2. Attrition 3. Adverse effects, measured by use of laboratory values. Assessed at baseline and at week 8 (EOT) and spontaneous reporting
Notes	**Sample calculation:** yes **Ethics approval:** yes **Funding source:** no funding received **Conflicts of interest:** No conflicts of interest were reported. **Comments from trial authors (limitations):** "Small size of the samples, short duration of the trial, and sex-based sampling were among the weaknesses of this trial". (Shafti 2010, p. 46)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment**: No information on method for random sequence generation to permit a judgement of low or high risk of bias

Shafti 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	**Comment**: Insufficient information on concealment of random sequence allocation to permit a judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** The article referred to the trial being double-blind, however, there was insufficient information on how blinding of participants and personnel was carried out and maintained to permit a judgement of low or high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** The article referred to the trial being double-blind, however, there was insufficient information on how blinding of outcome assessors was carried out and maintained to permit a judgement of low or high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment**: No attrition
Selective reporting (reporting bias)	Unclear risk	**Comment**: No protocol found
Vested Interest (funding and/or author affiliations)	Low risk	**Comment**: No conflicts of interest reported
Other bias	Low risk	**Comment**: No other sources found

Shafti 2014

Study characteristics	
Methods	8-week trial with 2 arms: 1. olanzapine 2. aripiprazole **Duration of trial:** 8 weeks **Country:** Iran **Setting:** inpatient
Participants	**Method of recruitment of participants:** “selected from outpatients among clientele of two psychiatric clinics and also inpatients from the female wards of Razi Psychiatric Hospital.” (Shafti 2014, p. 39) **Overall sample size:** 24 **Diagnosis of borderline personality disorder:** DSM-IV-TR **Means of assessment:** no information **Age:** 27.4 years (SD = no information; range = no information) **Sex:** 100% women **Comorbidity**: "Patients were excluded from the trial if any prominent co-morbid mental disorder was present.” (Shafti 2014, p. 39) **Inclusion criteria** 1. Female gender 2. BPD according to DSM-IV-TR criteria

Shafti 2014 *(Continued)*

	Exclusion criteria 1. Any prominent comorbid mental disorder on axis I, including major depressive disorder, bipolar disorder, psychosis or substance dependence 2. Mental retardation 3. Identifiable neurological morbidity
Interventions	**Experimental group** **Treatment name:** olanzapine **Number randomised to group:** 12 **Duration:** 8 weeks **Control/comparison group** **Comparison name:** aripiprazole **Number randomised to group:** 12 **Duration:** 8 weeks **Both groups** **Concomitant psychotherapy:** not allowed **Concomitant pharmacotherapy:** No other concurrent psychotropic medication permitted during testing. No further information **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary outcomes:** 1. Mental health status (functioning), measured by Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impressions-Severity Scale (CGI-S). Assessed at baseline and at week 8 (EOT) **Secondary outcomes** 1. Anger, measured by the Buss-Durkee Hostility Inventory (BDHI). Assessed at baseline and at week 8 (EOT) 2. Attrition, measured in terms of patients lost after randomisation in each group 3. Adverse effects, measured by use of spontaneous reporting
Notes	**Sample calculation:** "Post hoc analysis showed an intermediary power = 0.46 for of this trial, which became power = 0.76 in compromise power analysis." (Shafti 2014, p. 41) **Ethics approval:** ethical committee of Tehran University **Funding source:** funded by grants from universities, authorities or research foundations **Conflicts of interest:** No conflicts of interest were reported. **Comments from trial authors (limitations):** The open-label procedure, small sample size, short duration of assessment, inexact comparable doses, and gender-based sampling were among the weak points of this trial". (Shafti 2014, p. 42)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** inadequate information on method used to generate random sequence to permit judgement of low or high risk of bias
Allocation concealment (selection bias)	High risk	**Comment:** An open-label trial. No allocation concealment

Shafti 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	**Comment:** No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	**Comment:** No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Quote:** "analysis for efficacy was based on data from the same number of patients in both groups (n = 12 in each), because all of the patients remained in and completed the entire 8 weeks of the study." (Shafti 2014 p. 40)
Selective reporting (reporting bias)	Unclear risk	**Comment:** No protocol found
Vested Interest (funding and/or author affiliations)	Low risk	**Quote: "**S.S.S., H.K.: The authors reported no conflict of interest related to this article. Funded by Department of Research" (Shafti 2014 p. 43)
Other bias	Low risk	**Comment:** No other sources found

Simpson 2004

Study characteristics	
Methods	12-week trial with 2 arms: 1. DBT + fluoxetine 2. DBT + placebo **Duration:** 12 weeks (after a 1-week placebo run-in) **Country:** USA **Setting**: partial hospitalisation
Participants	**Method of recruitment of participants: "**Participants were recruited from all admissions to the Women's Partial Program, a 5-day DBT-based, partial hospital program, using a brief self-report questionnaire." (Simpson 2004, p. 380) **Overall sample size:** 25 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** SCID-II **Mean age:** 36.26 years (SD = no information; range = no information **Sex**: 100% women **Comorbidity**: recruited patients were already hospitalised with comorbid Axis I pathology. No further information **Inclusion criteria:** no information **Exclusion criteria** 1. Primary diagnosis of substance dependence 2. Seizure disorder

Simpson 2004 *(Continued)*

3. Unstable medical conditions
4. Lifetime history of schizophrenia or bipolar disorder
5. MAOI treatment in the prior 2 weeks
6. Previous adequate trial of fluoxetine
7. Pregnancy, lactating women or unwillingness to use effective contraception

Interventions	**Experimental group** **Treatment name:** fluoxetine **Number randomised to group:** 12 **Duration**: 12 weeks **Control/comparison group** **Medication name:** placebo **Number randomised to group:** 13 **Duration**: 12 weeks **Both groups** **Concomitant psychotherapy:** Patients were recruited from a partial hospital programme and all received DBT (weekly, 1-hour sessions of individual DBT; weekly, 2-hour skills group; round-the-clock emergency consultation availability). **Concomitant pharmacotherapy**: The only other psychotropic allowed was 50-100 mg/day trazodone for insomnia. **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary outcomes** 1. Self-mutilating behaviour, measured by OAS-M-assault against self. Assessed at baseline and week 10* 2. Suicidal ideation, measured by OAS-M-suicidality. Assessed at baseline and week 10* 3. Mental health status (functioning), measured by GAF. Assessed at baseline and week 10* **Secondary outcomes** 1. Impulsivity, measured by OAS-M-aggression and STAXI-anger out. Assessed at baseline and week 10* 2. Psychotic symptoms/dissociation, measured by DES. Assessed at baseline and week 10* 3. Depression, measured by BDI. Assessed at baseline and week 10* 4. Attrition, measured by number of patients lost after randomisation * "The post-treatment assessment was conducted during week 10 to minimise the influence of "termination issues" expected to affect this population". (Simpson 2004, p. 381)
Notes	**Sample calculation:** no information **Ethics approval:** no information **Funding source:** funded or partially funded by pharmaceutical industry **Conflicts of interest:** No conflicts of interest were reported besides funding from the pharmaceutical industry. **Comments from trial authors (limitations)** 1. "Although bipolar disorder was an exclusion criterion, it is possible that some non-responders had an undetected subclinical presentation of bipolar disorder, which would worsen the anti-depressant treatment". (Simpson 2004, p. 384) 2. It is possible that 40 mg/day as administered was insufficient; however, it did not account for the improvement found among participants in the placebo condition and lack of comparable improvement among participants in the fluoxetine condition. 3. "The limited length of treatment might also have affected the study outcome". (Simpson 2004, p. 384). **Comments from review authors:**

Simpson 2004 *(Continued)*

1. Data were only available for the 20 completers (fluoxetine: n = 9; placebo: n = 11)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** The article referred to the trial as being randomised, however, there was no information on how the randomisation procedure was carried out to permit a judgement of low or high risk of bias.
Allocation concealment (selection bias)	Unclear risk	**Comment:** No information given on allocation concealment to permit a judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** No information given how blinding of participants was attempted, especially in light of the day clinic setting with possibly shared group therapy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "A non-treating study psychiatrist was available to break the blind in event of a clinical emergency." (Simpson 2004 p. 381) **Comment:** In contrast, the treating clinician was probably blind.
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** Of the 25 patients enrolled, 12 were randomised to fluoxetine and 13 to placebo. 20 completed treatment (9 in fluoxetine group, 11 in placebo group). Reasons for early termination: Negative experience of the placebo washout period, which led to a reversal of their willingness to tolerate a potential assignment to the placebo condition: 3 in fluoxetine group, 0 in placebo group Sought hospitalisation at another facility: 0/1 Intolerable lack of improvement: 0/1 **Comment:** Reasons for early termination specified (Simpson 2004 p. 381) Continuous outcomes were only reported for trial completers, while dropouts could be imputed as having the negative outcome for dichotomous data.
Selective reporting (reporting bias)	Unclear risk	**Comment:** Insufficient information to permit judgement of 'Yes' or 'No'
Vested Interest (funding and/or author affiliations)	High risk	**Quote:** "Support for this study was provided by the Department of Psychiatry and Human Behaviour at Brown Medical School and Eli Lilly." (Simpson 2004, p. 379)
Other bias	Low risk	**Quote:** "Diary card records of pill ingestion were reviewed, and pill counts were made as a compliance measure." (Simpson 2004 p. 381) **Quote:** "1-week placebo run-in" (Simpson 2004 p. 380), "the only other medication allowed was 50 to 100 mg/day of trazodone for insomnia." (Simpson 2004 p. 381)

Soler 2005

Study characteristics

Methods	12-week trial with 2 arms: 1. olanzapine + DBT

Soler 2005 *(Continued)*

	2. placebo + DBT **Duration:** 12 weeks (after a 4-week selection phase during which the pre-intervention baseline was established but no therapeutic intervention was given) **Country**: Spain **Setting:** outpatient
Participants	**Method of recruitment of participants:** Patients were referred from clinical services. **Overall sample size:** 60 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** SCID-II and DIB-R **Mean age:** 40.74 years (SD = no information; range = no information) **Sex:** 86.57% women **Comorbidity**: no information; however, patients with unstable comorbid axis I disorders were excluded. **Inclusion criteria** 1. Meeting DSM-IV diagnostic criteria for borderline personality disorder assessed by SCID-II and the DIB-R 2. Aged 18–45 years 3. CGI-S of illness score ≥ 4 **Exclusion criteria** 1. Comorbid unstable axis I disorder 2. Women that did not use medically accepted contraception 3. Patients receiving psychotherapy
Interventions	**Experimental group** **Treatment name:** olanzapine **Number randomised to group:** 30 **Duration:** 12 weeks **Control/comparison group** **Comparison name:** placebo (no further details) **Number randomised to group:** 30 **Duration:** 12 weeks **Both groups** **Concomitant psychotherapy:** All patients received DBT (weekly, 150-minute skills training group sessions; phone calls). **Concomitant pharmacotherapy:** Participants could continue treatment with benzodiazepines, antidepressants and mood stabilisers, but doses could not be modified. **Proportions of participants taking standing medication during trial observation period:** Participants were taking other medications before or during the treatment in both groups. In the olanzapine group, 73.3% of participants were taking benzodiazepine, 80% were taking antidepressants and 33.3% were taking mood stabilisers. In the placebo group, 60% of participants were taking benzodiazepine, 70% were taking antidepressants and 16.7% were taking mood stabilisers.
Outcomes	**Primary outcomes** 1. Suicidal behaviour/self-mutilating behaviour, measured by behavioural, biweekly reports of episodes of self-injuring behaviour/suicide attempts. Assessed at baseline and every 2 weeks for 12 weeks (EOT)

Soler 2005 *(Continued)*

2. Mental health status (functioning), measured by CGI-S. Assessed at baseline and every 2 weeks for 12 weeks (EOT)

Secondary outcomes

1. Impulsivity, measured by behavioural, biweekly reports of episodes of impulsivity/aggressive behaviour. Assessed at baseline and every 2 weeks for 12 weeks (EOT)
2. Depression, measured by Ham-D. Assessed at baseline and every 2 weeks for 12 weeks (EOT)
3. Attrition
4. Adverse effects, measured by patients' reports and scales assessing extrapyramidal side effects, weight, cholesterol levels. Assessed biweekly for 12 weeks

Notes

Sample calculation: no information

Ethics approval: no information

Funding source: funded or partially funded by pharmaceutical industry

Conflicts of interest: No conflicts of interest were reported besides partial funding from the pharmaceutical industry.

Comments from trial authors (limitations)

1. "results cannot be fully extrapolated to inpatients, to patients with active comorbid axis I disorders, or to those with less clinically severe disorders". (Soler 2005, p. 1223)
2. "We are unaware of any possible drug-drug interactions, the 'masking' effect of psychotherapy, or whether olanzapine is useful as maintenance treatment." (Soler 2005, p. 1223)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** insufficient information on methods used to generate random sequence to permit a judgement of low or high risk of bias
Allocation concealment (selection bias)	Unclear risk	**Comment**: No information given on allocation concealment to permit a judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** The trial was referred to as being double-blind, however, insufficient information was given on how blinding of participants and personnel was carried out (packaging of trial medication etc.) and maintained, to permit a judgement of low or high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** The trial was referred to as being double-blind, however, insufficient information was given on how blinding of outcome assessors was carried out and maintained, to permit a judgement of low or high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Quote**: "All analyses were conducted on an intent-to-treat basis. The endpoint was based on a last-observation-carried-forward strategy. Patients were included in the analyses only if they had a baseline measure and at least one post-baseline measure." (Soler 2005 p. 1222) **Quote**: "Sixty subjects were randomly assigned to dialectical behaviour therapy plus olanzapine or placebo and started the experimental phase; 42 subjects (70%) completed the study.There were no between-group differences regarding demographic variables or concomitant treatments at baseline. Neither dialectical behaviour therapy intervention time nor dropout rates differed significantly between the two groups (eight of the 30 patients who received olanzapine versus 10 of the 30 who received placebo dropped out before the end of the study." (Soler 2005 p. 1222 et seq.)

Soler 2005 *(Continued)*

		Comment: reasons for dropouts given; numbers balanced across groups Continuous outcomes based on ITT (LOCF) Of the 60 patients enrolled, 42 completed treatment (22 in active drug group, 20 in placebo group) Reasons for early termination: No reasons given
Selective reporting (reporting bias)	Low risk	**Comment**: The trial protocol was available and all of the prespecified primary and secondary outcomes that were of interest in the review were reported in the way they were prespecified.
Vested Interest (funding and/or author affiliations)	High risk	**Quote**: "Supported by grants from the Fondo de Investigación Sanitaria (Ministry of Health, Spain) and from Eli Lilly and Co. Madrid." (Soler 2005 p. 1223)
Other bias	Low risk	**Comment:** No indication of other bias

Soloff 1989

Study characteristics	
Methods	5-week trial with 3 arms: 1. amitriptyline 2. haloperidol 3. placebo **Duration:** 5 weeks (after 1-week washout) **Country:** USA **Setting:** inpatient (after 3 weeks, some allowed to complete as outpatients)
Participants	**Method of recruitment of participants:** Patients were referred for trial evaluation if their primary clinician made a presumptive clinical diagnosis of borderline personality disorder, schizotypal personality disorder, or both. **Overall sample size:** 90 **Diagnosis of borderline personality disorder:** DSM-III **Means of assessment:** DIB; GAS score of 50 or less; and either a score of 17 or higher on Ham-D or 66 or greater on the Inpatient Multidimension Rating Scale (IMPS) **Mean age:** 25.1 years (SD = no information; range = no information) **Sex:** 75.56% women, 24.44% men **Comorbidity:** Patients meeting research diagnostic criteria by clinical history or interview on the Schedule for Affective Disorders and Schizophrenia for a current diagnosis of major depression were included but coded for separate statistical analysis. Method of recruitment suggested that patients with comorbid schizotypal personality disorder were included. No further information **Inclusion criteria** 1. Presumptive clinical diagnosis of BPD, SPD or BPD/SPD by primary clinician 2. A cutoff score of 7.0 or more the DIB

Soloff 1989 *(Continued)*

	Exclusion criteria 1. Schizophrenia 2. Mania-related disorders 3. Chronicity of illness 4. Organicity
Interventions	**Experimental group** **Treatment name:** amitriptyline **Number randomised to group:** 29 **Duration:** 5 weeks **Comparison group** **Comparison name:** haloperidol **Number randomised to group:** 28 **Duration:** 5 weeks **Control group** **Medication name:** placebo (no further details) **Number randomised to group:** 28 **Duration**: 5 weeks **All groups** **Concomitant psychotherapy:** Patients were treated as psychiatric inpatients for at least 3 weeks. No further details **Concomitant pharmacotherapy:** Biperiden hydrochloride (2 mg) was allowed, as needed, for extrapyramidal reactions. **Proportions of participants taking standing medication during trial observation period:** Patients were observed free of medication for at least one week prior to beginning intervention. No further information provided
Outcomes	**Primary outcomes:** mental health status (functioning), measured by GAS. Assessed at baseline and once weekly for 5 weeks (EOT) **Secondary outcomes** 1. Anger, measured by SCL-90-HOS and Buss-Durkee Hostility Inventory. Assessed at baseline and once weekly for 5 weeks (EOT) 2. Impulsivity, measured by Ward Scale of Impulsive Action Patterns, BIS and STIC. Assessed at baseline and once weekly for 5 weeks (EOT) 3. Interpersonal problems, measured by SCL-90-INT. Assessed at baseline and once weekly for 5 weeks (EOT) 4. Psychotic symptoms, measured by SCL-90-PAR, SCL-90-PSY, IMPS and SSI. Assessed at baseline and once weekly for 5 weeks (EOT) 5. Depression, measured by SCL-90-DEP, Ham-D and BDI. Assessed at baseline and once weekly for 5 weeks (EOT) 6. Attrition 7. Adverse effects. Assessed at baseline and once weekly for 5 weeks (EOT)
Notes	**Sample calculation:** no information **Ethics approval:** no information **Funding source:** funded by grants from universities, authorities or research foundations **Conflicts of interest:** No conflicts of interest were reported. **Comments from trial authors (limitations):** "Since our study was restricted to acutely decompensated patients, generalisability to less-disturbed populations remains to be demonstrated". (Soloff 1986, p. 696, in Soloff 1989)

Soloff 1989 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** Article referred to the trial as being randomised, however there was no information about the randomisation procedure to permit a judgement of low or high risk of bias.
Allocation concealment (selection bias)	Unclear risk	**Comment:** Insufficient information about allocation concealment to permit a judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Quote:** "Numbered tablets [...] were given". (Soloff 1986, p. 692) **Comment:** Trial was referred to as being double-blind. Trial medication appeared to have been concealed by packaging, however, there was no information about whether blinding was maintained throughout the trial and whether personnel were blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "Weekly ratings by two 'blind investigators', an onward psychiatrist serving as the non-blind psychiatrist (for safety)" (Soloff 1989, p. 693)
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Quote:** "Five patients failed to complete the minimum two weeks on medication needed for inclusion in outcome analysis, one taking amitriptyline, three taking haloperidol, and one taking placebo." (Soloff 1989, p. 242) Continuous outcomes based on LOCF/ITT A minimum of 2 weeks receiving medication was required to include data for endpoint analysis Of the 90 patients enrolled, 85 completed treatment (29 in amitriptyline group, 28 in haloperidol group, 28 in placebo group) Reasons for early termination: Failed to complete the minimum 2 weeks on medication needed for inclusion in outcome analysis (1 in amitriptyline group, 3 in haloperidol group, 1 in placebo group) **Comment:** Reasons for dropouts not further specified. Total number of dropouts small, though, and balanced across groups
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol found
Vested Interest (funding and/or author affiliations)	Low risk	**Quote:** "This work was supported by NIMH grants 35392, MHCRC 30915, and MH00658." (Soloff 1989 p. 245)
Other bias	Low risk	**Comment**: no apparent other sources of bias found

Soloff 1993

Study characteristics

Methods	5-week trial with 3 arms: 1. haloperidol 2. phenelzine sulphate 3. placebo

Soloff 1993 *(Continued)*

	Duration: 5 weeks (after 1-week washout) **Country:** USA **Setting:** patients in the hospital for a minimum of 2 weeks and after discharge were seen weekly as outpatients
Participants	**Method of recruitment of participants:** Patients were recruited from the inpatient services of the Western Psychiatric Institute and Clinic of the University of Pittsburgh (PA). **Overall sample size:** 108 **Diagnosis of borderline personality disorder:** DSM-III-R **Means of assessment:** DIB **Mean age:** 26.7 years (SD 7.2; range = no information) **Sex:** 75.93% women, 24.07% men **Comorbidity:** Patients with a current diagnosis of major depressive disorder without psychosis were included and coded for separate statistical analysis. **Inclusion criteria:** no information **Exclusion criteria** 1. Drug and/or alcohol-related deficits or physical dependence 2. Evidence of central nervous system disease 3. Physical disorders of known psychiatric consequence 4. Borderline mental retardation
Interventions	**Experimental group 1** **Treatment name:** haloperidol **Number randomised to group:** 30 **Duration:** 5-week acute treatment trial followed by 16 weeks continuation treatment for medication responders **Experimental group 2** **Treatment name:** phenelzine sulphate **Number randomised to group:** 34 **Duration:** 5-week acute treatment trial followed by 16 weeks continuation treatment for medication responders **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 28 **Duration:** 5-week acute treatment trial followed by 16 weeks continuation treatment for medication responders **All groups** **Concomitant psychotherapy:** not specified. Patients were inpatients; some were allowed to complete as outpatients after 2 weeks. **Concomitant pharmacotherapy:** At the start, patients were kept free of medication for at least 7 days, in order to washout street drugs or prescribed medications. **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary outcomes** 1. BPD severity, measured by Borderline Syndrome Index at baseline and once weekly for 5 weeks (EOT) 2. Mental health status (functioning), measured by GAS at baseline and once weekly for 5 weeks (EOT)

Soloff 1993 *(Continued)*

Secondary outcomes

1. Anger, measured by SCL-90-HOS, BDHI, and ADDS-reactivity at baseline and once weekly for 5 weeks (EOT)
2. Impulsivity, measured by Ward Scale of Impulsive Action Patterns at baseline and once weekly for 5 weeks (EOT)
3. Interpersonal problems, measured by ADDS-rejection sensitivity at baseline and once weekly for 5 weeks (EOT)
4. Psychotic symptoms, measured by SCL-90-PAR, SCL-90-PSY, IMPS and SSI at baseline and once weekly for 5 weeks (EOT)
5. Depression, measured by SCL-90-DEP, Ham-D and BDI at baseline and once weekly for 5 weeks (EOT)
6. Attrition, measured at week 5 (EOT)
7. Adverse effects: weight gain, measured at week 5 (EOT)

Notes

Sample calculation: no information

Ethics approval: no information

Funding source: funded by grants from universities, authorities or research foundations

Conflicts of interest: No conflicts of interest were reported.

Comments from trial authors (limitations)

1. Failure to replicate phenelzine efficacy [preceding study: Soloff 1989] may be attributable to our conservative daily dose of phenelzine sulfate (average, 60.45 ± 9.55 mg) or the modest length of our treatment trial (5 weeks) (Soloff 1993, p. 384).
2. Differences in sample characteristics between studies also may have contributed to our failure to replicate previous reports of efficacy for phenelzine against symptoms of ADD or in patients with ADD and comorbid BPD (Soloff 1993, p. 384).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** insufficient information on methods used to generate random sequence to permit a judgement of low or high risk of bias
Allocation concealment (selection bias)	Unclear risk	**Comment:** Insufficient information to permit judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote**; "Average daily doses of medication, including placebo pseudo-dose, are given". (Soloff 1993 p. 380) **Comment**: The measures undertaken to ensure blinding seem elaborate and were described in detail, so the blinding of participants seems to have been thoroughly ensured.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote**: "Medication could be increased up to six tablets (haloperidol, 6 mg; phenelzine sulfate, 90 mg; placebo, six tablets)" (Soloff 1993 p. 378). Average daily doses of medication, including placebo pseudo-dose, were given (Soloff 1993 p. 380). **Comment**: The measures undertaken to ensure blinding seem elaborate and were described in detail, so the blinding of the rating trial personnel seems to have been thoroughly ensured.
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Quote**: "Sixteen patients failed to complete the minimum 3 weeks of medication required for end-point analysis". (Soloff 1993 p. 380) **Comment**: Reasons for these dropouts not further specified. Total number of dropouts small, though, and balanced across groups. Continuous outcomes

Soloff 1993 *(Continued)*

		based on all cases with a minimum of 3 weeks of medication exposure. Of the 108 patients enrolled, 92 completed treatment (30 in haloperidol group, 34 in phenelzine group, 28 in placebo group). Reasons for early termination: Relating to medication assignment (e.g. side effects), clinical worsening, factors unrelated to the protocol; not specified by group Patients failing to complete the minimum 3 weeks of medication required for endpoint analysis: 6 in the haloperidol group, 4 in the phenelzine group, 6 in the placebo group
Selective reporting (reporting bias)	Unclear risk	**Comment**: no protocol found
Vested Interest (funding and/or author affiliations)	Low risk	**Quote:** "This study was supported by National Institute of Mental Health grant MH35392 and by Clinical Research Center grant MH30915." (p. 697) **Quote**: "This work was supported by grants MH35392, MH00658, and CRC30915 from the National Institute of Mental Health,Bethesda, Md." (Soloff 1993, p.385)
Other bias	Low risk	**Comment**: no apparent other sources of bias found

Tritt 2005

Study characteristics	
Methods	8-week trial with 2 arms: 1. lamotrigine 2. placebo **Duration**: 8 weeks **Country**: Germany **Setting**: outpatient
Participants	**Method of recruitment of participants:** Recruitment of patients was accomplished primarily through family doctors' advertisements. **Overall sample size:** 27 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** SCID-II **Mean age:** 29.15 years (SD = no information; range = no information) **Sex:** 100% women **Comorbidity:** no information **Inclusion criteria** 1. Women 2. Perceive that the excessive burdens caused by the situations in their lives had produced feelings of constantly increasing anger **Exclusion criteria**

Tritt 2005 *(Continued)*

1. Actively suicidal
2. Abusing alcohol or drugs
3. Major depression, bipolar disorder or schizophrenia
4. Current use of lamotrigine or other psychotropic medication
5. Psychotherapy
6. Pregnant or planning to become pregnant or not using contraception
7. Somatically ill

Interventions	**Experimental group** **Treatment name:** lamotrigine **Number randomised to group:** 18 **Duration**: 8 weeks **Control/comparison group** **Medication name:** placebo **Number randomised to group:** 9 **Duration**: 8 weeks **Both groups** **Concomitant psychotherapy:** Other psychotropic medication was not allowed. **Concomitant pharmacotherapy:** Other psychotropic medication was an exclusion criterion. No further information provided **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary outcomes:** none **Secondary outcomes** 1. Anger, measured by STAXI-trait. Assessed at baseline and weekly for 8 weeks (EOT) 2. Impulsivity, measured by STAXI-anger out. Assessed at baseline and weekly for 8 weeks (EOT) 3. Attrition 4. Adverse effects, measured by non-structured questionnaire, patients were asked to note down any new symptoms and weight. Assessed at baseline and weekly for 8 weeks (EOT)
Notes	**Sample calculation:** no information **Ethics approval:** yes **Funding source:** no funding received **Conflicts of interest:** No conflicts of interest were reported. **Comments from trial authors (limitations)** 1. "In spite of a valid power analysis, the sample size was relatively small, and consisted only of women with BPD". (Tritt 2005, p. 290) 2. "In particular, the exclusion of substance abusers limits the generalisability of our findings". (Tritt 2005, p. 290) 3. "The length of this trial was only 2 months, which reduced the dropout rate, in particular in the placebo group, and possible side-effects." (Tritt 2005, p. 290) **Comments from review authors:** continuous outcomes based on ITT data (LOCF)

Risk of bias

Bias	Authors' judgement	Support for judgement

Tritt 2005 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	**Comment:** insufficient information on methods used to generate random sequence to permit a judgement of low or high risk of bias
Allocation concealment (selection bias)	Unclear risk	**Comment:** There was no information on how sequence allocation was concealed to permit a judgement of low or high risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote**: "Tablets were supplied in numbered boxes." (Tritt 2005, p. 288) **Quote**: "Each individual received one blinded capsule medication daily [...] Both subjects and clinicians were blinded regarding assignment." (Tritt 2005, p. 288)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** The trial was referred to as being double-blind, however, insufficient information was given on how blinding of outcome assessors was carried out and maintained, to permit a judgement of low or high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	**Quote**: "Thirty-eight subjects were eligible to take part in the study [...] The necessary sample size was calculated [...] This resulted in a group size of n = 27 patients [...] active drug (n = 18) compared to placebo (n = 9)". (Tritt 2005, p. 288) **Comment**: not clear why or how the 27 participants were finally chosen out of the 38 potential participants
Selective reporting (reporting bias)	High risk	**Comment**: All outcomes (i.e. one assessment instrument) reported as planned to be assessed were also reported. However, it seemed implausible to use only one assessment instrument in such a complex trial. There was no protocol available to check the predefined outcome measure(s).
Vested Interest (funding and/or author affiliations)	Low risk	**Quote**: "The study was conducted independently of any institutional influence and was not funded." (Tritt 2005, p. 288)
Other bias	Low risk	**Comment**: no apparent other sources of bias found

Zanarini 2001

Study characteristics	
Methods	6-month trial with 2 arms: 1. olanzapine 2. placebo **Duration**: 6 months **Country**: USA **Setting**: outpatient
Participants	**Method of recruitment of participants:** through advertisement in Boston-area newspapers seeking women aged between 18 and 40 years, who were disturbed by moodiness, distrustfulness, impulsivity, and painful and difficult relationships **Overall sample size:** 28 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment**: DIB-R

Zanarini 2001 *(Continued)*

Mean age: 26.7 years (SD = no information; range = no information)

Sex: 100% women

Comorbidity: no information

Inclusion criteria: meeting both DIB-R and DSM-IV criteria for BPD and not meeting current criteria for major depression

Exclusion criteria

1. Actively abusing alcohol or drugs
2. Acutely suicidal
3. Current or lifetime schizophrenia
4. Schizoaffective disorder
5. Bipolar disorder
6. Medically ill
7. Seizure disorder
8. Pregnant or planning to become pregnant
9. Breastfeeding
10. Not using reliable forms of contraception
11. Having been treated with olanzapine
12. Being prescribed any psychotropic medication that patients thought was helpful

Interventions	**Experimental group** **Treatment name:** olanzapine **Number randomised to group:** 19 **Duration**: 6 months **Control/comparison group** **Comparison name:** placebo **Number randomised to group:** 9 **Duration**: 6 months **Both groups** **Concomitant psychotherapy:** not specified **Concomitant pharmacotherapy:** No other psychotropic medication was allowed. **Proportions of participants taking standing medication during trial observation period:** Patients currently prescribed any psychotropic medication that they thought was helping to alleviate troublesome symptoms were excluded. No further information provided
Outcomes	**Primary outcomes** 1. Mental health status, measured by GAF. Assessed at baseline and weeks 1, 2, 3 and 4, then monthly for 5 months **Secondary outcomes** 1. Anger, measured by SCL-90-HOS. Assessed at baseline and weeks 1, 2, 3 and 4, then monthly for 5 months 2. Interpersonal problems, measured by SCL-90-INT. Assessed at baseline and weeks 1, 2, 3 and 4, then monthly for 5 months 3. Dissociative symptoms, measured by DES. Assessed at baseline and weeks 1, 2, 3 and 4, then monthly for 5 months 4. Psychotic symptoms, measured by SCL-90-PAR, SCL-90-PS and PANSS. Assessed at baseline and weeks 1, 2, 3 and 4, then monthly for 5 months 5. Depression, measured by SCL-90-DEP and Ham-D. Assessed at baseline and weeks 1, 2, 3 and 4, then monthly for 5 months 6. Attrition

Zanarini 2001 *(Continued)*

7. Adverse effects, measured by weight, Simpson-Angus Scale, BARS, AIMS and structured questionnaire. Assessed at baseline and week 1,2,3 and 4, then monthly for 5 months

Notes

Sample calculation: no information

Ethics approval: no information

Funding source: funded or partially funded by pharmaceutical industry

Conflicts of interest: No conflicts of interest were reported besides partial funding from the pharmaceutical industry.

Comments from trial authors (limitations)

1. "the sample size was small". (Zanarini 2001, p. 853)
2. "the sample consisted only of women with BPD. Whether these results would also apply to men meeting criteria for BPD is unknown". (Zanarini 2001, p. 853)
3. "the sample was composed of moderately ill outpatients who were not suffering from a concurrent major depressive episode, abusing substances or taking concurrent medications. It is unknown if similar results would be obtained in a more severely impaired sample of borderline patients, particularly those who are inpatients at the time of their participation in a controlled trial of olanzapine begins." (Zanarini 2001, p. 853)
4. " only 1 participant in the placebo condition and 8 participants in the olanzapine completed the entire 6-month trial." (Zanarini 2001, p. 853)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "random number sequence" (Zanarini 2001, p. 850)
Allocation concealment (selection bias)	Unclear risk	**Comment:** There was no information on how sequence allocation was concealed to permit a judgement of low or high risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote**: "Tablets were supplied in numbered bottles containing drug or placebo as determined by a random number sequence." (Zanarini 2001, p. 850) **Quote**: "Each tablet contained either 2.5 mg of olanzapine or matching inert placebo. [...] Both subjects and clinicians were blinded to olanzapine/placebo assignment. The blind was broken after the acquisition of all endpoint data for all subjects." (Zanarini 2001, p. 850)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** The trial was referred to as being double-blind, however, insufficient information was given on how blinding of outcome assessors was carried out and maintained, to permit a judgement of low or high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Quote**: "Thirty subjects completed all aspects of pre-randomization assessment. However, 2 of these subjects were excluded [...] because it was determined that they were responding well to a selective serotonin reuptake inhibitor. Twenty-eight subjects entered the trial and were randomly assigned [...] All [...] completed at least 2 post-baseline visits and were included in all subsequent analyses." (Zanarini 2001, p. 851) **Comment**: Of the 28 patients enrolled, 9 completed treatment (8 in olanzapine group, 1 in placebo group) Reasons for early termination: Sedation: 1 in olanzapine group, 0 in placebo group Increased anxiety or depression: 3/2 Perceived weight gain: 2/0 Lost to follow-up: 5/6

Zanarini 2001 *(Continued)*

		Continuous outcomes based on ITT sample (LOCF) **Comment**: high dropout rate overall, but adequately addressed
Selective reporting (reporting bias)	High risk	**Quote**: "Due to the small number of subjects, results pertaining to secondary outcome measures will not be reported." (Zanarini 2001, p. 851)
Vested Interest (funding and/or author affiliations)	High risk	**Quote**: "Supported, in part, by a grant from Eli Lilly" (Zanarini 2001, p. 849)
Other bias	Low risk	**Comment**: no apparent other sources of bias found

Zanarini 2003

Study characteristics	
Methods	8-week trial with 2 arms: 1. ethyl-eicosapentaenoic acid (E-EPA) 2. placebo: mineral oil **Duration**: 8 weeks **Country**: USA **Setting**: outpatient
Participants	**Method of recruitment of participants:** "Patients recruited through advertisements in Boston newspapers with the ads asking, “Are you extremely moody? Do you often feel out of control? Are your relationships painful and difficult?" (Zanarini 2003, p. 167) **Overall sample size**: 30 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** DIB-R **Mean age:** 26.3 years (SD 6.2; range = no information) **Sex**: 100% women **Comorbidity**: no information; however, exclusion criteria suggest comorbid mental disorders were not allowed **Inclusion criteria** 1. DSM-IV criteria for borderline personality disorder 2. Woman between the ages of 18 and 40 years **Exclusion criteria** 1. Major depressive episode 2. Current or lifetime schizophrenia 3. Schizoaffective disorder 4. Bipolar I or bipolar II disorder
Interventions	**Experimental group** **Treatment name:** ethyl-eicosapentaenoic acid (E-EPA) **Number randomised to group:** 20 **Duration**: 8 weeks

Zanarini 2003 *(Continued)*

	Control/comparison group **Comparison name:** placebo: mineral oil **Number randomised to group:** 10 **Duration:** 8 weeks **Both groups** **Concomitant psychotherapy:** no information **Concomitant pharmacotherapy:** Patients were excluded if they were currently being prescribed any psychotropic medication or taking E-EPA supplements; however, no further information was provided. **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary outcomes :** none **Secondary outcomes** 1. Impulsivity, measured by MOAS. Assessed at baseline and weeks 1, 2, 3, 4, 6, and 8 (EOT) 2. Depression, measured by MADRS. Assessed at baseline and weeks 1, 2, 3, 4, 6, and 8 (EOT) 3. Attrition 4. Adverse effects, measured by structured questionnaire. Assessed at baseline and weeks 1, 2, 3, 4, 6, and 8 (EOT)
Notes	**Sample calculation:** no information **Ethics approval:** no information **Funding source:** funded by grants from universities, authorities or research foundations **Conflicts of interest:** Trial medication was provided by a pharmaceutical company. **Comments from trial authors (limitations):** "The main limitations of this study are that only women were studied and all participants were moderately ill. Whether similar results would be found for male participants or participants with a more severe symptom picture is unknown." Zanarini 2003, p. 168)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** insufficient information on methods used to generate random sequence to permit a judgement of low or high risk of bias
Allocation concealment (selection bias)	Unclear risk	**Comment**: no information given on allocation concealment to permit a judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** The trial was referred to as being double-blind, however, insufficient information was given on how blinding of participants and personnel was carried out (packaging of trial medication etc.) and was maintained, to permit a judgement of low or high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** The trial was referred to as being double-blind, however, insufficient information was given on how blinding of outcome assessors was carried out and maintained, to permit a judgement of low or high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Quote**: "The three subjects who discontinued their participation (two taking E-EPA and one taking placebo) did so because of life events unrelated to the study." (Zanarini 2003, p. 168) **Comments:** Of the 30 patients enrolled, 27 completed treatment (18 in E-EPA group, 9 in placebo group) Reasons for early termination: Life events unrelated to the trial: 2 in E-EPA group, 1 in placebo group

Zanarini 2003 *(Continued)*

		Continuous outcomes were based on completers only.
Selective reporting (reporting bias)	Unclear risk	**Comment**: no protocol found
Vested Interest (funding and/or author affiliations)	High risk	**Quotes**: "Capsules were supplied by Laxdale Pharmaceuticals (Stirling, U.K.)." (Zanarini 2003, p. 167), "Supported by an Independent Investigator Award from the National Alliance for Research on Schizophrenia and Depression to Dr. Zanarini." (Zanarini 2003, p. 169)
Other bias	Low risk	**Comment**: no apparent other sources of bias found

Zanarini 2004

Study characteristics	
Methods	8-week trial with 3 arms: 1. fluoxetine 2. olanzapine 3. fluoxetine + olanzapine **Duration**: 8 weeks **Country**: USA **Setting**: outpatient
Participants	**Method of recruitment of participants:** "Recruitment [...] was accomplished primarily through advertisement in Boston, Mass. area newspapers." (Zanarini 2004, p. 904) **Overall sample size:** 45 **Diagnosis of borderline personality disorder:** DSM-IV **Means of assessment:** DIB-R **Mean age:** 23 years (SD 5.7; range = no information) **Sex**: 100% women **Comorbidity**: Current major depression, current or lifetime schizophrenia, schizoaffective disorder and bipolar disorder were exclusion criteria. In terms of Axis I disorders, 93.3% had a history of a mood disorder, 51.1% had a history of a substance use disorder, 48.9% had a history of an anxiety disorder and 44.4% had a history of an eating disorder. **Inclusion criteria** 1. Meeting both DIB-R and DSM-IV criteria for borderline personality disorder 2. Women 3. Aged 18 to 40 years **Exclusion criteria** 1. Current major depression 2. Current or lifetime schizophrenia 3. Schizoaffective disorder 4. Bipolar disorder

Zanarini 2004 *(Continued)*

Interventions	**Experimental group** **Treatment name**: fluoxetine **Number randomised to group:** 14 **Duration**: 8 weeks **Comparison group 1** **Treatment name:** olanzapine **Number randomised to group**: 16 **Duration**: 8 weeks **Comparison group 2** **Treatment name:** fluoxetine + olanzapine **Number randomised to group:** 15 **Duration**: 8 weeks **All groups** **Concomitant psychotherapy:** not specified **Concomitant pharmacotherapy**: Current prescription to any psychotropic medication was an exclusion criterion. No other information provided **Proportions of participants taking standing medication during trial observation period:** no information
Outcomes	**Primary outcomes:** none **Secondary outcomes** 1. Impulsivity, measured by OAS-M total. Assessed at baseline and every week for 8 weeks (EOT) 2. Depression, measured by MADRS. Assessed at baseline and every week for 8 weeks (EOT) 3. Attrition 4. Adverse effects, measured by weight at baseline and EOT, and by the Simpson-Angus Rating Scale, BARS, AIMS and structured questionnaire. Assessed at baseline and every week for 8 weeks (EOT)
Notes	**Sample calculation:** no information **Ethics approval:** yes **Funding source:** funded or partially funded by pharmaceutical industry **Comments from trial authors (limitations)** 1. [...] there was no placebo group for comparison, particularly for OFC, which has never been compared with placebo in a study of borderline personality disorder." (Zanarini 2004, p. 907) 2. "[...] the study was limited to women with borderline personality disorder, and there is no way of knowing if men with borderline personality disorder would have the same response pattern as the women in this study." (Zanarini 2004, p. 907)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** insufficient information on methods used to generate random sequence to permit a judgement of low or high risk of bias
Allocation concealment (selection bias)	Unclear risk	**Comment:** insufficient information to permit judgement of high or low risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote**: "Dose was adjusted by an unblinded psychiatrist according to perceived response and side effects. Both subjects and raters were blinded to study assignment. The blind was broken after acquisition of all endpoint data for all subjects." (Zanarini 2004, p. 904)

Zanarini 2004 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote**: "Dose was adjusted by an unblinded psychiatrist according to perceived response and side effects. Both subjects and raters were blinded to study assignment. The blind was broken after acquisition of all endpoint data for all subjects." (Zanarini 2004, p. 904)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comments**: Reasons for dropout specified (Zanarini 2004 p. 905), but outcome data were only reported for completers. Of the 45 patients enrolled, 42 completed treatment (13 in fluoxetine group, 16 in olanzapine group, 13 in fluoxetine + olanzapine group) Reasons for early termination: Onset of a number of psychosocial stressors culminating in a suicide gesture: 1/0/0 Dizziness and headaches: 0/0/1 Lost to follow-up: 0/0/1
Selective reporting (reporting bias)	Unclear risk	**Comment**: no protocol found
Vested Interest (funding and/or author affiliations)	High risk	**Quote**: "Supported by a grant from Eli Lilly, Indianapolis, Ind." (Zanarini 2004, p. 903)
Other bias	Low risk	**Comment**: no apparent other sources of bias found

Zanarini 2007

Study characteristics	
Methods	12-week with 3 arms: 1. olanzapine (2.5 mg/day) 2. olanzapine (5-10 mg/day) 3. placebo **Duration:** 12 weeks (after a 2-week screening period) **Country:** Argentina, Chile, Italy, Peru, Poland, Romania, Turkey, USA, and Venezuela **Setting:** outpatient
Participants	**Method of recruitment of participants:** no information **Overall sample size:** 451 **Diagnosis of borderline personality disorder:** DSM-IV-TR **Means of assessment:** Diagnostic Interview for Borderline Personality Disorders, 4th Version (DIBP-IV) and ZAN-BPD **Age:** 32.98 years (SD 10.83; range = no information) **Sex**: 73.61% women **Comorbidity** 1. Patients in the olanzapine 2.5 mg condition had the following axis I disorders: major depression (20%), other mood disorders (2.7%), substance use disorder (8.7%), anxiety disorder (7.3%) and eating disorder (2.7%). They also had the following axis II disorders: odd cluster (0.7%), anxious cluster (13.3%) and non-borderline personality disorder dramatic cluster (2%).

Zanarini 2007 *(Continued)*

2. Patients in the olanzapine 5-10 mg condition had the following axis I disorders: major depression (22.8%), other mood disorders (4.1%), substance use disorder (7.6%), anxiety disorder (8.3%) and eating disorder (5.5%). They also had the following axis II disorders: odd cluster (2.8%), anxious cluster (11.7%) and non-borderline personality disorder dramatic cluster (6.9%).
3. Patients in the placebo condition had the following axis I disorders: major depression (21.3%), other mood disorders (6%), substance use disorder (9.3%), anxiety disorder (5.3%) and eating disorder (6%). They also had the following axis II disorders: odd cluster (2%), anxious cluster (15.3%) and non-borderline personality disorder dramatic cluster (6%).

Inclusion criteria

1. Male and female outpatients
2. Aged 18-65 years
3. Meeting DSM-IV criteria for borderline personality disorder as determined by the DIPD-IV, with a ZAN-BPD total score of ≥ 9 at visit 2

Exclusion criteria

1. Bipolar disorder, schizophrenia or major depressive disorder within last 3 months
2. Substance dependence within last 3 months
3. Current PTSD, current panic disorder or current obsessive-compulsive disorder
4. Comorbid cluster A axis II PD
5. Active suicidality
6. Pregnancy

Interventions

Experimental group
Treatment name: olanzapine (2.5 mg/day)
Number randomised to group: 150
Duration: 12 weeks

Comparison group
Treatment name: olanzapine (5-10 mg/day, mean dose 6.66 mg/day)
Number randomised to group: 148 (106 women, 42 men)
Duration: 12 weeks

Control group
Comparison name: placebo
Number randomised to group: 153 (117 women, 36 men)
Duration: 12 weeks

All groups
Concomitant psychotherapy: Beginning any type of psychotherapy within the 3 months prior to visit 1 or during the acute phase of the trial was not allowed. Ongoing psychotherapy > 3 months at the time of visit 1 was allowed; however, if there was an increase in psychotherapy frequency or change in type of psychotherapy during trial periods 1 or 2, the patients were discontinued.
Concomitant pharmacotherapy: The use of benzodiazepine or hypnotics or lorazepam and episodic use of anticholinergics or benztropine mesylate or biperiden or trihexyphenidyl was allowed during the trial at a specific dose; however, the use of anticholinergics as prophylaxis for extrapyramidal symptoms was not allowed.
Proportions of participants taking standing medication during trial observation period: no information

Outcomes

Primary outcomes

1. BPD severity, measured by number of patients in each group with response/no response, i.e. 50% reduction, at least, in ZAN-BPD total score. Assessed at baseline and weeks 2, 4, 6, 8, 10, and 12 (EOT)
2. Suicidal behaviour, measured by ZAN-BPD-suicidal or self-mutilating behaviour. Assessed at baseline and weeks 2, 4, 6, 8, 10, and 12 (EOT)
3. Suicidal ideation, measured by OAS-M-suicidal ideation. Assessed at baseline and weeks 2, 4, 6, 8, 10, and 12 (EOT)

Zanarini 2007 *(Continued)*

4. Mental health status (functioning), measured by Sheehan Disability Scale-total and GAF. Assessed at baseline and weeks 2, 4, 6, 8, 10, and 12 (EOT)

Secondary outcomes

1. Anger, measured by ZAN-BPD-intense anger, OAS-M-irritability and SCL-90-R-HOS. Assessed at baseline and weeks 2, 4, 6, 8, 10, and 12 (EOT)
2. Affective instability, measured by ZAN-BPD-affective instability. Assessed at baseline and weeks 2, 4, 6, 8, 10, and 12 (EOT)
3. Feelings of emptiness, measured by ZAN-BPD-chronic feelings of emptiness. Assessed at baseline and weeks 2, 4, 6, 8, 10, and 12 (EOT)
4. Impulsivity, measured by ZAN-BPD-impulsivity and OAS-M-aggression. Assessed at baseline and weeks 2, 4, 6, 8, 10, and 12 (EOT)
5. Interpersonal problems, measured by ZAN-BPD unstable interpersonal relationships and SCL-90-R-INT. Assessed at baseline and weeks 2, 4, 6, 8, 10, and 12 (EOT)
6. Avoidance of abandonment, measured by ZAN-BPD-frantic efforts to avoid abandonment. Assessed at baseline and weeks 2, 4, 6, 8, 10, and 12 (EOT)
7. Identity disturbance, measured by ZAN-BPD-identity disturbance. Assessed at baseline and weeks 2, 4, 6, 8, 10, and 12 (EOT)
8. Dissociative symptoms, measured by ZAN-BPD-paranoid ideation of disassociation and SCL-90-R-PAR. Assessed at baseline and weeks 2, 4, 6, 8, 10, and 12 (EOT)
9. Depression, measured by MADRS and SCL-90-R-DEP. Assessed at baseline and weeks 2, 4, 6, 8, 10, and 12 (EOT)
10. Attrition
11. Adverse effects, measured by weight at baseline and EOT, and the Simpson-Angus Scale, BARS and AIMS assessed at baseline and weeks 2, 4, 6, 8, 10, and 12 (EOT)

Notes

Sample calculation: no information

Ethics approval: no information

Funding source: funded or partially funded by pharmaceutical industry

Conflicts of interest: "Dr. Zanarini has received grant/research support from Eli Lilly. Dr. Schulz has been a consultant for Eli Lilly and has received research grants from Eli Lilly and AstraZeneca. Drs. Detke, Tanaka, Deberdt and Kryzhanovskaya are employees and stock shareholders of Eli Lily. Drs. Zhao, Lin and Corya are employees of Eli Lilly". (Zanarini 2007, p. 1361)

Comments from trial authors (limitations)

1. "This study employed particularly stringent exclusion criteria [...] to focus results more clearly on any changes in borderline personality disorder and not some underlying comorbid disorder [...] many borderline patients do suffer from comorbid disorders. This means that results cannot be generalised to patients with concomitant disorders." (Zanarini 2007, p. 1360)
2. "This study was limited to current outpatients." (Zanarini 2007, p. 1360)
3. "While over 60% of each study group completed the trial, the 30%-39% dropout rates that were found limit the confidence that we can place in our findings." (Zanarini 2007, p. 1360)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "patients were randomised to 1 of 3 treatment groups." (Eli Lilly 2008, p. 3) **Comment:** randomisation conducted centrally

Zanarini 2007 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	**Comment:** Insufficient information on how allocation sequence was concealed and maintained until randomised trial phase started to permit a judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** Article stated that the trial was blinded, however, there was Insufficient information about how blinding in the randomised phase was carried out and maintained (e.g. identical capsules of trial medication).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** Insufficient information about outcome assessors and how they were blinded to permit a judgement of low or high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Quote**: "451 were randomly assigned (148 [...] to olanzapine 5-to-10 mg/day treatment group, 150 [...] to olanzapine 2.5-mg/day treatment group, and 153 to placebo)." (Eli Lilly 2008, p. 14), "last observation carried forward" (Eli Lilly 2008, p. 3) **Comments:** continuous data based on LOCF data; dichotomous data based on ITT sample Of the 451 patients enrolled, 294 completed the full 12 weeks of the double-blind treatment phase (97/103/94). In this review, only the groups receiving olanzapine 5 to 10 mg/day or placebo group were included.
Selective reporting (reporting bias)	Low risk	**Comment**: The trial protocol was available and all of the study's prespecified (primary and secondary) outcomes that were of interest in the review were reported in the way they were prespecified.
Vested Interest (funding and/or author affiliations)	High risk	**Comment**: Eli Lilly was the trial sponsor. Most trial results used here were from the company's trial report (the remaining references were either clinical trial register entries or congress abstracts and did not provide detailed data).
Other bias	Low risk	**Comment:** no indication of other bias

Ziegenhorn 2009

Study characteristics	
Methods	18-week trial with 2 arms: 1. clonidine 2. placebo **Duration of trial:** 8 weeks (4 weeks + 4-week cross-over) **Country:** Germany **Setting:** inpatient
Participants	**Methods of recruitment of patients:** patients admitted to an intensive inpatient treatment programme **Overall sample size:** 18 (17 were included in the analysis due to 1 nonstarter) **Diagnosis of Borderline personality disorder:** DSM-IV

Ziegenhorn 2009 *(Continued)*

Means of assessment: Mini International Neuropsychiatric Interview for DSM-IV; SCID-II

Mean age: 32 years (SD 8; range = 19-44)

Sex: 94.44% women

Comorbidity: 88% had comorbid disorders: PTSD, eating disorders and/or substance abuse

Inclusion criteria

1. DSM-IV criteria for BPD
2. On a stable psychotropic medication regimen of no more than 3 psychotropic drugs
3. Presented prominent signs of hyperarousal, as evidenced by a score of at least 20 on the hyperarousal subscale (D) of the clinician-administered PTSD scale (CAPS-D)

Exclusion criteria

1. Pregnancy
2. Severe nonpsychiatric diseases
3. Acute psychotic disorders
4. Current major depressive disorder
5. Drug or alcohol dependence at the time of inclusion

Interventions

Experimental group
Treatment name: clonidine
Number randomised to group: 18
Duration: 4 weeks

Control/comparison group
Comparison name: placebo
Number randomised to group: 18
Duration: 4 weeks

Both groups
Concomitant psychotherapy: no information
Concomitant pharmacotherapy: allowed. Patients were included if they were on a stable psychotropic medication regimen of up to 3 psychotropic drugs.
Proportions of participants taking standing medication during trial observation period: 10 participants took antidepressants, three took antipsychotics and one took valproate.

Outcomes

Primary outcomes

1. BPD severity, measured by the borderline symptom list (BSL). Assessed at baseline, week 2 and week 6 (cross-over)
2. Suicide-related outcomes, measured by SCL-90-R. Assessed at baseline, week 2 and week 6 (cross-over)
3. Mental health status, measured by the SCL-90-R. Assessed at baseline, week 2 and week 6 (cross-over)

Secondary outcomes

1. Anger, measured by CAPS-D14, which was used to quantify the symptom complex of hyperarousal (sleep problems, irritability/anger, concentration problems, hypervigilance, and exaggerated startle). Assessed at baseline, week 2 and week 6 (cross-over)
2. Interpersonal problems, measured by SCl-90-R. Assessed at baseline, week 2 and week 6 (cross-over)
3. Dissociation and psychotic-like symptoms, measured by SCl-90-R. Assessed at baseline, week 2 and week 6 (cross-over)
4. Depression, measured by the Beck Depression Inventory. Assessed at baseline, week 2 and week 6 (cross-over)
5. Attrition, measured in terms of patients lost after randomisation in each group
6. Adverse effects, measured by spontaneous reporting

Ziegenhorn 2009 *(Continued)*

Notes	**Sample calculation:** no information **Ethics approval:** yes **Funding source:** no funding received **Conflicts of interest:** No conflicts of interest were reported. **Comments from trial authors (limitations)** 1. "All participants in this study were inpatients who might represent a more severely affected group than the general BPD population." (Ziegenhorn 2009, p. 173) 2. "Unblinding of patients to the treatment condition by adverse effects might have biased results towards improvements. Nonetheless, doses were escalated slowly, and adverse effects were infrequent." (Ziegenhorn 2009, p. 173)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "After a baseline evaluation, patients were assigned to receive either clonidine or placebo capsules first using a block randomisation procedure." (Ziegenhorn 2009, p. 170) **Comment:** Insufficient information about the block randomisation procedure to permit a judgement of low or high risk of bias
Allocation concealment (selection bias)	Unclear risk	**Comment:** No information provided on concealment of random sequence allocation to permit a judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Quote**: "Unblinding of patients to the treatment condition by adverse effects might have biased results towards improvements. Nonetheless, doses were escalated slowly, and adverse effects were infrequent". (Ziegenhorn 2009, p. 173) **Comment:** The trial was referred to as being double-blind, however, there was insufficient information on how the blinding was carried out and maintained to permit a judgement of low or high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "Each patient was evaluated by 2 blinded researchers independently." (Ziegenhorn 2009, p. 170)
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** 7 dropouts. 1 patient excluded before randomisation and initiation of treatment. Potential risk of bias. Last observation was carried forward and was used as an imputation method
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol found, but the trial reported a protocol being approved by the ethics board
Vested Interest (funding and/or author affiliations)	Low risk	**Comment:** There were no sources of support, and none of the authors had any conflicts of interest to declare.
Other bias	Low risk	**Comment:** no apparent other source of bias

ADDS: Atypical Depression Diagnostic Scale.
ADHD: attention deficit hyperactivity disorder.
ADP: Assessment of DSM-IV Personality Disorders Questionnaire.
A&E: accident and emergency.

AIAQ: Anger, Irritability and Assault Questionnaire.
AIDS: acquired immune deficiency syndrome.
AIMS: Abnormal Involuntary Movements Scale.
ALS: Affective Lability Scale.
ANOVA: analysis of variance.
ASI: Addiction Severity Index
ATP: according to protocol.
BARS: Barnes Akathisia Rating Scale.
BDHI: Buss-Durkee Hostility Inventory.
BDI: Beck Depression Inventory.
BEST: Borderline Evaluation of Severity over Time.
BIS: Barrett Impulsiveness Scale.
BMDP: The Biomedical Data, Program.
BPD(SI): Borderline Personality Disorder (Severity Index).
BPRS: Brief Psychiatric Rating Scale.
BSL: Borderline SymptomList.
CAPS-D: Clinician Administered PTSD Scale.
CBZ: carbamazepine.
CGI-BPD: Clinical Global Impression scale for Borderline Personality Disorder.
CGI-I: Clinical Global Impression scale - Improvement.
CGI-S: Clinical Global Impression scale - Severity.
CI: confidence interval.
CNS: central nervous system.
CSSRS: Columbia Suicidal Severity Rating Scale.
DBT: Dialectal Behavioural Therapy.
DES: Dissociative Experiences Scale.
DHA: docosahexaenoic.
DIB/DIB-R: Gunderson's Diagnostic Interview for Borderline Patients (R: Revised version).
DIPD-IV: Diagnostic Interview for DSM-IV Personality Disorders.
DIS-Q: Dissociation Questionnaire.
DOTES: Dosage Record and Emergent Treatment Symptom Scale.
DSHI: Deliberate Self-Harm Inventory.
DSM-III: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition.
DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised.
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.
DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision.
DSM-V: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition.
DSS: Dissociative States Scale.
EEG: electroencephalogram.
E-EPA: ethyl eicosapentaenoic acid.
EKG: electrocardiogram.
EOT: end of treatment.
EPA: eicosapentaenoic acid.
ER: emergency room
et seq: and what follows.
GAD: generalised anxiety disorder.
GAF: Global Assessment of Functioning Scale.
GAS: Global Assessment scale.
HAM-D/HDRS-24: Hamilton Depression Rating Scale (HDRS-24: 24-item version).
HSCL: Hopkins Symptoms Check List.
IBS: irritable bowel syndrome.
IMPS: Inpatient Multidimension Rating Scale.
IMS: Involuntary Movement Scale.
IPDE: International Personality Disorder Examination.
IQ: intelligence quotient.
ITT: intention-to-treat.
lb: pounds.
LOCF: last-observation-carried-forward.
MADRS: Montgomery Åsberg Depression Rating Scale.
MAOIs: monoamine oxidase inhibitors.
MMT: methadone maintenance treatment
MOAS/OAS-M: Modified Overt Aggression Scale.

NMDAR: N-methyl-D-aspartate.
NSSI: non-suicidal self-injury.
OCD: obsessive compulsive disorder.
OFC: olanzapine-fluoxetine combination
PANSS: Positive and Negative Syndrome Scale.
PDRS: Personality Disorder Rating Scale.
PLC: placebo.
POMS: Profile of Mood States scale.
PTSD: post-traumatic stress disorder.
SCID-I: Structured Clinical Interview for DSM, Version 1.
SCID-II: Structured Clinical Interview for DSM, Version 2.
SCL-90/HSCL: (Hopkins) Symptom Check list-90 (Symptom scales: DEP: Depression, GSI: Global Severity Index; HOS: hostility INT; Interpersonal sensitivity, PAR; Paranoid ideation, PSY; Psychotisism) R: Revised version.
SD: standard deviation.
SFQ: Social Functioning Questionnaire.
SHI: Self-Harm Inventory.
SIB: Schedule of Interviewing Schizotypal Personalities - Borderline Score.
SNOOP: Systematic Nurses' Observation of Psychopathology.
SOFAS: Social Occupational Functioning Assessment Scale.
SPD: sensory processing disorder.
SSI: Scale for Suicidal Ideation
SSRI: selective serotonin reuptake inhibitors.
STAXI: State-Trait Anger Expression Inventory.
STIC: Self Report test of Impulsive Control
TCAs: tricyclic antidepressants.
TG: topiramate group
UKU: udvalg for kliniske undersogelser.
Zan-BPD: Zanarini Rating Scale for Borderline Personality Disorder.

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

Study	Reason for exclusion
ACTRN12615000705583	Unavailable trial: trial withdrawn due to recruitment difficulties
Bellino 2006b	Ineligible comparator: fluoxetine vs fluoxetine + interpersonal therapy; testing the effects of additional psychotherapy compared to pharmacotherapy alone
Coccaro 1997	Subsample data unavailable (sought subsample data for BPD subpopulation (33% of overall sample; Stoffers-Winterling J 2018 [pers comm]) but did not retrieve requested information)
Hollander 2005	Subsample data unavailable (less than 70% had a full diagnosis of BPD; authors of the 2010 review approached study authors for subsample data but did not retrieve them)
ISRCTN11135486	Unavailable trial: trial never started because funding provider withdrew (Malevani email reply on 17 June 2020)
Koenigsberg 2003	Subsample data unavailable (less than 70% of participants had BPD; no subsample data retrieved by authors of the preceding version of this review despite contacting the study authors (Stoffers 2010))
La Malfa 2003	Subsample data unavailable (less than 70% of participants had BPD; separate data on BPD patients available but number of BPD patients allocated to each group unclear; the authors of the previous version of this review were unable to retrieve subsample data (Stoffers 2010))
Links 1990	Ineligible patient population: participants with BPD features (mean DIB score 9.47, SD = 0.75); exact number of individuals with full BPD unclear
Marchesi 2006	Ineligible patient population: participants had no official BPD diagnosis

Study	Reason for exclusion
NCT00255554	Unavailable trial: trial not funded and never started
NCT00463775	Unavailable trial: trial withdrawn as recruitment not progressing as planned
NCT00633802	Unavailable trial: trial discontinued due to personnel changes
NCT01103180	Unavailable trial: trial terminated due to problems with recruitment
NCT03395314	Ineligible intervention: intervention duration shorter than 2 weeks
Parsons 1989	Subsample data unavailable (less than 70% participants with BPD; no subsample available)
Rombold 2014	Subsample data unavailable (less than 70% participants with BPD; retrieved subsample data for PD but fewer than 5 participants in total had BPD)
Russell 2003	Ineligible patient population: participants had PD but not BPD
Serban 1984	Subsample data unavailable (less than 70% participants had BPD; unable to retrieve subsample data)
Verkes 1998	Subsample data unavailable (participants were suicide-attempt repeaters, not clear how many patients actually had BPD; the authors of the previous version of this review were unable to retrieve subsample data (Stoffers 2010))
Wollmer 2022	Ineligible intervention: intervention duration shorter than 2 weeks

BPD: borderline personality disorder
DIB: Diagnostic Interview for Borderline Patients
PD: personality disorder
SD: standard deviation
vs: versus

Characteristics of studies awaiting classification *[ordered by study ID]*

NCT00437099

Methods	**Allocation**: randomised **Intervention model:** parallel assignment (3 arms) **Blinding:** triple (participant, investigator and outcomes assessor) **Duration of trial:** 12 weeks **Timing of assessment:** baseline, week 2, 4, 6, 8, 10, and 12
Participants	**Inclusion criteria** 1. BPD according to DSM-IV 2. CGI-Severity (BPD) > 3 3. 18-65 years **Exclusion criteria** 1. Serious medical illness 2. History of omacor® allergy

NCT00437099 *(Continued)*

3. Current diagnostic unipolar depression, bipolar disorder type I, obsessive-compulsive disorder, schizophrenia and other psychotic disorders
4. DIB-R > 8
5. Suicidal thinking that requires hospital admission
6. Meets DSM-IV criteria for alcohol, benzodiazepine, opioid or psychostimulant dependence in the six months prior to trial entry
7. Transaminase elevation within three times the upper limits of normality
8. Treatment with stable doses of antidepressants or mood stabilisers for fewer than six weeks
9. Treatment with stable doses of antipsychotics for more than one week in the last three months
10. Received electroconvulsive therapy for the six months prior to trial entry
11. Received DBT in the last 12 months prior to trial entry
12. Pregnant or nursing
13. Participated in any other investigational trial in the last six months prior to trial entry
14. Current treatment or expectation to start any treatment with drugs that may interact with the trial

Interventions

Experimental 1
Drug name: omega-3-acid ethyl esters: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)
Brand name: Omacor®
Drug dose: 1.680 mg/day
Route of administration: oral
Administration: capsule
Additional intervention: cognitive behaviour therapy (CBT)

Experimental 2
Drug name: omega-3-acid ethyl esters: EPA and DHA
Brand name: Omacor®
Drug dose: 3.360 mg/day
Route of administration: oral
Administration: capsule
Additional intervention: CBT

Comparator
Drug name: placebo
Brand name: N/A
Drug dose: N/A
Route of administration: oral
Administration: no information
Additional intervention: CBT

Outcomes

Primary outcomes

1. Affective symptoms, measured with the Hamilton Depression Scale (Ham-D) and the Young Mania Rating Scale (YMRS) at weeks 0, 2, 4, 6, 8, 10, 12
2. Impulsivity and aggression, measured with a self-control task of impulsivity and the Point Subtraction Aggression Paradigm at weeks 0, 6, 12

Secondary outcomes

1. Impulsivity, measured with the Barratt Impulsivity Scale-11 (BIS-11) at weeks 0, 2, 4, 6, 8, 10, 12
2. Anger, measured with the State-Trait Anger Expression Inventory 2 (STAXI-2) at weeks 0, 2, 4, 6, 8, 10, 12
3. Anxiety, measured with the State-Trait Anxiety Inventory (STAI-E) at weeks 0, 6, 12
4. Brief Psychiatric Rating Scale (BPRS) administered at weeks 0, 6, 12
5. Global Activity Scale (EEAG) administered at weeks 0, 6, 12
6. Consumption of addictive substances with urine and breath drug testing and self-reports every week throughout the study
7. Social Adaptation Self-evaluation Scale (SASS) administered at weeks 0, 6, 12

NCT00437099 *(Continued)*

8. Number of suicidal and parasuicidal episodes assessed every week throughout the study
9. Number of visits to a psychiatric emergency service assessed every week throughout the study
10. Plasmatic brain-derived neurotrophic factor (BDNF) assessed at weeks 0, 12
11. Adverse events assessed every week throughout the study
12. Clinical impression measured with the CGI at weeks 0, 2, 4, 6, 8, 10, 12
13. Adverse events assessed at each study visit
14. Immediate memory measured with the Immediate Memory Task at weeks 0, 6, 12
15. Impulsivity measured with the Two Choice Delayed Reward Test at weeks 0, 6, 12

Notes	**Study start date:** February 2009 **Source of funding:** Hospital Universitari Vall d'Hebron Research Institute **Conflicts of interest:** none reported **Recruitment status:** unknown, as reported on trial register; did not receive reply from PI on request and unable to identify publication

NCT01912391

Methods	**Allocation:** randomised **Intervention model:** parallel assignment (2 arms) **Blinding:** double (participant and investigator) **Duration:** 12 weeks **Timing of assessment:** baseline and every week for 12 weeks
Participants	**Inclusion criteria** 1. Aged 18-65 years 2. Healthy volunteers 3. Primary diagnosis of borderline disorder 4. Participant has symptomatology of BPD for at least 1 year **Exclusion Criteria** 1. Not pregnant or breastfeeding 2. Unlikely to adhere to trial procedures and restrictions 3. Failed treatment due to lack of efficacy of monoamine oxidase inhibitor (MAOI) medication 4. Anticipates need for surgery during the trial 5. Has another predominant personality disorder other than BPD 6. Has an active history of substance abuse or dependence, e.g. positive drug screen 7. Has other health issues that could interfere with trial interpretation 8. Reports recent suicide attempts or homicide attempts in the past 3 months 9. Substance abuse or dependence: clean for 1 year 10. History of a primary malignancy < 5 years 11. Has a medical condition(s) that is excluded, per protocol, or is unstable 12. Abnormal screening laboratory values, per protocol, or other clinically significant, unexplained laboratory abnormality 13. Currently participating or has participated in a trial within 30 days 14. Donated blood products or has had phlebotomy of > 300 mL within 8 weeks
Interventions	**Experimental**

NCT01912391 *(Continued)*

	Drug name: selegiline **Brand name:** Emsam **Drug dose:** 12 mg/day **Route of administration:** transdermal patch **Administration:** once daily **Comparator** **Drug name:** placebo **Brand name:** N/A **Drug dose:** N/A **Route of administration:** transdermal patch **Administration:** once daily
Outcomes	**Primary outcome:** Hopkins Symptom Checklist 90-Revised (SCL 90-R) scale assessed at weeks 1-12 **Secondary outcomes** 1. Hamilton Depression Inventory 17 Questions (HAM-D), assessed at weeks 1-12 2. Clinical Global Impression of Change-Clinician (CGIc), assessed at weeks 3-12 3. Clinical Global Impression Change-Patient (CGIp), assessed at weeks 3-12 4. Sheehan Disability Scale (SDS), assessed at weeks 1, 4, 12
Notes	**Trial start date:** October 2012 **Source of funding:** Mood and Anxiety Research, Incorporated **Conflicts of interest:** The Study Director, Paul Markovitz, is the Director of Mood and Anxiety Research. **Recruitment status:** completed

BDNF: brain-derived neurotrophic factor.
BIS-11: Barratt Impulsivity Scale-11.
BPD: borderline personality disorder.
BPRS: Brief Psychiatric Rating Scale.
CBT: cognitive behavioural therapy.
CGI: Clinical Global Impression scale.
DBT: Dialectal Behavioural Therapy.
DHA: docosahexaenoic acid.
DIB-R: Diagnostic Interview for Borderline Patients-Revised.
DSM-IV: Diagnostic Manual of Mental Disorders, 4th edition
EEAG: Global Activity Scale.
EPA: eicosapentaenoic acid.
HAM-D: Hamilton Depression Inventory.
MAOI: monoamine oxidase inhibitor.
N/A: not applicable.
PI: principal investigator.
SASS: Social Adaptation Self-evaluation Scale,
SCL-90-R: Symptom Checklist 90-Revised.
SDS: Sheehan Disability Scale.
STAI: State-Trait Anxiety Inventory.
STAXI: State-Trait Anger Expression Inventory.
YMRS: Young Mania Rating Scale.

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

ACTRN12617001317381

Study name	**Public title:** Estrogen for the treatment of borderline personality disorder

ACTRN12617001317381 *(Continued)*

	Scientific title: A randomised placebo controlled trial of estradiol for the treatment of women with borderline personality disorder
Methods	**Allocation:** randomised **Intervention model:** parallel assignment **Blinding:** double (participant and treatment administration) **Duration:** 12 weeks **Timing of assessment:** baseline, week 2, week 4, week 6, week 8, week 10, week 12
Participants	**Inclusion criteria** 1. Age 18-43 years 2. Female participants 3. Primary diagnosis of BPD, assessed by the Diagnostic Interview for Borderline Patients-Revised 4. Be willing to use appropriate barrier contraceptive precaution for the duration of the trial **Exclusion criteria** 1. Known, suspected or history of breast, endometrial or ovarian cancer, or known or suspected oestrogen-dependent neoplasia 2. Current pregnancy, lactation or use of hormone therapies for contraception or other purposes 3. Chronic inflammatory or autoimmune disease (e.g. arthritis, lupus) 4. Unexplained vaginal bleeding 5. Peri/post-menopause (either naturally or through surgical intervention) 6. Liver dysfunction or disease 7. History of blood clots (e.g. deep vein thrombosis, pulmonary embolism) 8. Previous arterial thromboembolic disease (e.g. stroke) 9. Lifetime diagnosis of schizophrenia, schizoaffective disorder, substance-induced psychotic disorder, major depression with psychosis, bipolar I disorder (DSM-5) measured by the structured clinical interview for DSM-5 10. Risk of suicide such that inpatient admission is required, as determined by PI Kulkarni (psychiatrist), based on the presence of suicidal behaviour (Zan-BPD self-mutilation/suicidality subscale) and clinical assessment 11. Taking more than 4 psychotropic medications 12. New/planned changes to psychotropic medication/psychotherapy plans 13. Substance abuse or dependence in last 3 months 14. Smoking more than 20 cigarettes per day 15. Recent (less than or equal to 3 months) traumatic life events measured by the Holmes-Rahe Life Stress Inventory
Interventions	**Experimental** **Drug name:** estradiol **Brand name:** no information **Drug dose:** 100 mcg twice weekly **Route of administration:** transdermal **Administration:** patch **Comparator** **Drug name:** placebo **Brand name:** N/A **Drug dose:** N/A **Route of administration:** transdermal **Administration:** patch
Outcomes	**Primary outcomes** 1. Mean change over time in the Borderline Personality Disorder Severity Index (BPDSI-IV) from baseline (visit 1) over the 84-day treatment period

ACTRN12617001317381 *(Continued)*

2. Proportion of participants in each group achieving clinical improvement, defined by a decrease of ≥ 11.7 points on the BPDSI-IV

Secondary outcomes

1. Potential change in emotional regulation, assessed by the Difficulties in Emotion Regulation Scale; a 36-item scale that assesses ways that emotions are experienced, approached and processed
2. Potential change in cognitive and affective empathy, assessed by the Multifaceted Empathy Test
3. Potential change in Assessment of Quality of Life scores
4. Potential change in Dissociative Experience Scales, a 28-question, self-reported assessment for multi-modulatory experiences of dissociation

Starting date	13 January 2020
Contact information	**Name:** Jayashri Kulkarni **Address:** Monash Alfred Psychiatry Research Centre, Level 4, 607 St Kilda Rd Melbourne VIC 3004, Australia **Phone:** +61 3 9076 6564 **Email:** jayashri.kulkarni@monash.edu
Notes	**Source of funding:** Monash Alfred Psychiatry Research Centre

Arteaga-Henríquez 2020

Study name	**Public title:** Treating impulsivity in adults with probiotics (PROBIA) **Scientific title:** Randomized placebo-controlled treatment of impulsivity in adults with probiotics
Methods	**Allocation:** randomised **Intervention model:** parallel assignment (2 arms) **Blinding:** none, open-label **Duration:** 10 weeks **Timing of assessment:** baseline, week 5, week 10 and week 11
Participants	**Inclusion criteria** 1. Adults with a high level of impulsivity (with or without ADHD) based on a CGI-S-score ≥ 4 2. Affective Reactivity Index (ARI) score ≥ 5 indicating a high level of multi dimensional impulsivity 3. Research diagnosis of ADHD or BPD (or both) confirmed by structured diagnostic interview according to DSM-5 (ADHD: Diagnostic Interview for Adult ADHD (DIVA 2.0); BPD: Structured Clinical Interview for DSM-IV (SCID-II)) 4. Not currently taking any antibiotics or probiotics 5. Deemed reliable and compliant with the protocol by the investigator 6. Ability to speak and comprehend the native language of the country in which the assessments take place **Exclusion criteria** 1. Being treated with a concomitant medication, which is prohibited within the trial according to the list of prohibited medications 2. Patients must be on stable medication (i.e. current dose given since more than 30 days): up-titration not allowed and careful clinical screening done at all visits to check whether lower dosage is needed due to increased side effects as a result of treatment with Synbiotic 2000 Forte 3. Presence of major psychiatric disorders with psychotic symptoms 4. Neurological disorder involving brain or other central function (e.g. intellectual disability with an assessed IQ < 70, epilepsy, MS, narcolepsy) or other major psychiatric condition requiring hospitalisation (e.g. significant mood disorder or psychosis)

Arteaga-Henríquez 2020 *(Continued)*

5. Major physical illness of the cardiovascular, endocrine, pulmonal, or the gastrointestinal system
6. History of or present clinically relevant somatic acute or chronic disorder that, in the opinion of the investigator, might confound the results of tolerability/safety assessment, or prohibit the patients from completing the trial, or would not be in the best interest of the patient
7. Participant has a documented allergy, hypersensitivity, or intolerance to any of the ingredients of the intervention
8. Participant has taken another investigational product or taken part in a clinical trial within 30 days prior to entering the trial

Interventions	**Experimental** **Drug name:** 3 LAB species known to have anti-inflammatory effects and restoring the intestinal barrier, and 4 fermentable fibres: pediococcus pentosaceus 5-33:3; lactobacillus paracasei subsp. paracasei 19; and lactobacillus plantarum 2362 in combination with the following four fermentable fibres: betaglucan, inulin, pectin and resistant starch **Brand name**: probiotic Synbiotic 2000 Forte (SF) **Drug dose:** one dose daily **Route of administration:** oral **Administration**: powder (to be spread on top of cold foods such as muesli, salad or yogurt) **Comparator** **Drug name:** placebo (non-digestible carbohydrate with similar texture and flavour to SF) **Brand name**: N/A **Drug dose:** one dose daily **Route of administration:** oral **Administration:** powder (to be spread on top of cold foods such as muesli, salad or yogurt)
Outcomes	**Primary outcomes** 1. Self-rating of affective reactivity 2. CGI-I total score **Secondary outcomes** 1. CGI-S 2. ADHD symptom severity total score 3. Impulsive behaviour, assessed by self-rated multi-dimensional impulsivity 4. Aggression and emotional lability 5. Compulsivity 6. Sleep problems 7. Somatic complaints and side effects 8. Body composition parameters 9. Weight in kilograms 10. Concentrations of blood biomarkers, including hormones, neurotransmitters and nutrients 11. Microbiome composition 12. Nutritional intake, assessed by 24-hour dietary recall 13. Treatment adherence, assessed by the Probabilistic Medication Adherence Scale 14. Functioning problems, assessed by the Functioning Assessment Short Test 15. Emotion regulation difficulties, assessed by Difficulties in Emotion Regulation Scale 16. Change in gastrointestinal symptoms, assessed by Bristol Stool Scale 17. Physical activity duration and intensity, assessed by a movement sensor 18. Neurocognitive measures: detectability, omissions, commissions, perseverations, hit reaction time, hit reaction time standard deviation and variability, assessed by Conners' Continuous Performance Test II 19. Perceived stress, assessed by Perceived Stress Scale
Starting date	22 February 2019

Arteaga-Henríquez 2020 *(Continued)*

Contact information	**Name:** Josep Antoni Ramos-Quiroga **Email:**jaramos@vhir.org
Notes	**Source of funding:** no information

Chanen 2019

Study name	**Public title:** VERBATIM: a randomised controlled trial of aripiprazole for the treatment of auditory verbal hallucinations in borderline personality disorder **Scientific title:** A randomised controlled trial of aripiprazole for the treatment of auditory verbal hallucinations in borderline personality disorder
Methods	**Allocation:** randomised **Intervention model:** parallel assignment (2 arms) **Blinding:** quadruple (participant, treatment administration, outcome assessors and data analysts) **Duration:** 12 weeks (and 2-week follow-up) **Timing of assessment:** baseline and every week for 12 weeks
Participants	**Inclusion criteria** 1. Aged 15-25 years 2. Male and female participants 3. BPD according to DSM-5 4. Auditory verbal hallucinations (AVH) 5. Ability to give informed consent and adhere to trial procedures 6. Sufficient fluency in English **Exclusion criteria** 1. DSM-5 schizophreniform disorder, schizophrenia, schizoaffective disorder, psychotic disorder due to another medical condition, catatonia, delusional disorder, bipolar I disorder, or substance/medication induced psychotic disorder 2. Prior sensitivity or allergy to aripiprazole or formulation 3. Antipsychotic treatment for 4 weeks or more at a dose equal to or greater than 200 mg chlorpromazine equivalent within 8 weeks of trial entry 4. Pregnancy, lactation, or if sexually active, no effective contraception 5. Clinically significant liver or thyroid function, or haematological findings which, in the opinion of the investigator, may present a safety issue for the participant or confound the trial results 6. Acute or unstable systemic medical disorder 7. Psychiatric condition due to a medical condition 8. Severe disturbance, such that the person is unable to comply with either the requirements of informed consent or the treatment protocol 9. Does not meet the Orygen Youth Health Clinical Service's eligibility criteria 10. For magnetic resonance imaging scans: lifetime history of head injury, loss of consciousness for more than 10 minutes, seizures, thyroid disorder or other significant medical illness that, in the opinion of the investigator, would preclude participation in the trial
Interventions	**Experimental** **Drug name:** aripiprazole **Brand name:** no information **Drug dose:** individual titration. Week 1 = 2 mg/day; week 2 = 5 mg/day; week 3 = 10 mg/day; week 4 to week 12 = increments to 15 mg once daily, 20 mg once daily then 30 mg (maximum allowed doses) once daily **Route of administration:** oral **Administration:** capsule

Chanen 2019 *(Continued)*

	Additional intervention: CAT **Comparator** **Drug name:** placebo **Brand name:** N/A **Drug dose:** N/A **Route of administration:** oral **Administration:** capsule **Additional intervention:** CAT
Outcomes	**Primary outcome:** 1. AVH severity **Secondary outcomes** 1. BPD severity 2. General psychopathology 3. Functioning 4. Experience of psychotic symptoms 5. Changes in neurobiological mechanisms underlying AVHs that are associated with treatment
Starting date	1 September 2016
Contact information	**Name:** Andrew Chanen **Affiliation:** Orygen, The National Centre of Excellence in Youth Mental Health **Address**: 35 Poplar Rd, (Locked Bag 10), Parkville, Victoria, 3052 **Phone**: +61393422800
Notes	**Source of funding:** National Health and Medical Research Council

DRKS00015817

Study name	**Public title:** Stellate ganglion block in patients with borderline personality disorder and post-traumatic stress disorder **Scientific title:** as above
Methods	**Allocation:** randomised **Intervention model:** parallel assignment **Blinding:** no information **Duration:** 8 weeks **Timing of assessment:** Baseline, twice a week (the Dissociations Tension Scale-4 (DSS-4) and Clinical Global Impression Skala (CGI)) and once a week (Beck Depression Inventory (BDI), Borderline Symptom List-23 (BSL-23), State Trait Anxiety Inventory-S (STAI-S), PTSD Checklist for DSM-5 (PCL-5) and the Patient and Observer Scare Assessment Scale (POSAS)) for 8 weeks, and baseline and week 8 (Questionnaire of Dissociative Symptoms (FDS) and the Symptom Checklist-90-R (SCL-90-R)).
Participants	**Inclusion criteria** 1. 18 to 50 years 2. Diagnosis of BPD (minimum 5 criteria according to DSM 5) + PTSD **Exclusion criteria** 1. Chronic pain 2. Bipolar-I-disorder or schizophrenia 3. Cognitive impairment

DRKS00015817 *(Continued)*

	4. Allergies on local anaesthetics 5. Intake of oral anticoagulants
Interventions	**Experimental (arm 1)** Stationary patients with post-traumatic stress disorder and borderline personality disorder receive in addition to a standard therapy (dialectical behavorial therapy, after week 4) a series of 8 stellate ganglion blocks (2 per week) on both sides, with each 3 mL Ropivacain 1% **Comparator (arm 2)** Stationary patients with post-traumatic stress disorder and borderline personality disorder receive the same procedure as in arm 1 without the stellate ganglion block
Outcomes	**Primary outcomes** 1. DSS-4 2. CGI 3. BDI 4. BSL-23 5. STAI-S 6. PCL-5 7. FDS 8. SCL-90-R **Secondary outcome** 1. POSAS
Starting date	02 January 2019
Contact information	**Name:** Mr. Prof. Dr. med. Christian Schmahl **Affiliation:** Klinik für Psychosomatik und Psychotherapeutische Medizin, Zentralinstitut für Seelische Gesundheit **Address:** Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany **Phone:** 0621 1703-4021 **Email:** christian.schmahl@zi-mannheim.de
Notes	**Source of funding:** Klinik für Anästhesiologie und Operative Intensivmedizin, Schmerzzentrum,Universitätsmedizin Mannheim

EUCTR2020-003469-20-ES

Study name	**Public title:** A phase IIb study to evaluate the safety and efficacy of vafidemstat in an adult borderline personality disorder population **Scientific title:** A double-blind, randomized, placebo-controlled, adaptive 14-week phase IIb trial to evaluate the efficacy and safety of vafidemstat in an adult borderline personality disorder (BPD) population (PORTICO)
Methods	**Allocation:** randomised **Intervention model:** parallel assignment **Blinding:** double-blind **Duration:** 14 weeks **Timing of assessment:** Baseline, specific weeks (no further information), and week 14
Participants	**Inclusion criteria** 1. Men and women 2. 18-65 years of age

EUCTR2020-003469-20-ES *(Continued)*

3. Participant must meet DMS-5 diagnostic criteria for BPD at least 3 months before the screening visit. The Mini-International Neuropsychiatric Interview (MINI) will be administered at screening in order to confirm BPD diagnosis, as well as to confirm participant does not meet other relevant exclusion criteria.
4. Agitation-Aggression Psychiatric Inventory (AAPI) subscale of > 16 (severity x frequency) summed across the four (4) items comprising the Agitation/Aggression (A/A) subscale, and the sum of the A/A subscale severity scores > 6
5. Participant is known to the site or investigator and has been treated by the site or investigator for at least the last 3 months prior to the screening visit.
6. Stable living environment for > 6 months before the screening visit
7. Body mass index (BMI) of at least 18.5 kg/m^2, but no more than 30 kg/m^2
8. Willing and able to adhere to the prohibitions, restrictions and requirements in protocol
9. Otherwise healthy and medically stable based on medical history
10. Clinical and neurological examinations and laboratory tests, as well as 12-lead ECG performed during screening that confirms participant is healthy and medically stable
11. Able to read and write fluently and must have adequate hearing and visual acuity to complete the required testing outlined in protocol
12. Outpatient consulting general practitioner or a psychiatrist/neurologist/psychologist
13. Participants should be stable in their regimen of background therapy as per the Summary of Product Characteristics (SmPC) for concomitant medications at the screening visit and they should maintain treatment throughout the study and not initiate any prohibited medications during the trial. Participants should agree to inform their study physician of any medication changes throughout the trial.
14. Enrolled Participants will need to maintain their pre-screening psychotherapy schedule throughout the trial duration. That is, Participants receiving psychotherapy will need to have it started at least 3 months before the screening visit and remain in psychotherapy throughout the trial. Participants not receiving psychotherapy should not initiate psychotherapy during the trial.
15. Fertile male and female participants must use highly efficient contraception, from the screening visit until 30 days after last dose of the IMP, defined as: a method with less than 1% failure rate.
16. Female participants of childbearing potential must have a negative urine pregnancy test at screening and baseline.
17. Signed informed consent by patient prior to the initiation of any study specific procedure

Exclusion criteria

1. DSM-5 diagnosis of intellectual disability, autism spectrum disorder, schizophrenia, schizoaffective disorder, bipolar disorder (or related disorders) or major depressive disorder (MDD) with psychosis. Current DSM-5 diagnosis of conduct disorder, anorexia nervosa, bulimia nervosa, binge-eating disorder, oppositional defiant disorder, paranoid personality disorder or obsessive-compulsive disorder
2. Current DSM-5 diagnosis of panic disorder or post-traumatic stress disorder (PTSD)
3. History of moderate or severe substance or alcohol use disorder according to DSM-5, with the exception of nicotine and caffeine, within 6 months before screening
4. Use of illicit drugs for at least one week before screening and participants unwilling to abstain from use of these substances during the study
5. Clinically significant, advanced or unstable disease that is likely to result in rapid deterioration of the participant's condition or affect their safety during the study
6. Positive results for HIV, hepatitis C or hepatitis B at the screening visit
7. Uncontrolled hypo- or hyperthyroidism at screening visit, based on laboratory parameters
8. Clinically significant infection within the previous 30 days
9. Use of prohibited chronic medication (the concomitant use of MAO inhibitors and antidepressants; atypical antipsychotics; mood stabilisers and nootropics in stable doses for at least 2 months before screening are allowed for the treatment of psychiatric comorbidities (as per inclusion/exclusion criteria) when these medications are prescribed as per their labelled indications).
10. Esketamine in the past 90 days before the screening visit
11. Electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS) in the past 90 days before the screening visit

EUCTR2020-003469-20-ES *(Continued)*

	12.Any regular intake of medications acting directly on central nervous system that investigator considers relevant to the study 13.Member or immediate family of the study personnel or subordinate to any of the study personnel 14.Enrolment in another investigational study or intake of investigational drug within the previous 3 months 15.Suicide attempt within the 6 months prior to the screening visit or significant risk of suicide 16.Any condition that in the opinion of the investigator makes the participant unsuitable for inclusion in the study
Interventions	**Experimental** **Drug name:** Vafidemstat **Brand name:** N/A **Drug dose:** 1.2 mg **Route of administration:** oral **Administration:** no information **Comparator:** placebo
Outcomes	**Primary outcomes** 1. Clinical Global Impression-Severity focused on Agitation/Aggression (CGI-S A/A) 2. The Borderline Personality Disorder Checklist (BPDCL) **Secondary outcomes** 1. Borderline Evaluation of Severity over Time (BEST) 2. Beck Depression Inventory – II (BDI-II) 3. State-Trait Anger Expression Inventory 2 (STAXI-2) 4. State-Trait Anxiety Inventory (STAI) 5. Safety a. Number, frequency and severity of Treatment Emergent Adverse Events (TEAEs) b. Number, frequency and severity of Serious TEAEs c. Number and percentage of withdrawn subjects due to TEAEs d. Physical examination parameters, vital signs and ECG parameters e. Clinical laboratory parameters (hematology, including platelets, and clinical chemistry) f. Columbia – Suicide Severity Rating Scale (C-SSRS) g. Use of concomitant medication throughout the study period
Starting date	19 November 2020
Contact information	**Name:** Clinical Operations **Affiliation:** Oryzon Genomics S.A. **Address:** Sant Ferran 74 08940 Cornellà de Llobregat, Barcelona Spain **Phone:** 34647796923 **Email:** sgutierrez@oryzon.com
Notes	**Source of funding:** Oryzon Genomics S.A

EudraCT 2018-002471-18-GB

Study name	**Public title:** Clozapine in the treatment of borderline personality disorder **Scientific title:** The clinical effectiveness and cost effectiveness of clozapine for inpatients with borderline personality disorder: randomised controlled trial - CALMED
Methods	**Allocation:** randomised

EudraCT 2018-002471-18-GB *(Continued)*

Intervention model: parallel assignment
Blinding: double (participant and treatment administration)
Duration: 6 months
Timing of assessment: baseline, 3 months, 6 months, 12 months, 18 months

Participants

Inclusion criteria

1. Aged 18 years and over
2. Currently an inpatient on a mental health unit
3. Meeting DSM-IV diagnostic criteria for BPD
4. Failure to make an adequate clinical response to taking antipsychotic medication other than clozapine for at least three months
5. Have a satisfactory, pretreatment, full blood count (white blood cell count ≥ 3.5 and absolute neutrophil count ≥ 2.0)
6. Have had their weight and blood glucose recorded in their clinical records
7. Male and female participants

Exclusion criteria

1. Current clinical diagnosis of schizophrenia, or bipolar I disorder
2. Prescribed clozapine within the last two weeks
3. Known to be pregnant, trying to conceive, breastfeeding, or a woman of childbearing potential and not using a highly effective birth control
4. Due to be discharged from the unit within the following two weeks
5. Unable to speak sufficient English to complete the baseline assessment
6. Unwilling or unable to provide written informed consent to take part in the trial
7. Unable to undergo regular blood tests
8. Contraindication to clozapine or other listed condition, namely:
   a. known history of primary bone marrow disorders or impaired bone marrow function
   b. severe renal or cardiac disorders (e.g. myocarditis), or a known history of cardiac illness or abnormal cardiac findings on physical examination
   c. hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption
   d. hypersensitivity to magnesium stearate, silica, colloidal anhydrous, povidone K30, talc, maize starch or lactose monohydrate
   e. known history of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy)
   f. history of clozapine-induced agranulocytosis
   g. uncontrolled epilepsy
   h. alcoholic and other toxic psychoses, drug intoxication, comatose conditions
   i. circulatory collapse or CNS depression of any cause (or both)
   j. active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure
   k. paralytic ileus

Interventions

Experimental
Drug name: clozapine
Brand name: Clozaril
Drug dose: 12.5 mg/day to 400 mg/day
Route of administration: oral
Administration: capsule

Comparator
Drug name: placebo
Brand name: N/A
Drug dose: N/A
Route of administration: oral

EudraCT 2018-002471-18-GB *(Continued)*

	Administration: capsule
Outcomes	**Primary outcome** 1. Total score on Zan-BPD **Secondary outcomes** 1. Total score on ZAN-BPD 2. General mental health, measured using Brief Psychiatric Rating Scale 3. Incidence and severity of suicidal behaviour, measured using Acts of Deliberate Self-Harm Inventory 4. Level of aggressive behaviour, measured using Overt-Aggression Scale-Modified 5. Health-related quality of life, assessed with the standardised measure of health-related quality of life instrument developed by the EuroQol Group 6. Side effects of medication, measured using the Antipsychotic Non-Neurological Side Effects Scale, and motor and extrapyramidal side effects, measured using the Extrapyramidal Side Effects Scale 7. Incidence of withdrawal of trial medication due to adverse effects 8. Medication adherence, measured at three and six months using the Brief Adherence Rating Scale 9. Resource use, collected using a modified version of the Adult Service Use Schedule and by examining clinical records at 6, 12 and 18 months. This will include detailed information about length of inpatient treatment and type of ward (high, medium, low secure, psychiatric intensive care, general adult etc.), contacts with community mental health services and emergency medical services, and the type and dose of psychotropic medication that people are prescribed.
Starting date	18 January 2019
Contact information	**Name:** Mike Crawford **Affiliation:** Imperial College London **Adress:** Du Cane Road W12 0NN London United Kingdom **Phone:** 02083834161 **Email:** m.crawford@imperial.ac.uk
Notes	**Source of funding:** no information

IRCT20210106049948N1

Study name	**Public title:** Memantine and borderline personality disorder **Scientific title:** The effect of memantine on the symptoms of borderline personality disorder in the Iranian population
Methods	**Allocation:** randomised **Intervention model:** parallel assignment **Blinding:** double-blinding. “The researcher does not know whether the patient being evaluated belongs to the placebo group or the memantine group. The patients also do not know if they have used placebo or memantine. Drugs and placebos are similar in appearance, such as color, shape, and so on. The patient (placebo or memantine groups) receive the drug in encoded packets. The coding is done by the psychiatrist and the evaluator and the patient is blind”. **Duration:** 12 weeks **Timing of assessment:** baseline and at the end of weeks 2, 4, 6, 8, and 12
Participants	**Inclusion criteria** 1. Ages 16-45 2. A diagnosis of BPD using the BEST tool for disease. **Exclusion criteria**

IRCT20210106049948N1 *(Continued)*

	1. Clinical evidence of any pathology in the central nervous system, neurological disorders, head injuries, epilepsy, or history of seizures 2. Pregnancy or breastfeeding 3. Taking medications that may interact with memantine
Interventions	**Experimental** **Drug name:** memantine **Brand name:** not stated **Drug dose:** 10 mg daily in week 9, 20 mg daily week 10-12 **Route of administration:** oral **Administration:** The treatment group will receive a placebo daily for the first 8 weeks, then memantine daily the last 4 weeks. **Comparator** **Drug name:** placebo **Brand name:** not stated **Drug dose:** not stated **Route of administration:** oral **Administration:** The placebo group take a placebo daily for 12 weeks.
Outcomes	**Primary outcomes** 1. BPD symptoms, measured with BEST 2. Number of suicides
Starting date	21 April 2021
Contact information	**Name:** Fariba Karimzadeh **Address:** Cellular and Molecular Research Center, Iran University of Medical Sciences, Hemmat Highway 1449614535 Tehran Iran **Phone:** +98 21 8670 4725 **Email:** fariba_karimzade@yahoo.com
Notes	**Source of funding:** Iran University of Medical Sciences

IRCT20210531051453N1

Study name	**Public title:** Effect of omega-3 fatty acid in borderline personality disorder **Scientific title:** Study the effectiveness of omega-3 fatty acids as adjuvant treatment on depression, aggression and poor impulse control in hospitalized patients of borderline personality disorder
Methods	**Allocation:** randomised **Intervention model:** parallel assignment **Blinding:** double-blinded **Duration:** 6 weeks **Timing of assessment:** at baseline and 12 weeks after the trial
Participants	**Inclusion criteria** 1. Definitive diagnosis of Borderline Personality Disorder based on DSM-V 2. Aged 18-60 3. Disorder leading to referral for treatment and hospitalisation 4. IQ > 70 5. Patient and patients have conscious consent to participant in the study. **Exclusion criteria**

IRCT20210531051453N1 *(Continued)*

	1. Having any psychological disorders (except substance abuse disorder) 2. Having diabetes, metabolic disorders, serious medical or neurological diseases 3. Having extrapyramidal symptoms such as hands tremor, mouthwatering, neck dystonia, rigidity, and akathisia 4. Pregnancy and/or breastfeeding
Interventions	**Experimental** **Drug name:** omega-3 **Brand name:** Actover Pharmaceutical Company **Drug dose:** 2 grams per day **Route of administration:** oral **Administration:** daily for 6 weeks **Comparator** **Drug name:** olanzapine **Brand name:** Abidi Pharmaceutical Company **Drug dose:** 5-15 mg per day, according to patent's response **Route of administration:** oral **Administration:** daily for 6 weeks
Outcomes	**Primary outcome** 1. Depression, using the Hamilton scale **Secondary outcomes** 1. Aggression, using the Bus and Perry scale 2. Impulse control, using an impulse control measurement based on the Barrat scale
Starting date	8 January 2020
Contact information	**Name:** Ensieh Sadri **Address:** No 17, South Ebrahimi Ave, East Ferdos Blvd, Tehran 1481958465 Tehran Iran (Islamic Republic of) **Phone:** +98 21 4405 7355 **Email:** sadri.ensieh@gmail.com
Notes	**Source of funding:** University of Social Welfare and Rehabilitation Sciences

NCT04100096

Study name	**Public title:** A trial of brexpiprazole in the treatment of borderline personality disorder **Scientific title:** A multicenter, randomized, flexible-dose, double-blind trial of brexpiprazole versus placebo for the treatment of adults with borderline personality disorder
Methods	**Allocation:** randomised **Intervention model:** parallel assignment (2 arms) **Blinding:** quadruple (participant, care provider, investigator and outcomes assessor) **Duration:** 12 weeks **Timing of assessment:** baseline and up to 12 weeks
Participants	**Inclusion criteria** 1. Male or female participants 2. Aged 18 to 65 years 3. Primary DSM-5 diagnosis of BPD confirmed by the SCID-5-PD at screening 4. Participants who, in the investigator's judgement, require treatment with a medication for BPD

NCT04100096 *(Continued)*

5. Participants willing to discontinue all prohibited medications to meet protocol-required washouts prior to and during the trial period

Exclusion criteria

1. Sexually active males or females of childbearing potential who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of IMP. Consensual sexual activity that cannot biologically result in pregnancy may not be subject to required birth control methods, following discussion with the medical monitor. Male participants must also agree not to donate sperm from trial screening through 30 days after the last dose of IMP.
2. Women who are breastfeeding or who have a positive pregnancy test result (or both) prior to receiving IMP
3. Participants with a concurrent DSM-5 diagnosis of schizophrenia or schizoaffective disorder. Also, participants with a concurrent diagnosis of bipolar I disorder, bipolar II disorder, delirium, dementia, amnesia, eating disorder, antisocial personality disorder, or other cognitive disorders. Participants with MDD, PTSD, ADHD, panic disorder, or generalised anxiety can be included if symptoms have been stable, these disorders are not the primary focus of treatment and changes in any treatment for these disorders would not likely be required for the duration of the trial.
4. Participants currently in psychotherapy specifically used to target BPD symptoms at time of screening
5. Participants who have had electroconvulsive treatment or transcranial magnetic stimulation
6. Participants with a current diagnosis of substance or alcohol use disorder within 90 days prior to screening visit
7. Participants who fulfil the following criteria related to suicide or suicidal ideation (or both) are excluded: participants who have a significant risk of committing violent acts, serious self-harm, or suicide based on history or routine psychiatric status examination, or those who are homicidal or considered to be a high risk to others, or participants with a response of 'yes' on the C-SSRS Suicidal Ideation Item 5, OR participants with a response of 'yes' on the C-SSRS Suicidal Behavior Items, OR participants who have had 3 suicide attempts, OR participants who have had 3 or more hospitalisations due to suicidal behaviour. Note, participants who have engaged in non-suicidal self-injurious behaviour within the 90 days prior to screening or at day 0 are eligible, unless the behaviour is better described as an actual attempt, interrupted attempt, or aborted attempt according to C-SSRS definition or investigator judgement (or both) and therefore exclusionary. Participants with a response of 'yes' on the C-SSRS Suicidal Ideation Item 4 within the 90 days prior to screening or at Day 0 may be included following discussion with a medical monitor.
8. Participants with hypothyroidism or hyperthyroidism or an abnormal result for free T4 at screening
9. Participants who currently have clinically significant neurological, hepatic, renal, metabolic, haematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders
10. Participants with uncontrolled hypertension, symptomatic hypotension, or orthostatic hypotension
11. Participants with epilepsy or a history of seizures, except for a single seizure episode
12. Participants who received brexpiprazole in any prior clinical trial or participants who have taken or are taking commercially available brexpiprazole (Rexulti®)
13. Participants with a history of neuroleptic malignant syndrome, serotonin syndrome, or clinically significant tardive dyskinesia
14. Participants with a history of true allergic response to more than 1 class of medication
15. Participants who are currently either inpatient or partially hospitalised
16. Participants who participated in a clinical trial within 90 days prior to screening or who participated in more than 2 clinical trials within a year prior to screening

Interventions	**Experimental** **Drug name:** brexpiprazole **Brand name:** Rexulti® **Drug dose:** 2-3 mg/day (flexible dose) **Route of administration:** oral **Administration:** tablet

NCT04100096 *(Continued)*

	Comparator **Drug name:** placebo **Brand name:** N/A **Drug dose:** N/A **Route of administration:** oral **Administration:** tablet
Outcomes	**Primary outcomes** 1. Zan-BPD total score **Secondary outcomes** 1. CGI-S 2. Patient's Global Impression of Severity and Patient's Global Impression of Change scales 3. CGI-I
Starting date	17 October 2019
Contact information	**Name:** Otsuka Call Center **Phone:** 844-687-8522 **Email:** OtsukaRMReconciliation@rmpdc.org
Notes	**Source of funding:** Otsuka Pharmaceutical Development & Commercialization, Inc

NCT04566601

Study name	**Public title:** A study to test different doses of BI 1358894 and find out whether they reduce symptoms in people with borderline personality disorder **Scientific title:** A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of 4 oral doses of BI 1358894 once daily over 12 week treatment period in patients with borderline personality disorder
Methods	**Allocation:** randomised **Intervention model:** parallel assignment (4 arms) **Blinding:** quadruple (participant, care provider, investigator, outcomes assessor) **Duration:** 12 weeks **Timing of assessment:** baseline and week 10
Participants	**Inclusion criteria** 1. Patients meeting diagnostic criteria of borderline personality disorder (BoPD) per Diagnostic and Statistical Manual of Mental Disorders (DSM-5) at screening visit, confirmed by Structured Interview for DSM-5 Personality Disorder (SCID-5-PD) 2. Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) of ≥ 9 at screening (visit 1) and randomisation (visit 2), with question #2 affective instability score of ≥ 2 3. Male or female patients, 18-65 years of age at the time of consent 4. Women of childbearing potential (WOCBP) able and willing to use two methods of contraception, which include one highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1%, plus one barrier method 5. Signed and dated written informed consent in accordance with International Council on Harmonization (ICH) - Good Clinical Practice (GCP) and local legislation prior to admission to the trial Further inclusion criteria also apply. **Exclusion criteria**

NCT04566601 *(Continued)*

	1. Current diagnosis of paranoid, schizoid, schizotypal and antisocial personality disorders, as confirmed by SCID-5-PD at screening visit 2. Lifetime diagnosis for schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar I disorder, or delusional disorder as confirmed by the SCID-5 at the screening visit 3. Any other mental disorder that is the primary focus of treatment in the last 6 months prior to randomisation, as per the clinical judgement of the investigator 4. Inpatient stay or hospitalisation due to worsening of BoPD within 3 months prior to randomisation 5. Initiation or change in any type or frequency of psychotherapy for BoPD within the last 3 months prior to randomisation 6. Any ongoing use of psychotropic medications within 7 days prior to randomisation or during the course of study 7. Any suicidal behaviour in the past 1 year 8. Any suicidal ideation of type 4 or 5 in the Columbia Suicidal Severity Rating Scale (C-SSRS) in the past 3 months Further exclusion criteria also apply.
Interventions	**Experimental** **Drug name:** BI 1358894 **Brand name:** N/A **Drug dose:** 4 drug doses (unspecified in protocol) **Route of administration:** oral **Administration:** once daily **Comparator** **Drug name:** placebo **Brand name:** N/A **Drug dose:** N/A **Route of administration:** oral **Administration:** once daily
Outcomes	**Primary outcomes** 1. Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) **Secondary outcomes** 1. Response defined as ≥ 30% ZAN-BPD reduction. 2. Difficulties in Emotion Regulation Scale (DERS-16) 3. State-Trait Anxiety Inventory (STAI-S) 4. Patient Health Questionnaire (PHQ-9) 5. Clinical Global Impression Severity scale (CGI-S) 6. Patient Global Impression Severity scale (PGI-S)
Starting date	13 November 2020
Contact information	**Name:** Boehringer Ingelheim **Email:**clintriage.rdg@boehringer-ingelheim.com
Notes	**Source of funding:** Boehringer Ingelheim

NCT05356013

Study name	**Public title:** Calypta in borderline personality disorder **Scientific title:** A Double-Blind, Placebo-Controlled Study of Caplyta in the Treatment of Borderline Personality Disorder

NCT05356013 *(Continued)*

Methods	**Allocation:** randomised **Intervention model:** parallel assignment **Blinding:** quadruple (participant, care provider, investigator, outcome assessors) **Duration:** 8 weeks **Timing of assessment:** baseline and weekly for 8 weeks
Participants	**Inclusion criteria** 1. Men and women age 18-65 2. Primary diagnosis of BPD 3. Zanarini scale score of at least 9 at baseline 4. Currently receiving for at least the last 2 months prior to study entry some form of weekly cognitive behavioural therapy 5. Ability to understand and sign the consent form **Exclusion criteria** 1. Unstable medical illness based on history or clinically significant abnormalities on baseline physical examination 2. Participants with schizophrenia or bipolar I disorder 3. Participants with an active substance use disorder 4. Current pregnancy or lactation, or inadequate contraception in women of childbearing potential 5. Participants considered an immediate suicide risk based on the Columbia Suicide Severity rating Scale (C-SSRS) (www.cssrs.columbia.edu/docs) 6. Illegal substance use based on urine toxicology screening (excluding marijuana given the high rates of marijuana use in BPD and the lack of interaction with Caplyta) 7. Use of any new psychotropic medication started within the last 3 months prior to study initiation 8. Previous treatment with Caplyta 9. Cognitive impairment that interferes with the capacity to understand and self-administer medication or provide written informed consent
Interventions	**Experimental:** caplyta All participants who are randomised to Caplyta will receive 42 mg/day starting the first week of the study. Participants will be seen every two weeks for 8 weeks. Dosage changes and reductions will not be permitted. After study conclusion (week 8), the dose will be discontinued. **Comparator:** placebo All participants who are randomised to placebo will receive an identical placebo pill to the experimental drug starting the first week of the study. Participants will be seen every two weeks for 8 weeks. After study conclusion (week 8), the dose will be discontinued.
Outcomes	**Primary outcomes** 1. Zanarini Rating Scale for Borderline Personality Disorder 2. A clinician-administered scale assessing Borderline Personality Scale severity **Secondary outcomes** • Modified Overt Aggression Scale • Young Mania Rating Scale • Self-Report Version of Zanarini Scale • Borderline Evaluation of Severity Over Time • Barratt Impulsiveness Scale (BIS) • Minnesota Impulsive Disorders Interview (MIDI) • Symptom Checklist-90-Revised (SCL-90-R) • Hamilton Depression Rating Scale

NCT05356013 *(Continued)*	• Hamilton Anxiety Rating Scale • Quality of Life Inventory • Sheehan Disability Scale (SDS)
Starting date	Not specified (first posted 2 May 2022)
Contact information	**Name:** Jon E Grant, MD, JD, MPH, University of Chicago (Primary Investigator) **Other contact information:** **Name:** Eve K Chesivoir **Phone:** 7737029066 **E-mail:** chesivoir@yoda.bsd.uchicago.edu **Name:** Stephanie Valle **Phone:** 7738343778 **E-mail:** svalle@yoda.bsd.uchicago.edu
Notes	**Source of funding:** University of Chicago and Intra-Cellular Therapies, Inc.

A/A: Agitation/Aggression subscale.
AAPI: Agitation-Aggression Psychiatric Inventory.
ADHD: attention deficit hyperactivity disorder.
AVH: auditory verbal hallucinations.
BDI: Beck Depression Inventory.
BEST: Barrett Evaluation of Severity over TIme.
BIS: Barrett Impulsiveness Scale.
BMI: body mass index.
BoPD: borderline personality disorder.
BPD: borderline personality disorder.
BPDSI-IV: Borderline Personality Disorder Severity Index, 4th edition.
BSL-23: Borderline Symptom List-23.
CAT: Cognitive Analytical Therapy.
CGI-I: Clinical Global Impression-Improvement.
CGI-S: Clinical Global Impression–Severity.
CNS: Central nervous system.
C-SSRS: Columbia Suicide Severity Rating Scale.
DERS-16: Difficulties in Emotion Regulation Scale.
DSM-IV: Diagnostic Manual of Mental Disorders, 4th edition.
DSM-5: Diagnostic Manual of Mental Disorders, 5th edition.
DSS-4: Dissociation Tension Scale-4.
ECG: Electrocardiogram.
ECT: Electroconvulsive therapy.
EuroQoL: European Quality of Life.
FDS: Fragebogen zu dissoziativen Symptomen.
GCP: Good clinical practice.
HIV: Human immunodeficiency virus.
ICH: International Council on Harmonization.
IMP: Investigational medicinal product.
IQ: Intelligence quotient.
LAB: Laboratory.
MAO: Monoamine oxidase inhibitors.
MDD: Major depressive disorder.
MIDI: Minnesota Impulsive Disorders Interview.
MINI: The *Mini*-International Neuropsychiatric Interview.
MS: Multiple sclerosis.
N/A: Not applicable.
PCL-5: PTSD Checklist for DSM-5.
PGI-S: Patient Global Impression Severity Scale.
PHQ-9: Patient Health Questionnaire-9.

PI: Principal investigator.
POSAS: Patient and Observer Scare Assessment Scale.
PTSD: Post-traumatic stress disorder.
SCID-II: Structured clinical interview for DSM-IV.
SCID-5-PD: Structured Clinical Interview for DSM-5 Personality Disorders.
SCL-90-R: Symptom Check List-90-Revised.
SDS: Sheehan Disability Scale.
SF: Social functioning.
SmPC: Summary of Product Characteristics.
STAI-S: State-Trait Anxiety Inventory.
T4: Thyroxine.
TMS: Transcranial magnetic stimulation.
WOCBP: Women of childbearing potential.
Zan-BPD: Zanarini Rating Scale for Borderline Personality Disorder.

DATA AND ANALYSES

Comparison 1. Medications compared with placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Primary: BPD symptom severity at end of treatment (continuous outcomes, SMDs)	11		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1.1 Antipsychotics	8	951	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.45, 0.08]
1.1.2 Antidepressants	2	87	Std. Mean Difference (IV, Random, 95% CI)	0.27 [-0.65, 1.18]
1.1.3 Mood stabilisers	4	265	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.43, 0.57]
1.2 Primary: BPD symptom severity at end of treatment (continuous outcomes, MDs)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 Clonidine	1	34	Mean Difference (IV, Fixed, 95% CI)	-13.11 [-65.36, 39.14]
1.2.2 Naltrexone	1	32	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.29, 0.49]
1.2.3 Memantine hydrochloride	1	33	Mean Difference (IV, Fixed, 95% CI)	2.00 [-1.62, 5.62]
1.2.4 Alprazolam	1	25	Mean Difference (IV, Fixed, 95% CI)	-0.58 [-1.63, 0.47]
1.3 Primary: Self-harm at end of treatment (continuous outcomes, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.3.1 Antidepressants	1	20	Mean Difference (IV, Fixed, 95% CI)	0.45 [-10.55, 11.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Primary: Self-harm at end of treatment (dichotomous outcomes, RRs)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.4.1 Antipsychotics	2	76	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.15, 2.84]
1.4.2 Mood stabilisers	1	276	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.79, 1.48]
1.4.3 Omega-3 fatty acids	1	49	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.51, 2.97]
1.5 Primary: Suicide-related outcomes at end of treatment (continuous outcomes, SMDs)	9		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.5.1 Antipsychotics	7	854	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.18, 0.29]
1.5.2 Antidepressants	2	45	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-1.62, 1.09]
1.5.3 Mood stabilisers	2	44	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.96, 1.25]
1.6 Primary: Suicide-related outcomes at end of treatment (continuous outcomes, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.6.1 Alprazolam	1	25	Mean Difference (IV, Fixed, 95% CI)	0.75 [-0.18, 1.68]
1.7 Primary: Suicide-related outcomes at end of treatment (dichotomous outcomes, RRs)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.7.1 Antipsychotics	2	61	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.31, 1.73]
1.7.2 Antidepressants	1	58	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.71, 1.41]
1.7.3 Omega-3 fatty acids	1	49	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.28, 0.95]
1.8 Primary: Psychosocial functioning at end of treatment (continuous outcomes, SMDs)	11		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.8.1 Antipsychotics	7	904	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.33, -0.00]
1.8.2 Antidepressants	4	161	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.57, 0.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8.3 Mood stabilisers	2	214	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.28, 0.26]
1.9 Primary: Psychosocial functioning at end of treatment (continuous outcomes, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.9.1 Omega-3 fatty acids	1	15	Mean Difference (IV, Fixed, 95% CI)	-19.90 [-32.69, -7.11]
1.10 Primary: Psychosocial functioning at end of treatment (dichtotomous outcomes, RRs)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.10.1 Mood stabilisers	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.37, 1.11]
1.11 Secondary: Anger at end of treatment (continuous outcomes, SMDs)	19		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.11.1 Antipsychotics	10	1025	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.55, -0.18]
1.11.2 Antidepressants	6	224	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.64, -0.11]
1.11.3 Mood stabilisers	5	135	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.10, -0.24]
1.11.4 Omega-3 fatty acids	2	76	Std. Mean Difference (IV, Random, 95% CI)	-0.48 [-0.95, -0.01]
1.12 Secondary: Anger at end of treatment (continuous outcomes, MDs)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.12.1 Naltrexone	1	32	Mean Difference (IV, Fixed, 95% CI)	1.65 [-4.54, 7.84]
1.12.2 Alprazolam	1	25	Mean Difference (IV, Fixed, 95% CI)	-0.57 [-1.48, 0.34]
1.13 Secondary: Affective instability at end of treatment (continuous outcomes, SMDs)	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.13.1 Antipsychotics	4	691	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.31, -0.01]
1.13.2 Mood stabilisers	2	222	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.68, 0.26]
1.14 Secondary: Affective instability at end of treatment (continous outcomes, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

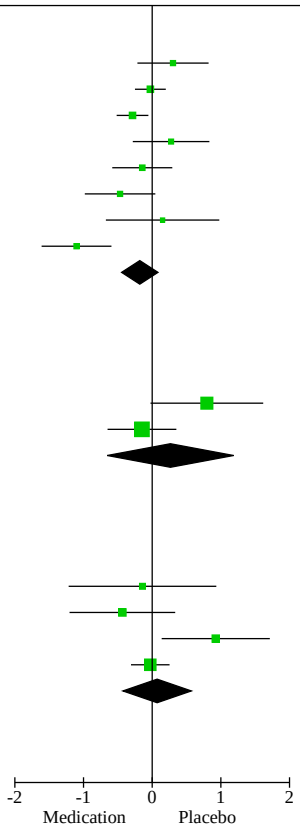
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.14.1 Antidepressants	1	38	Mean Difference (IV, Fixed, 95% CI)	-1.66 [-3.26, -0.06]
1.15 Secondary: Chronic feelings of emptiness at end of treatment (continuous outcomes, SMDs)	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.15.1 Antipsychotics	4	691	Std. Mean Difference (IV, Random, 95% CI)	-0.00 [-0.16, 0.15]
1.16 Secondary: Impulsivity at end of treatment (continuous outcomes, SMDs)	14		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.16.1 Antipsychotics	10	1038	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.20, 0.04]
1.16.2 Antidepressants	4	182	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.49, 0.15]
1.16.3 Mood stabilisers	4	265	Std. Mean Difference (IV, Random, 95% CI)	-0.56 [-1.46, 0.35]
1.17 Secondary: Impulsivity at end of treatment (continuous outcomes, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.17.1 Alprazolam	1	25	Mean Difference (IV, Fixed, 95% CI)	0.67 [-0.36, 1.70]
1.18 Secondary: Impulsivity at end of treatment (dichtotomous outcomes, RRs)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.18.1 Mood stabilisers	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.53, 1.46]
1.19 Secondary: Interpersonal problems at end of treatment (continuous outcomes, SMDs)	12		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.19.1 Antipsychotics	8	907	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.34, -0.08]
1.19.2 Antidepressants	2	119	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.69, 0.55]
1.19.3 Mood stabilisers	4	300	Std. Mean Difference (IV, Random, 95% CI)	-0.58 [-1.14, -0.02]
1.20 Secondary: Abandonment at end of treatment (continuous outcomes, SMDs)	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.20.1 Antipsychotics	4	691	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.17, 0.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.21 Secondary: Identity disturbance at end of treatment (continuous outcomes, SMDs)	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.21.1 Antipsychotics	4	691	Std. Mean Difference (IV, Random, 95% CI)	-0.09 [-0.25, 0.07]
1.22 Secondary: Dissociation and psychotic-like symptoms at end of treatment (continuous outcomes, SMDs)	12		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.22.1 Antipsychotics	8	907	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.50, -0.06]
1.22.2 Antidepressants	3	139	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.62, 0.18]
1.22.3 Mood stabilisers	3	270	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.66, 0.20]
1.23 Secondary: Dissociation and psychotic-like symptoms at end of treatment (continuous outcomes, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.23.1 Omega-3 fatty acids	1	15	Mean Difference (IV, Fixed, 95% CI)	-2.80 [-5.70, 0.10]
1.24 Secondary: Depression at end of treatment (continuous outcomes, SMDs)	21		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.24.1 Antipsychotics	12	1138	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.42, -0.01]
1.24.2 Antidepressants	5	187	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.82, 0.08]
1.24.3 Mood stabilisers	6	344	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-0.80, -0.08]
1.24.4 Omega-3 fatty acids	2	42	Std. Mean Difference (IV, Random, 95% CI)	-0.54 [-1.18, 0.11]
1.25 Secondary: Depression at end of treatment (continuous outcomes, MDs)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.25.1 Clonidine	1	34	Mean Difference (IV, Fixed, 95% CI)	-2.54 [-10.27, 5.19]
1.25.2 Naltrexone	1	32	Mean Difference (IV, Fixed, 95% CI)	2.50 [-4.22, 9.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.25.3 Alprazolam	1	25	Mean Difference (IV, Fixed, 95% CI)	0.27 [-0.73, 1.27]
1.26 Secondary: Depression at end of treatment (dichotomous outcomes, RRs)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.26.1 Omega-3 fatty acids	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.28, 0.81]
1.27 Secondary: Attrition at end of treatment (dichotomous outcomes, RRs)	30		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.27.1 Antipsychotics	13	1216	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.89, 1.38]
1.27.2 Antidepressants	6	289	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.65, 1.76]
1.27.3 Mood stabilisers	9	530	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.69, 1.15]
1.27.4 Omega-3 fatty acids	2	79	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.21, 1.79]
1.27.5 Memantine hydrochloride	1	33	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.45, 5.52]
1.27.6 Clonidine	1	34	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.13, 3.50]
1.28 Secondary: Non-serious adverse events at end of treatment (dichotomous outcomes, RRs)	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.28.1 Antipsychotics	5	814	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.90, 1.29]
1.28.2 Mood stabilisers	1	276	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.70, 1.01]
1.28.3 Memantine hydrochloride	1	33	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.79, 2.52]
1.29 Secondary: Serious adverse events at end of treatment (dichotomous outcomes, RRs)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.29.1 Memantine hydrochloride	1	33	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.29.2 Brexpiprazole	1	80	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 71.51]

Analysis 1.1. Comparison 1: Medications compared with placebo, Outcome 1: Primary: BPD symptom severity at end of treatment (continuous outcomes, SMDs)

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Antipsychotics								
Soloff 1993 (1)	24.03	13.24	30	20.08	12.44	28	11.4%	0.30 [-0.22 , 0.82]
Schulz 2007 (2)	-6.37	6.73	150	-6.19	6.89	155	17.6%	-0.03 [-0.25 , 0.20]
Zanarini 2007 (2)	-8.52	6.15	144	-6.69	6.58	147	17.5%	-0.29 [-0.52 , -0.06]
Goldberg 1986 (3)	15.2859	4.4436	24	14.0812	4.1812	26	10.6%	0.28 [-0.28 , 0.83]
Black 2014 (4)	7.9	4.8151	66	8.6	4.8	29	13.0%	-0.14 [-0.58 , 0.29]
Pascual 2008 (5)	3.88	0.6	30	4.3	1.1	30	11.5%	-0.47 [-0.98 , 0.05]
Cowdry 1988 (6)	4.3	1.77	10	4.08	1.04	13	6.8%	0.15 [-0.67 , 0.98]
Grant 2022 (7)	3.1	3.9	35	8.4	5.5	34	11.6%	-1.10 [-1.61 , -0.59]
Subtotal (95% CI)			**489**			**462**	**100.0%**	**-0.18 [-0.45 , 0.08]**
Heterogeneity: Tau² = 0.09; Chi² = 22.98, df = 7 (P = 0.002); I² = 70%								
Test for overall effect: Z = 1.34 (P = 0.18)								
1.1.2 Antidepressants								
Cowdry 1988 (8)	5.08	1.38	12	4.08	1.04	13	43.8%	0.80 [-0.02 , 1.62]
Soloff 1993 (9)	18.3	11.24	34	20.08	12.44	28	56.2%	-0.15 [-0.65 , 0.35]
Subtotal (95% CI)			**46**			**41**	**100.0%**	**0.27 [-0.65 , 1.18]**
Heterogeneity: Tau² = 0.33; Chi² = 3.71, df = 1 (P = 0.05); I² = 73%								
Test for overall effect: Z = 0.57 (P = 0.57)								
1.1.3 Mood stabilisers								
Moen 2012 (10)	28.7	7.1	10	30	11.4	5	14.8%	-0.14 [-1.22 , 0.93]
Reich 2009 (11)	-8.8	5	15	-6.6	4.8	12	22.3%	-0.43 [-1.20 , 0.34]
Cowdry 1988 (12)	5.14	1.17	15	4.08	1.04	13	21.7%	0.93 [0.14 , 1.71]
Crawford 2018 (13)	11.3	6.6	97	11.5	7.7	98	41.3%	-0.03 [-0.31 , 0.25]
Subtotal (95% CI)			**137**			**128**	**100.0%**	**0.07 [-0.43 , 0.57]**
Heterogeneity: Tau² = 0.14; Chi² = 6.62, df = 3 (P = 0.09); I² = 55%								
Test for overall effect: Z = 0.28 (P = 0.78)								
Test for subgroup differences: Chi² = 1.42, df = 2 (P = 0.49), I² = 0%								

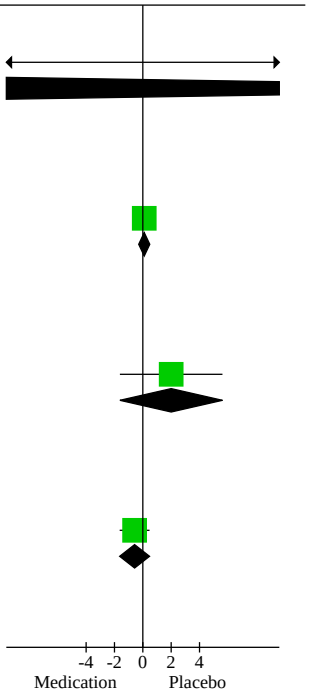


Footnotes

(1) Haloperidol versus placebo
(2) Olanzapine versus placebo
(3) Thiothixine versus placebo
(4) Quetiapine versus placebo (both active groups pooled into one), final scores (Tab. 4 + text p. 1179), baseline SDs (Tab. 4)
(5) Ziprasidone versus placebo
(6) Trifluoperazine hydrochloride versus placebo - cross-over data
(7) Brexpiprazole versus placebo
(8) Tranylcypromine sulfate versus placebo - cross-over data
(9) Phenelzine sulfate versus placebo
(10) Divalproex versus placebo
(11) Lamotrigine versus placebo
(12) Carbamazepine versus placebo - cross-over data
(13) Lamotrigine plus TAU versus placebo plus TAU

Analysis 1.2. Comparison 1: Medications compared with placebo, Outcome 2: Primary: BPD symptom severity at end of treatment (continuous outcomes, MDs)

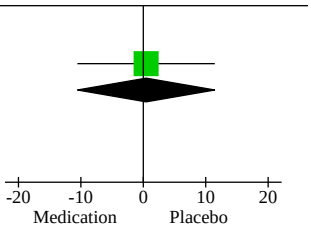
Study or Subgroup	Medication Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 Clonidine								
Ziegenhorn 2009 (1)	188.65	74.41	17	201.76	80.91	17	100.0%	-13.11 [-65.36 , 39.14]
Subtotal (95% CI)			**17**			**17**	**100.0%**	**-13.11 [-65.36 , 39.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.49 (P = 0.62)								
1.2.2 Naltrexone								
Schmahl 2012b (2)	2.2	0.46	16	2.1	0.65	16	100.0%	0.10 [-0.29 , 0.49]
Subtotal (95% CI)			**16**			**16**	**100.0%**	**0.10 [-0.29 , 0.49]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.50 (P = 0.62)								
1.2.3 Memantine hydrochloride								
Kulkarni 2018 (3)	9.2	5.6	17	7.2	5	16	100.0%	2.00 [-1.62 , 5.62]
Subtotal (95% CI)			**17**			**16**	**100.0%**	**2.00 [-1.62 , 5.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.08 (P = 0.28)								
1.2.4 Alprazolam								
Cowdry 1988 (4)	3.5	1.57	12	4.08	1.04	13	100.0%	-0.58 [-1.63 , 0.47]
Subtotal (95% CI)			**12**			**13**	**100.0%**	**-0.58 [-1.63 , 0.47]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.08 (P = 0.28)								
Test for subgroup differences: Chi² = 2.79, df = 3 (P = 0.42), I² = 0%								



Footnotes
(1) Clonidine versus placebo - Cross-over data
(2) Naltrexone versus placebo - cross-over data
(3) Memantine hydrochloride plus TAU versus placebo plus TAU
(4) Alprazolam versus placebo - cross-over data

Analysis 1.3. Comparison 1: Medications compared with placebo, Outcome 3: Primary: Self-harm at end of treatment (continuous outcomes, MDs)

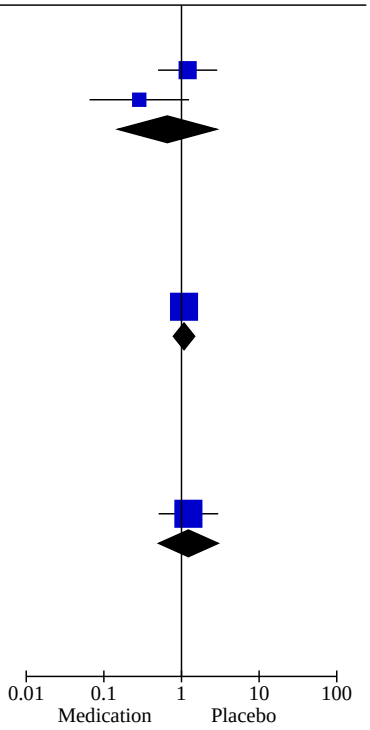
Study or Subgroup	Medication Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 Antidepressants								
Simpson 2004 (1)	7	12.37	9	6.55	12.64	11	100.0%	0.45 [-10.55 , 11.45]
Subtotal (95% CI)			**9**			**11**	**100.0%**	**0.45 [-10.55 , 11.45]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.08 (P = 0.94)								
Test for subgroup differences: Not applicable								



Footnotes
(1) Fluoxetine versus placebo

Analysis 1.4. Comparison 1: Medications compared with placebo, Outcome 4: Primary: Self-harm at end of treatment (dichotomous outcomes, RRs)

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Antipsychotics						
Linehan 2008 (1)	6	12	5	12	58.0%	1.20 [0.50 , 2.88]
Nickel 2006 (2)	2	26	7	26	42.0%	0.29 [0.07 , 1.25]
Subtotal (95% CI)		**38**		**38**	**100.0%**	**0.66 [0.15 , 2.84]**
Total events:	8		12			
Heterogeneity: Tau² = 0.76; Chi² = 3.00, df = 1 (P = 0.08); I² = 67%						
Test for overall effect: Z = 0.56 (P = 0.57)						
1.4.2 Mood stabilisers						
Crawford 2018 (3)	51	137	48	139	100.0%	1.08 [0.79 , 1.48]
Subtotal (95% CI)		**137**		**139**	**100.0%**	**1.08 [0.79 , 1.48]**
Total events:	51		48			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
1.4.3 Omega-3 fatty acids						
Hallahan 2007 (4)	7	22	7	27	100.0%	1.23 [0.51 , 2.97]
Subtotal (95% CI)		**22**		**27**	**100.0%**	**1.23 [0.51 , 2.97]**
Total events:	7		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						
Test for subgroup differences: Chi² = 0.52, df = 2 (P = 0.77), I² = 0%						



Footnotes

(1) Olanzapine versus placebo. Event: intentional self-injury during last week (week 21)

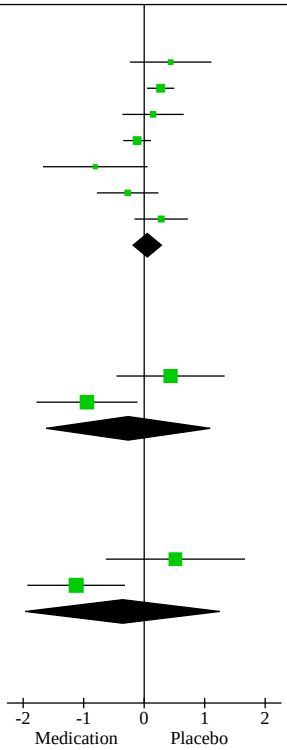
(2) Aripiprazole versus placebo. Event: self-injury during treatment

(3) Lamotrigine plus TAU versus placebo plus TAU event: deliberate self-harm in 6 months prior to 52-week assessment (yes or unknown)

(4) Omega-3 fatty acids versus placebo. Event: self-harm during treatment

Analysis 1.5. Comparison 1: Medications compared with placebo, Outcome 5: Primary: Suicide-related outcomes at end of treatment (continuous outcomes, SMDs)

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.5.1 Antipsychotics								
Bogenschutz 2004 (1)	-0.125	0.34157	16	-0.5263	1.17229	19	8.6%	0.44 [-0.24 , 1.11]
Schulz 2007 (1)	-0.28	1.21	150	-0.61	1.21	155	23.2%	0.27 [0.05 , 0.50]
Soler 2005 (1)	1.23	2.87	30	0.88	1.68	30	12.4%	0.15 [-0.36 , 0.65]
Zanarini 2007 (1)	-0.3	0.8	144	-0.2	0.9	147	23.0%	-0.12 [-0.35 , 0.11]
Cowdry 1988 (2)	3.1	1.45	10	4.08	0.9	13	5.9%	-0.81 [-1.67 , 0.05]
Pascual 2008 (3)	2.7	1.6	30	3.13	1.5	30	12.4%	-0.27 [-0.78 , 0.23]
Grant 2022	0.23	0.66	40	0.08	0.35	40	14.5%	0.28 [-0.16 , 0.72]
Subtotal (95% CI)			**420**			**434**	**100.0%**	**0.05 [-0.18 , 0.29]**
Heterogeneity: Tau² = 0.05; Chi² = 13.47, df = 6 (P = 0.04); I² = 55%								
Test for overall effect: Z = 0.43 (P = 0.67)								
1.5.2 Antidepressants								
Simpson 2004 (4)	2.13	3.48	9	1	1.18	11	49.3%	0.44 [-0.46 , 1.33]
Cowdry 1988 (5)	2.83	1.59	12	4.08	0.9	13	50.7%	-0.95 [-1.78 , -0.11]
Subtotal (95% CI)			**21**			**24**	**100.0%**	**-0.26 [-1.62 , 1.09]**
Heterogeneity: Tau² = 0.76; Chi² = 4.91, df = 1 (P = 0.03); I² = 80%								
Test for overall effect: Z = 0.38 (P = 0.70)								
1.5.3 Mood stabilisers								
Hollander 2001 (6)	0.9	1.2	12	0.3	0.6	4	46.8%	0.52 [-0.63 , 1.67]
Cowdry 1988 (7)	2.71	1.38	15	4.08	0.9	13	53.2%	-1.12 [-1.93 , -0.32]
Subtotal (95% CI)			**27**			**17**	**100.0%**	**-0.36 [-1.96 , 1.25]**
Heterogeneity: Tau² = 1.09; Chi² = 5.23, df = 1 (P = 0.02); I² = 81%								
Test for overall effect: Z = 0.44 (P = 0.66)								
Test for subgroup differences: Chi² = 0.44, df = 2 (P = 0.80), I² = 0%								

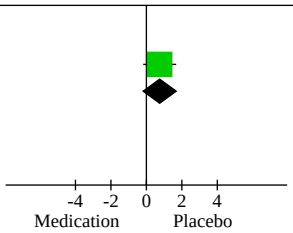


Footnotes

(1) Olanzapine versus placebo
(2) Trifluoperazine hydrochloride versus placebo - cross-over data
(3) Ziprasidone versus placebo
(4) Fluoxetine versus placebo
(5) Tranylcypromine sulfate versus placebo - crossover data
(6) Valproate semisodium versus placebo
(7) Carbamazepine versus placebo - crossover data

Analysis 1.6. Comparison 1: Medications compared with placebo, Outcome 6: Primary: Suicide-related outcomes at end of treatment (continuous outcomes, MDs)

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.6.1 Alprazolam								
Cowdry 1988 (1)	4.83	1.4	12	4.08	0.9	13	100.0%	0.75 [-0.18 , 1.68]
Subtotal (95% CI)			**12**			**13**	**100.0%**	**0.75 [-0.18 , 1.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.58 (P = 0.11)								
Test for subgroup differences: Not applicable								

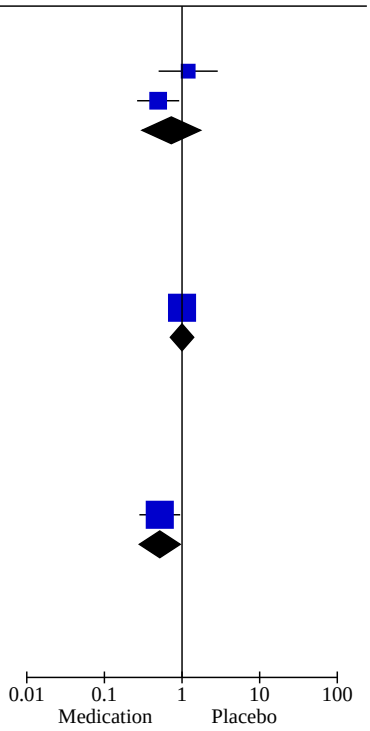


Footnotes

(1) Alprazolam versus placebo - cross-over data

Analysis 1.7. Comparison 1: Medications compared with placebo, Outcome 7: Primary: Suicide-related outcomes at end of treatment (dichotomous outcomes, RRs)

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Antipsychotics						
Linehan 2008 (1)	6	12	5	12	43.8%	1.20 [0.50 , 2.88]
Montgomery 1982a (2)	7	18	15	19	56.2%	0.49 [0.26 , 0.92]
Subtotal (95% CI)		**30**		**31**	**100.0%**	**0.73 [0.31 , 1.73]**
Total events:	13		20			
Heterogeneity: Tau² = 0.25; Chi² = 2.63, df = 1 (P = 0.10); I² = 62%						
Test for overall effect: Z = 0.72 (P = 0.47)						
1.7.2 Antidepressants						
Montgomery 1982b (3)	20	29	20	29	100.0%	1.00 [0.71 , 1.41]
Subtotal (95% CI)		**29**		**29**	**100.0%**	**1.00 [0.71 , 1.41]**
Total events:	20		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.7.3 Omega-3 fatty acids						
Hallahan 2007 (4)	8	22	19	27	100.0%	0.52 [0.28 , 0.95]
Subtotal (95% CI)		**22**		**27**	**100.0%**	**0.52 [0.28 , 0.95]**
Total events:	8		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.14 (P = 0.03)						
Test for subgroup differences: Chi² = 3.57, df = 2 (P = 0.17), I² = 43.9%						



Footnotes

(1) Olanzapine versus placebo. Event: Severe suicidality acc. to OAS-M-suicidality score (i.e. frequent suicide ideation and/or planning or behaviour)

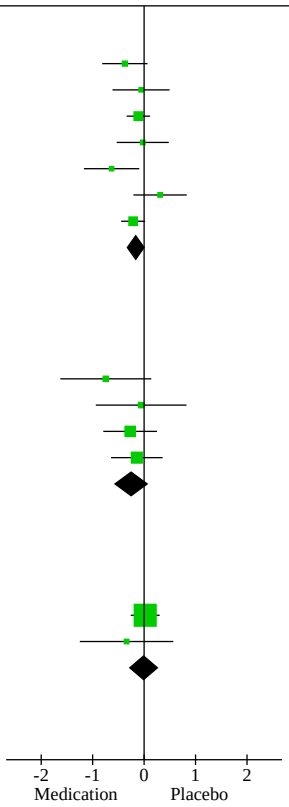
(2) Flupenthixol decanoate versus placebo. Event: Suicidal act during treatment

(3) Mianserin versus placebo. Event: Suicidal act during treatment

(4) Omega-3 fatty acids versus placebo. Event: Mild suicidality acc. to OAS-M-suicidality score >1 (i.e. at least slight suicidal tendency, thinking of bein

Analysis 1.8. Comparison 1: Medications compared with placebo, Outcome 8: Primary: Psychosocial functioning at end of treatment (continuous outcomes, SMDs)

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.8.1 Antipsychotics								
Black 2014 (1)	-1.045	1.1689	66	-0.62	1.0232	29	11.2%	-0.37 [-0.81 , 0.07]
Goldberg 1986 (2)	-72.42	9.25	24	-71.92	7.32	26	7.5%	-0.06 [-0.61 , 0.50]
Schulz 2007 (3)	-5.89	8.87	147	-4.92	8.44	151	28.3%	-0.11 [-0.34 , 0.12]
Soler 2005 (4)	3.93	1.5	30	3.97	1.45	30	8.8%	-0.03 [-0.53 , 0.48]
Soloff 1989 (5)	-55.35	12.36	28	-48.16	9.95	28	8.0%	-0.63 [-1.17 , -0.09]
Soloff 1993 (5)	-54.95	9.15	30	-58.43	12.8	28	8.5%	0.31 [-0.21 , 0.83]
Zanarini 2007 (6)	-7.74	8.09	144	-6	8.19	143	27.7%	-0.21 [-0.45 , 0.02]
Subtotal (95% CI)			**469**			**435**	**100.0%**	**-0.16 [-0.33 , -0.00]**
Heterogeneity: Tau² = 0.01; Chi² = 7.80, df = 6 (P = 0.25); I² = 23%								
Test for overall effect: Z = 1.97 (P = 0.05)								
1.8.2 Antidepressants								
Salzman 1995 (7)	-91.5	10.3	13	-82.6	13.1	9	12.5%	-0.74 [-1.63 , 0.14]
Simpson 2004 (8)	-59.92	13.15	9	-59.3	7.17	11	12.6%	-0.06 [-0.94 , 0.82]
Soloff 1989 (9)	-51.48	13.8	29	-48.16	9.95	28	35.9%	-0.27 [-0.79 , 0.25]
Soloff 1993 (10)	-60.1	10.7	34	-58.43	12.8	28	39.0%	-0.14 [-0.64 , 0.36]
Subtotal (95% CI)			**85**			**76**	**100.0%**	**-0.25 [-0.57 , 0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 1.57, df = 3 (P = 0.67); I² = 0%								
Test for overall effect: Z = 1.59 (P = 0.11)								
1.8.3 Mood stabilisers								
Crawford 2018 (11)	12.4	4.3	97	12.3	4.9	98	91.3%	0.02 [-0.26 , 0.30]
De la Fuente 1994 (12)	-67.12	16.17	9	-60.1	22.33	10	8.7%	-0.34 [-1.25 , 0.57]
Subtotal (95% CI)			**106**			**108**	**100.0%**	**-0.01 [-0.28 , 0.26]**
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 1 (P = 0.46); I² = 0%								
Test for overall effect: Z = 0.07 (P = 0.94)								
Test for subgroup differences: Chi² = 1.48, df = 2 (P = 0.48), I² = 0%								

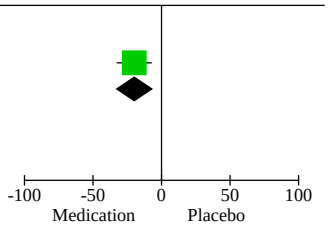


Footnotes

(1) Quetiapine vs. placebo (GAF). Active groups pooled. SDs calculated from SEs. Multiplied by (-1), neg. ES indicating beneficial effects
(2) Thiothixene versus placebo - GAS Multiplied by (-1), neg. ES indicating beneficial effects
(3) Olanzapine versus placebo - SDS, mean change from baseline to endpoint
(4) Olanzapine versus placebo - CGI-S
(5) Haloperidol versus placebo - GAS
(6) Olanzapine 5-10 mg/d - SDS, mean change from baseline to endpoint
(7) Fluoxetine versus placebo (GAS)
(8) Fluoxetine versus placebo - GAF
(9) Amitriptyline versus placebo - GAS
(10) Amitriptyline versus placebo GAS
(11) Lamotrigine plus TAU versus placebo plus TAU - SFQ
(12) Carbamazepine versus placebo - GAS

Analysis 1.9. Comparison 1: Medications compared with placebo, Outcome 9: Primary: Psychosocial functioning at end of treatment (continuous outcomes, MDs)

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.9.1 Omega-3 fatty acids								
Amminger 2013 (1)	-75.6	10.8	8	-55.7	14	7	100.0%	-19.90 [-32.69 , -7.11]
Subtotal (95% CI)			**8**			**7**	**100.0%**	**-19.90 [-32.69 , -7.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.05 (P = 0.002)								
Test for subgroup differences: Not applicable								

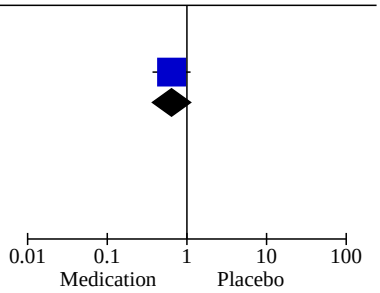


Footnotes

(1) Long-chain omega-3 polyunsaturated fatty acids versus placebo GAF

Analysis 1.10. Comparison 1: Medications compared with placebo, Outcome 10: Primary: Psychosocial functioning at end of treatment (dichtotomous outcomes, RRs)

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.10.1 Mood stabilisers						
Hollander 2001 (1)	7	12	4	4	100.0%	0.64 [0.37 , 1.11]
Subtotal (95% CI)		**12**		**4**	**100.0%**	**0.64 [0.37 , 1.11]**
Total events:	7		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.59 (P = 0.11)						
Test for subgroup differences: Not applicable						

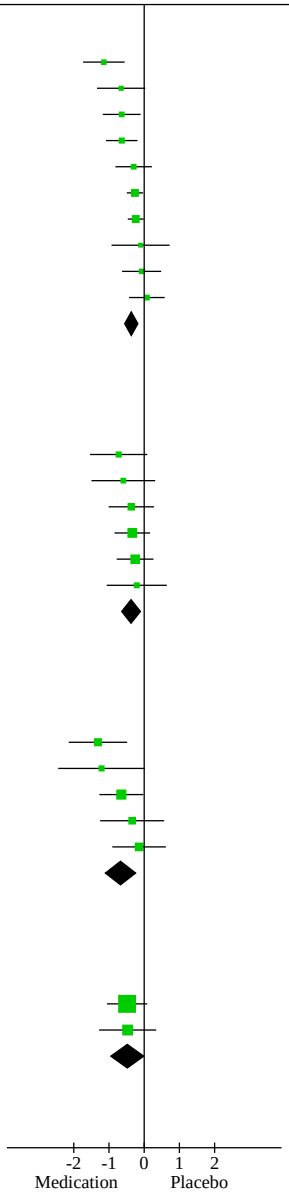


Footnotes

(1) Valproate semisodium. Event: Minimally improved to very much worse in terms of CGI-I score

Analysis 1.11. Comparison 1: Medications compared with placebo, Outcome 11: Secondary: Anger at end of treatment (continuous outcomes, SMDs)

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.11.1 Antipsychotics								
Nickel 2006 (1)	64.6	6.8	26	73.1	7.8	26	7.3%	-1.14 [-1.73 , -0.55]
Bogenschutz 2004 (2)	-2.1875	1.68201	16	-1.1053	1.55973	19	5.8%	-0.65 [-1.34 , 0.03]
Soloff 1989 (3)	0.78	0.82	28	1.39	1.05	28	8.3%	-0.64 [-1.18 , -0.10]
Black 2014 (4)	-1.87	2.3469	66	-0.37	2.3156	29	10.6%	-0.64 [-1.08 , -0.19]
Soloff 1993 (3)	0.79	0.66	30	1.04	0.97	28	8.7%	-0.30 [-0.82 , 0.22]
Zanarini 2007	-1.1	1.06	144	-0.81	1.14	147	18.9%	-0.26 [-0.49 , -0.03]
Schulz 2007 (2)	-0.91	1.21	150	-0.61	1.28	155	19.1%	-0.24 [-0.47 , -0.01]
Cowdry 1988 (5)	4	1.83	10	4.15	0.98	13	4.3%	-0.10 [-0.93 , 0.72]
Goldberg 1986 (6)	0.6167	0.695	24	0.6769	0.9236	26	8.0%	-0.07 [-0.63 , 0.48]
Pascual 2008 (7)	3.66	1.4	30	3.56	1.2	30	9.0%	0.08 [-0.43 , 0.58]
Subtotal (95% CI)			**524**			**501**	**100.0%**	**-0.37 [-0.55 , -0.18]**
Heterogeneity: Tau² = 0.03; Chi² = 15.79, df = 9 (P = 0.07); I² = 43%								
Test for overall effect: Z = 3.84 (P = 0.0001)								
1.11.2 Antidepressants								
Cowdry 1988 (8)	3.17	1.59	12	4.15	0.98	13	10.7%	-0.72 [-1.54 , 0.09]
Simpson 2004 (9)	2.56	3.81	9	7.45	10.05	11	8.6%	-0.59 [-1.50 , 0.31]
Rinne 2002 (10)	1.59	2	20	2.49	2.8	18	17.1%	-0.37 [-1.01 , 0.28]
Soloff 1993 (11)	0.73	0.85	34	1.04	0.97	28	27.8%	-0.34 [-0.84 , 0.17]
Soloff 1989 (12)	1.12	1.01	29	1.39	1.05	28	26.0%	-0.26 [-0.78 , 0.26]
Salzman 1995 (13)	0.31	0.48	13	0.44	0.73	9	9.7%	-0.21 [-1.06 , 0.64]
Subtotal (95% CI)			**117**			**107**	**100.0%**	**-0.37 [-0.64 , -0.11]**
Heterogeneity: Tau² = 0.00; Chi² = 1.28, df = 5 (P = 0.94); I² = 0%								
Test for overall effect: Z = 2.75 (P = 0.006)								
1.11.3 Mood stabilisers								
Cowdry 1988 (14)	2.93	0.83	15	4.15	0.98	13	19.9%	-1.31 [-2.14 , -0.48]
Hollander 2001 (15)	1.8	2.9	12	6	4.4	4	10.5%	-1.21 [-2.44 , 0.02]
Nickel 2005 (16)	26	2.6	22	27.6	2.2	20	29.5%	-0.65 [-1.27 , -0.03]
De la Fuente 1994 (17)	5.57	8.46	9	8.33	6.98	10	17.4%	-0.34 [-1.25 , 0.57]
Frankenburg 2002 (18)	1.5	0.7	20	1.6	0.6	10	22.6%	-0.15 [-0.91 , 0.61]
Subtotal (95% CI)			**78**			**57**	**100.0%**	**-0.67 [-1.10 , -0.24]**
Heterogeneity: Tau² = 0.06; Chi² = 5.38, df = 4 (P = 0.25); I² = 26%								
Test for overall effect: Z = 3.07 (P = 0.002)								
1.11.4 Omega-3 fatty acids								
Hallahan 2007 (19)	10.3	10.57	22	14.5	6.4	27	66.8%	-0.49 [-1.06 , 0.09]
Zanarini 2003 (20)	7.2	8.1	18	12.9	17.1	9	33.2%	-0.47 [-1.28 , 0.34]
Subtotal (95% CI)			**40**			**36**	**100.0%**	**-0.48 [-0.95 , -0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%								
Test for overall effect: Z = 2.01 (P = 0.04)								
Test for subgroup differences: Chi² = 1.81, df = 3 (P = 0.61), I² = 0%								



Footnotes

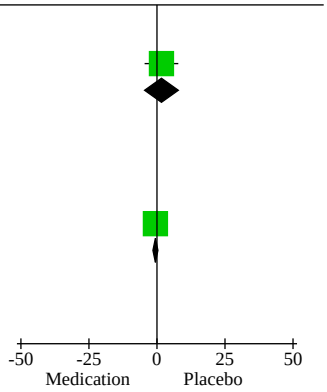
(1) Aripiprazole versus placebo
(2) Olanzapine versus placebo
(3) Haloperidol versus placebo
(4) Quetiapine versus placebo - OAS-M. Active groups pooled. SDs calculated from SEs.
(5) Trifluoperazine hydrochloride versus placebo - cross-over data
(6) Thiothixene versus placebo
(7) Ziprasidone versus placebo
(8) Tranylcypromine sulfate versus placebo - cross-over data
(9) Fluoxetine versus placebo
(10) Fluvoxamine versus placebo
(11) Phenelzine sulfate versus placebo
(12) Amitriptyline versus placebo
(13) Fluoxetine versus placebo - PDRS-anger
(14) Carbamazepine versus placebo - crossover data

Analysis 1.11. (Continued)

(13) Fluoxetine versus placebo - PDRS-anger
(14) Carbamazepine versus placebo - crossover data
(15) Valproate semisodium versus placebo
(16) Topiramate (males) versus placebo. cf. to (3)
(17) Carbamazepine versus placebo
(18) Valproate semisodium versus placebo. Frankenburg 2002 and Hollander 2001 were not pooled, as heterogeneity seemed considerable (I^2 78%), and could not definitely
(19) Omega-3 fatty acids vs. placebo
(20) Omega-3 fatty acids versus placebo

Analysis 1.12. Comparison 1: Medications compared with placebo, Outcome 12: Secondary: Anger at end of treatment (continuous outcomes, MDs)

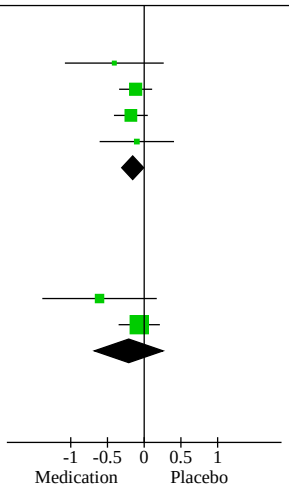
Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.12.1 Naltrexone								
Schmahl 2012b (1)	20.85	8.1	16	19.2	9.7	16	100.0%	1.65 [-4.54 , 7.84]
Subtotal (95% CI)			**16**			**16**	**100.0%**	**1.65 [-4.54 , 7.84]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.52 (P = 0.60)								
1.12.2 Alprazolam								
Cowdry 1988 (2)	4.58	1.31	12	5.15	0.98	13	100.0%	-0.57 [-1.48 , 0.34]
Subtotal (95% CI)			**12**			**13**	**100.0%**	**-0.57 [-1.48 , 0.34]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.22 (P = 0.22)								
Test for subgroup differences: Chi^2 = 0.48, df = 1 (P = 0.49), I^2 = 0%								



Footnotes
(1) Naltrexone versus placebo - Cross-over data
(2) Alprazolam versus placebo - Cross-over data

Analysis 1.13. Comparison 1: Medications compared with placebo, Outcome 13: Secondary: Affective instability at end of treatment (continuous outcomes, SMDs)

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.13.1 Antipsychotics								
Bogenschutz 2004 (1)	-1.875	2.06155	16	-1.0526	1.89952	19	4.9%	-0.41 [-1.08 , 0.27]
Schulz 2007 (1)	-0.93	1.33	150	-0.78	1.24	155	44.2%	-0.12 [-0.34 , 0.11]
Zanarini 2007 (1)	-1.29	1.21	144	-1.07	1.21	147	42.1%	-0.18 [-0.41 , 0.05]
Pascual 2008 (2)	4.44	0.6	30	4.53	1.1	30	8.7%	-0.10 [-0.61 , 0.41]
Subtotal (95% CI)			**340**			**351**	**100.0%**	**-0.16 [-0.31 , -0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 3 (P = 0.86); I² = 0%								
Test for overall effect: Z = 2.06 (P = 0.04)								
1.13.2 Mood stabilisers								
Reich 2009 (3)	-1.5	1.2	15	-0.8	1	12	26.5%	-0.61 [-1.39 , 0.17]
Crawford 2018 (4)	4.7	2.8	97	4.9	3.1	98	73.5%	-0.07 [-0.35 , 0.21]
Subtotal (95% CI)			**112**			**110**	**100.0%**	**-0.21 [-0.68 , 0.26]**
Heterogeneity: Tau² = 0.06; Chi² = 1.64, df = 1 (P = 0.20); I² = 39%								
Test for overall effect: Z = 0.88 (P = 0.38)								
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%								

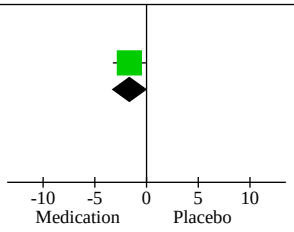


Footnotes

(1) Olanzapine versus placebo
(2) Ziprasidone versus placebo
(3) Lamotrigine versus placebo
(4) Lamotrigine vs. Placebo - Zan-BPD affective disturbance

Analysis 1.14. Comparison 1: Medications compared with placebo, Outcome 14: Secondary: Affective instability at end of treatment (continous outcomes, MDs)

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.14.1 Antidepressants								
Rinne 2002 (1)	4.17	2.64	20	5.83	2.39	18	100.0%	-1.66 [-3.26 , -0.06]
Subtotal (95% CI)			**20**			**18**	**100.0%**	**-1.66 [-3.26 , -0.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.03 (P = 0.04)								
Test for subgroup differences: Not applicable								



Footnotes

(1) Fluvoxamine versus placebo

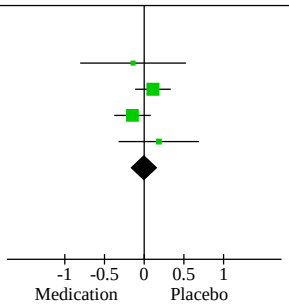
Analysis 1.15. Comparison 1: Medications compared with placebo, Outcome 15: Secondary: Chronic feelings of emptiness at end of treatment (continuous outcomes, SMDs)

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.15.1 Antipsychotics								
Bogenschutz 2004 (1)	-1.6875	2.12034	16	-1.4211	1.60955	19	5.5%	-0.14 [-0.81 , 0.53]
Schulz 2007 (1)	-0.69	1.35	150	-0.85	1.54	155	43.5%	0.11 [-0.11 , 0.33]
Zanarini 2007 (1)	-0.99	1.48	144	-0.78	1.36	147	41.7%	-0.15 [-0.38 , 0.08]
Pascual 2008 (2)	4.7	1.5	30	4.4	1.7	30	9.4%	0.18 [-0.32 , 0.69]
Subtotal (95% CI)			**340**			**351**	**100.0%**	**-0.00 [-0.16 , 0.15]**

Heterogeneity: Tau² = 0.00; Chi² = 3.18, df = 3 (P = 0.37); I² = 6%

Test for overall effect: Z = 0.05 (P = 0.96)

Test for subgroup differences: Not applicable



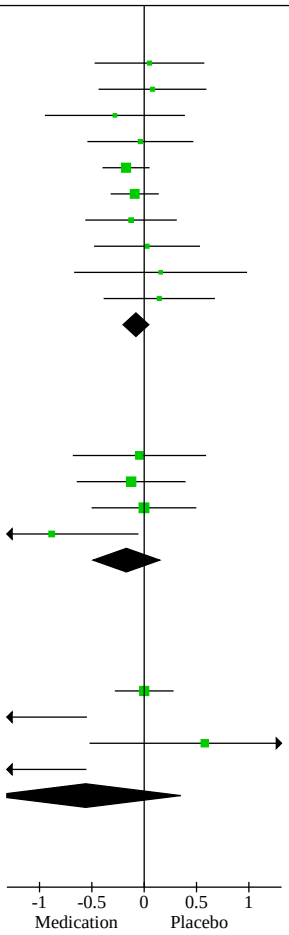
Footnotes

(1) Olanzapine versus placebo

(2) Ziprasidone versus placebo

Analysis 1.16. Comparison 1: Medications compared with placebo, Outcome 16: Secondary: Impulsivity at end of treatment (continuous outcomes, SMDs)

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.16.1 Antipsychotics								
Soloff 1989 (1)	104.02	15.71	28	103.06	21.48	28	5.5%	0.05 [-0.47 , 0.57]
Soloff 1993 (2)	240.95	37.6	30	237.74	42.02	28	5.7%	0.08 [-0.44 , 0.59]
Bogenschutz 2004 (3)	-1.5	1.50555	16	-0.9474	2.22295	19	3.4%	-0.28 [-0.95 , 0.39]
Soler 2005 (3)	5.77	9.53	30	6.12	9.43	30	5.9%	-0.04 [-0.54 , 0.47]
Schulz 2007 (3)	-0.7	1.27	150	-0.48	1.26	155	29.8%	-0.17 [-0.40 , 0.05]
Zanarini 2007	-0.9	1.1	144	-0.8	1.1	147	28.5%	-0.09 [-0.32 , 0.14]
Black 2014 (4)	-0.78	1.5398	66	-0.59	1.4001	29	7.9%	-0.13 [-0.56 , 0.31]
Pascual 2008 (5)	4	1.4	30	3.96	1.5	30	5.9%	0.03 [-0.48 , 0.53]
Cowdry 1988 (6)	4.3	1.64	10	4.08	1.09	13	2.2%	0.16 [-0.67 , 0.98]
Grant 2022	70.5	17.86	30	68.13	13.89	25	5.3%	0.14 [-0.39 , 0.68]
Subtotal (95% CI)			**534**			**504**	**100.0%**	**-0.08 [-0.20 , 0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 2.86, df = 9 (P = 0.97); I² = 0%								
Test for overall effect: Z = 1.26 (P = 0.21)								
1.16.2 Antidepressants								
Rinne 2002 (7)	0.7	0.66	20	0.73	0.64	18	22.0%	-0.05 [-0.68 , 0.59]
Soloff 1989 (8)	100.5	19.01	29	103.06	21.48	28	31.2%	-0.12 [-0.64 , 0.40]
Soloff 1993 (9)	237.66	34.73	34	237.74	42.02	28	33.2%	-0.00 [-0.50 , 0.50]
Cowdry 1988 (10)	2.92	1.44	12	4.08	1.09	13	13.6%	-0.88 [-1.71 , -0.05]
Subtotal (95% CI)			**95**			**87**	**100.0%**	**-0.17 [-0.49 , 0.15]**
Heterogeneity: Tau² = 0.01; Chi² = 3.45, df = 3 (P = 0.33); I² = 13%								
Test for overall effect: Z = 1.05 (P = 0.29)								
1.16.3 Mood stabilisers								
Crawford 2018 (11)	2.1	2	97	2.1	2.1	98	30.1%	0.00 [-0.28 , 0.28]
Reich 2009 (12)	-1.2	0.8	15	-0.1	0.7	12	24.2%	-1.41 [-2.27 , -0.55]
Moen 2012 (13)	23.9	10.3	10	18.2	6.4	5	21.3%	0.58 [-0.52 , 1.68]
Cowdry 1988 (14)	2.57	1.02	15	4.08	1.09	13	24.5%	-1.39 [-2.23 , -0.55]
Subtotal (95% CI)			**137**			**128**	**100.0%**	**-0.56 [-1.46 , 0.35]**
Heterogeneity: Tau² = 0.69; Chi² = 19.16, df = 3 (P = 0.0003); I² = 84%								
Test for overall effect: Z = 1.21 (P = 0.23)								
Test for subgroup differences: Chi² = 1.28, df = 2 (P = 0.53), I² = 0%								

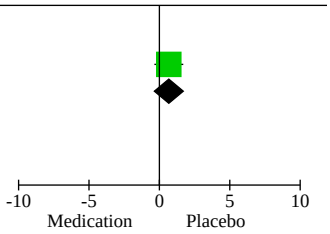


Footnotes

(1) Haloperidol versus placebo - BIS
(2) Haloperidol versus placebo BIS
(3) Olanzapine versus placebo
(4) Quetiapine versus placebo - BIS. Active groups pooled. SDs calculated from SEs.
(5) Ziprasidone versus placebo
(6) Trifluoperazine hydrochloride versus placebo - crossover data
(7) Fluvoxamine versus placebo
(8) Amitriptyline versus placebo
(9) Phenelzine sulfate versus placebo
(10) Tranylcypromine sulfate versus placebo - cross-over data
(11) Lamotrigine vs. placebo - Zan-BPD-impulsivity
(12) Lamotrigine versus placebo
(13) Divalproex versus placebo
(14) Carbamazepine versus placebo - cross-over data

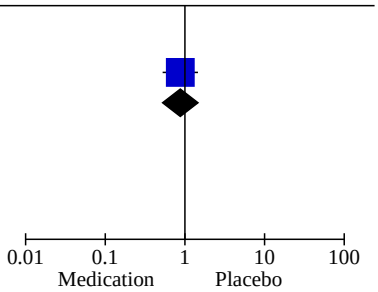
Analysis 1.17. Comparison 1: Medications compared with placebo, Outcome 17: Secondary: Impulsivity at end of treatment (continuous outcomes, MDs)

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.17.1 Alprazolam								
Cowdry 1988	4.75	1.48	12	4.08	1.09	13	100.0%	0.67 [-0.36 , 1.70]
Subtotal (95% CI)			**12**			**13**	**100.0%**	**0.67 [-0.36 , 1.70]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.28 (P = 0.20)								
Test for subgroup differences: Not applicable								



Analysis 1.18. Comparison 1: Medications compared with placebo, Outcome 18: Secondary: Impulsivity at end of treatment (dichtotomous outcomes, RRs)

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.18.1 Mood stabilisers						
De la Fuente 1994 (1)	7	10	8	10	100.0%	0.88 [0.53 , 1.46]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**0.88 [0.53 , 1.46]**
Total events:	7		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
Test for subgroup differences: Not applicable						

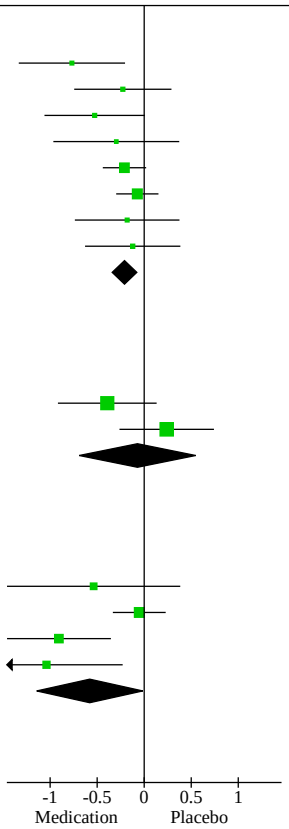


Footnotes

(1) Carbamazepine versus placebo. Event: Status quo or worsened after treatment according to Acting-out Scale

Analysis 1.19. Comparison 1: Medications compared with placebo, Outcome 19: Secondary: Interpersonal problems at end of treatment (continuous outcomes, SMDs)

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.19.1 Antipsychotics								
Nickel 2006 (1)	59.7	5.3	26	64.2	6.2	26	5.4%	-0.77 [-1.33 , -0.20]
Soloff 1993 (2)	0.57	0.7	30	0.73	0.69	28	6.4%	-0.23 [-0.74 , 0.29]
Soloff 1989 (2)	1.21	0.92	28	1.74	1.06	28	6.0%	-0.53 [-1.06 , 0.01]
Bogenschutz 2004 (3)	-2.125	1.74642	16	-1.5263	2.14394	19	3.8%	-0.30 [-0.97 , 0.37]
Zanarini 2007	-1	0.9	144	-0.8	1	147	32.2%	-0.21 [-0.44 , 0.02]
Schulz 2007 (3)	-0.87	1.22	150	-0.78	1.24	155	33.9%	-0.07 [-0.30 , 0.15]
Goldberg 1986 (4)	0.4583	0.9927	24	0.6209	0.7706	26	5.5%	-0.18 [-0.74 , 0.37]
Pascual 2008 (5)	4.37	1.1	30	4.5	1	30	6.7%	-0.12 [-0.63 , 0.38]
Subtotal (95% CI)			**448**			**459**	**100.0%**	**-0.21 [-0.34 , -0.08]**
Heterogeneity: Tau² = 0.00; Chi² = 6.73, df = 7 (P = 0.46); I² = 0%								
Test for overall effect: Z = 3.14 (P = 0.002)								
1.19.2 Antidepressants								
Soloff 1989 (6)	1.34	0.95	29	1.74	1.06	28	49.2%	-0.39 [-0.92 , 0.13]
Soloff 1993 (7)	0.9	0.71	34	0.73	0.69	28	50.8%	0.24 [-0.26 , 0.74]
Subtotal (95% CI)			**63**			**56**	**100.0%**	**-0.07 [-0.69 , 0.55]**
Heterogeneity: Tau² = 0.13; Chi² = 2.91, df = 1 (P = 0.09); I² = 66%								
Test for overall effect: Z = 0.23 (P = 0.82)								
1.19.3 Mood stabilisers								
De la Fuente 1994 (8)	6.14	7.17	9	11	9.76	10	18.5%	-0.54 [-1.46 , 0.38]
Crawford 2018 (9)	1.7	1.8	97	1.8	2	98	33.5%	-0.05 [-0.33 , 0.23]
Loew 2006 (10)	60.1	7.5	28	66.9	7.3	28	27.1%	-0.91 [-1.46 , -0.35]
Frankenburg 2002 (11)	1.5	0.5	20	2.2	0.9	10	20.8%	-1.04 [-1.85 , -0.23]
Subtotal (95% CI)			**154**			**146**	**100.0%**	**-0.58 [-1.14 , -0.02]**
Heterogeneity: Tau² = 0.23; Chi² = 11.06, df = 3 (P = 0.01); I² = 73%								
Test for overall effect: Z = 2.01 (P = 0.04)								
Test for subgroup differences: Chi² = 1.80, df = 2 (P = 0.41), I² = 0%								



Footnotes

(1) Aripiprazole versus placebo
(2) Haloperidol versus placebo
(3) Olanzapine versus placebo
(4) Thiothixene versus placebo
(5) Ziprasidone versus placebo
(6) Amitriptyline versus placebo
(7) Phenelzine sulfate versus placebo
(8) Carbamazepine versus placebo
(9) Lamotrigine vs. placebo - Zan-BPD disturbed relationships
(10) Topiramate versus placebo
(11) Valproate semisodium versus placebo

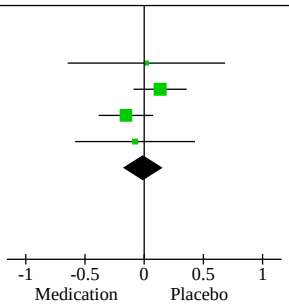
Analysis 1.20. Comparison 1: Medications compared with placebo, Outcome 20: Secondary: Abandonment at end of treatment (continuous outcomes, SMDs)

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.20.1 Antipsychotics								
Bogenschutz 2004 (1)	-0.8125	1.16726	16	-0.8421	1.83373	19	5.5%	0.02 [-0.65 , 0.68]
Schulz 2007 (1)	-0.54	1.26	150	-0.71	1.26	155	43.5%	0.13 [-0.09 , 0.36]
Zanarini 2007 (1)	-1.06	1.26	144	-0.87	1.2	147	41.7%	-0.15 [-0.38 , 0.08]
Pascual 2008 (2)	4.44	1.2	30	4.53	1.1	30	9.4%	-0.08 [-0.58 , 0.43]
Subtotal (95% CI)			**340**			**351**	**100.0%**	**-0.01 [-0.17 , 0.14]**

Heterogeneity: Tau² = 0.00; Chi² = 3.17, df = 3 (P = 0.37); I² = 5%

Test for overall effect: Z = 0.15 (P = 0.88)

Test for subgroup differences: Not applicable



Footnotes

(1) Olanzapine versus placebo

(2) Ziprasidone versus placebo

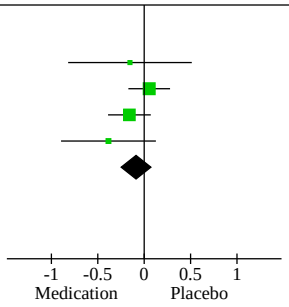
Analysis 1.21. Comparison 1: Medications compared with placebo, Outcome 21: Secondary: Identity disturbance at end of treatment (continuous outcomes, SMDs)

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.21.1 Antipsychotics								
Bogenschutz 2004 (1)	-1.375	1.78419	16	-1.1053	1.66315	19	5.7%	-0.15 [-0.82 , 0.51]
Schulz 2007 (1)	-0.78	1.33	150	-0.85	1.25	155	43.3%	0.05 [-0.17 , 0.28]
Zanarini 2007 (1)	-1.01	1.24	144	-0.82	1.14	147	41.5%	-0.16 [-0.39 , 0.07]
Pascual 2008 (2)	4.62	1.1	30	5.03	1	30	9.5%	-0.38 [-0.90 , 0.13]
Subtotal (95% CI)			**340**			**351**	**100.0%**	**-0.09 [-0.25 , 0.07]**

Heterogeneity: Tau² = 0.00; Chi² = 3.24, df = 3 (P = 0.36); I² = 7%

Test for overall effect: Z = 1.08 (P = 0.28)

Test for subgroup differences: Not applicable



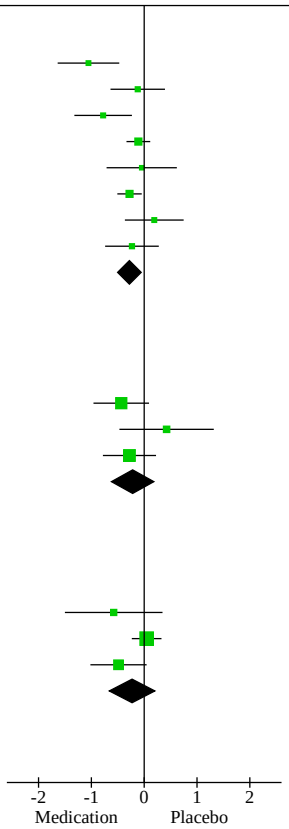
Footnotes

(1) Olanzapine versus placebo

(2) Ziprasidone versus placebo

Analysis 1.22. Comparison 1: Medications compared with placebo, Outcome 22: Secondary: Dissociation and psychotic-like symptoms at end of treatment (continuous outcomes, SMDs)

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.22.1 Antipsychotics								
Nickel 2006 (1)	60.2	5.1	26	68.3	9.4	26	9.3%	-1.05 [-1.64 , -0.47]
Soloff 1993 (2)	1.06	0.96	30	1.18	0.98	28	10.9%	-0.12 [-0.64 , 0.39]
Soloff 1989 (3)	0.75	0.73	28	1.44	1	28	10.2%	-0.78 [-1.32 , -0.23]
Schulz 2007 (4)	-0.66	1.18	150	-0.53	1.17	155	20.5%	-0.11 [-0.34 , 0.11]
Bogenschutz 2004 (4)	-0.8125	1.10868	16	-0.7368	1.88096	19	7.8%	-0.05 [-0.71 , 0.62]
Zanarini 2007 (4)	-0.97	1.12	144	-0.65	1.18	147	20.3%	-0.28 [-0.51 , -0.05]
Goldberg 1986 (5)	2.0313	0.9019	24	1.8654	0.8125	26	9.9%	0.19 [-0.37 , 0.75]
Pascual 2008 (6)	1.96	1.2	30	2.23	1.1	30	11.1%	-0.23 [-0.74 , 0.28]
Subtotal (95% CI)			**448**			**459**	**100.0%**	**-0.28 [-0.50 , -0.06]**
Heterogeneity: Tau² = 0.05; Chi² = 15.45, df = 7 (P = 0.03); I² = 55%								
Test for overall effect: Z = 2.46 (P = 0.01)								
1.22.2 Antidepressants								
Soloff 1989 (7)	1.03	0.86	29	1.44	1	28	40.0%	-0.43 [-0.96 , 0.09]
Simpson 2004 (8)	18.69	15.39	9	12.66	12	11	17.4%	0.42 [-0.47 , 1.32]
Soloff 1993 (9)	0.92	0.87	34	1.18	0.98	28	42.6%	-0.28 [-0.78 , 0.22]
Subtotal (95% CI)			**72**			**67**	**100.0%**	**-0.22 [-0.62 , 0.18]**
Heterogeneity: Tau² = 0.03; Chi² = 2.67, df = 2 (P = 0.26); I² = 25%								
Test for overall effect: Z = 1.07 (P = 0.29)								
1.22.3 Mood stabilisers								
De la Fuente 1994 (10)	4.85	7.4	9	9.22	7.08	10	16.3%	-0.58 [-1.50 , 0.35]
Crawford 2018 (11)	2.7	2.2	97	2.6	2.1	98	51.0%	0.05 [-0.23 , 0.33]
Loew 2006 (12)	67.5	7.2	28	71.1	7.4	28	32.7%	-0.49 [-1.02 , 0.05]
Subtotal (95% CI)			**134**			**136**	**100.0%**	**-0.23 [-0.66 , 0.20]**
Heterogeneity: Tau² = 0.07; Chi² = 4.09, df = 2 (P = 0.13); I² = 51%								
Test for overall effect: Z = 1.04 (P = 0.30)								
Test for subgroup differences: Chi² = 0.09, df = 2 (P = 0.95), I² = 0%								

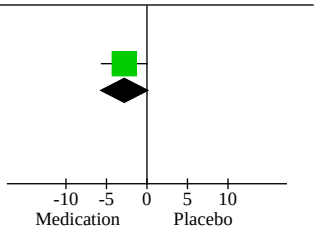


Footnotes

(1) Aripiprazole versus placebo
(2) Halperidol versus placebo
(3) Halperidol versus placebo - SCL-90-R psychoticism
(4) Olanzapine versus placebo
(5) Thiothixene versus placebo
(6) Ziprsidone versus placebo
(7) Amitriptyline versus placebo
(8) Fluoxetine versus placebo
(9) Phenelzine sufate versus placebo
(10) Carbamazepine versus placebo
(11) Lamotrigine vs. placebo - Zan-BPD cognitive disturbance
(12) Topiramate versus placebo

Analysis 1.23. Comparison 1: Medications compared with placebo, Outcome 23: Secondary: Dissociation and psychotic-like symptoms at end of treatment (continuous outcomes, MDs)

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.23.1 Omega-3 fatty acids								
Amminger 2013 (1)	5.9	2.4	8	8.7	3.2	7	100.0%	-2.80 [-5.70 , 0.10]
Subtotal (95% CI)			**8**			**7**	**100.0%**	**-2.80 [-5.70 , 0.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.90 (P = 0.06)								
Test for subgroup differences: Not applicable								

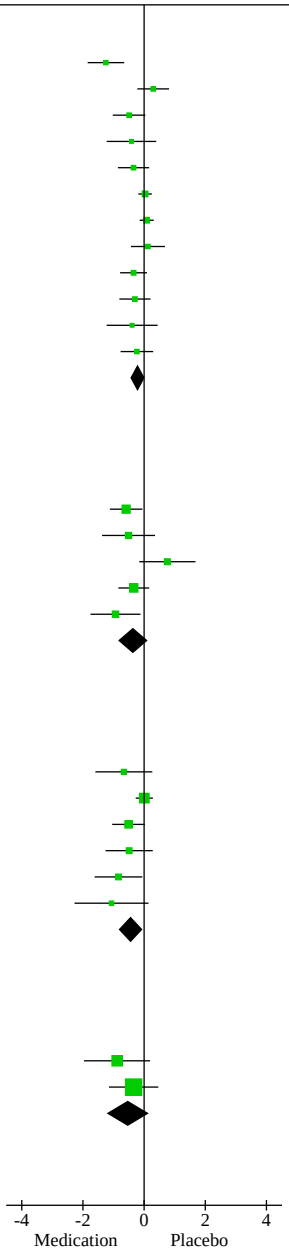


Footnotes

(1) Long-chain omega-3 polyunsaturated fatty acids versus placebo

Analysis 1.24. Comparison 1: Medications compared with placebo, Outcome 24: Secondary: Depression at end of treatment (continuous outcomes, SMDs)

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.24.1 Antipsychotics								
Nickel 2006 (1)	13.9	2.8	26	18.8	4.7	26	6.9%	-1.25 [-1.85 , -0.65]
Soloff 1993 (2)	23.5	13.16	30	19.54	13.04	28	8.0%	0.30 [-0.22 , 0.82]
Soloff 1989 (3)	16.22	12.32	28	23.04	14.88	28	7.8%	-0.49 [-1.02 , 0.04]
Linehan 2008 (4)	12.6	7.2	12	15.4	5.8	12	4.7%	-0.41 [-1.22 , 0.40]
Soler 2005 (4)	13.71	5.46	30	15.8	6.41	30	8.2%	-0.35 [-0.86 , 0.16]
Schulz 2007	-0.11	4.9	155	-0.26	4.5	159	13.6%	0.03 [-0.19 , 0.25]
Zanarini 2007	-1.4	4.6	144	-1.8	4.8	147	13.5%	0.08 [-0.15 , 0.31]
Goldberg 1986 (5)	1.6905	1.398	24	1.5065	1.5058	26	7.5%	0.12 [-0.43 , 0.68]
Black 2014 (6)	-0.95	1.0597	66	-0.59	0.9693	29	9.4%	-0.35 [-0.79 , 0.09]
Pascual 2008 (7)	14.24	6.5	30	16.07	5.5	30	8.2%	-0.30 [-0.81 , 0.21]
Cowdry 1988 (8)	3.6	1.9	10	4.23	1.23	13	4.5%	-0.39 [-1.22 , 0.44]
Grant 2022	-3.81	7.41	30	-2.09	6.91	25	7.8%	-0.24 [-0.77 , 0.30]
Subtotal (95% CI)			**585**			**553**	**100.0%**	**-0.22 [-0.42 , -0.01]**
Heterogeneity: Tau² = 0.07; Chi² = 26.94, df = 11 (P = 0.005); I² = 59%								
Test for overall effect: Z = 2.04 (P = 0.04)								
1.24.2 Antidepressants								
Soloff 1989 (9)	15.34	10.71	29	23.04	14.88	28	25.5%	-0.59 [-1.12 , -0.06]
Salzman 1995 (10)	3.92	3.64	13	6	4.36	9	16.0%	-0.51 [-1.37 , 0.36]
Simpson 2004 (10)	25	18.04	9	13.91	9.54	11	14.9%	0.76 [-0.16 , 1.68]
Soloff 1993 (11)	15.69	9.46	34	19.54	13.04	28	26.4%	-0.34 [-0.84 , 0.16]
Cowdry 1988 (12)	2.83	1.64	13	4.23	1.23	13	17.1%	-0.94 [-1.75 , -0.12]
Subtotal (95% CI)			**98**			**89**	**100.0%**	**-0.37 [-0.82 , 0.08]**
Heterogeneity: Tau² = 0.13; Chi² = 8.36, df = 4 (P = 0.08); I² = 52%								
Test for overall effect: Z = 1.61 (P = 0.11)								
1.24.3 Mood stabilisers								
De la Fuente 1994 (13)	12.28	13.65	9	22.66	16.06	10	10.9%	-0.66 [-1.59 , 0.27]
Crawford 2018 (14)	28.8	16.1	97	28.7	15.5	98	32.3%	0.01 [-0.27 , 0.29]
Loew 2006 (15)	70.3	5.2	28	72.7	4	28	21.4%	-0.51 [-1.04 , 0.02]
Frankenburg 2002 (16)	1.8	0.6	20	2.2	1.1	10	14.2%	-0.49 [-1.26 , 0.28]
Cowdry 1988 (17)	3.14	1.29	15	4.23	1.23	13	14.0%	-0.84 [-1.62 , -0.06]
Hollander 2001 (16)	8.2	9.1	12	18	7	4	7.3%	-1.07 [-2.27 , 0.14]
Subtotal (95% CI)			**181**			**163**	**100.0%**	**-0.44 [-0.80 , -0.08]**
Heterogeneity: Tau² = 0.08; Chi² = 9.18, df = 5 (P = 0.10); I² = 46%								
Test for overall effect: Z = 2.41 (P = 0.02)								
1.24.4 Omega-3 fatty acids								
Amminger 2013 (18)	12	11	8	21	7.6	7	35.8%	-0.88 [-1.96 , 0.20]
Zanarini 2003 (19)	6.2	4.9	18	8	5.5	9	64.2%	-0.34 [-1.15 , 0.46]
Subtotal (95% CI)			**26**			**16**	**100.0%**	**-0.54 [-1.18 , 0.11]**
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%								
Test for overall effect: Z = 1.63 (P = 0.10)								
Test for subgroup differences: Chi² = 1.84, df = 3 (P = 0.61), I² = 0%								



Footnotes

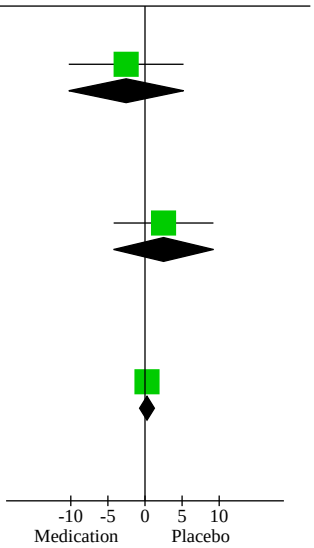
(1) Aripiprazole versus placebo
(2) Haloperidol versus placebo. cf. to (1)
(3) Haloperidol versus placebo
(4) Olanzapine versus placebo
(5) Thiothixene versus placebo
(6) Quetiapine versus placebo - MADRS. Active groups pooled. SDs calculated from SEs.
(7) Ziprasidone versus placebo
(8) Trifluoperazine hydrochloride versus placebo - crossover data
(9) Amitriptyline versus placebo
(10) Fluoxetine versus placebo
(11) Phenelzine sulfate versus placebo
(12) Tranylcypromine sulfate versus placebo - cross-over data

Analysis 1.24. (Continued)

(10) Fluoxetine versus placebo
(11) Phenelzine sulfate versus placebo
(12) Tranylcypromine sulfate versus placebo - cross-over data
(13) Carbamazepine versus placebo
(14) Lamotrigine plus TAU versus placebo plus TAU
(15) Topiramate versus placebo
(16) Valproate semisodium versus placebo
(17) Carbamazepine versus placebo - cross-over data
(18) Long-chain omega-3 polyunsaturated fatty acids versus placebo
(19) Omega-3 fatty acids versus placebo

Analysis 1.25. Comparison 1: Medications compared with placebo, Outcome 25: Secondary: Depression at end of treatment (continuous outcomes, MDs)

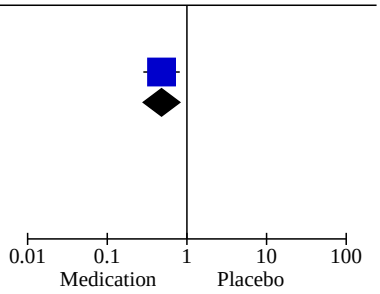
Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.25.1 Clonidine								
Ziegenhorn 2009 (1)	26.71	10.78	17	29.25	12.18	17	100.0%	-2.54 [-10.27 , 5.19]
Subtotal (95% CI)			**17**			**17**	**100.0%**	**-2.54 [-10.27 , 5.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.64 (P = 0.52)								
1.25.2 Naltrexone								
Schmahl 2012b (2)	33.6	8.2	16	31.1	11	16	100.0%	2.50 [-4.22 , 9.22]
Subtotal (95% CI)			**16**			**16**	**100.0%**	**2.50 [-4.22 , 9.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.73 (P = 0.47)								
1.25.3 Alprazolam								
Cowdry 1988 (3)	4.5	1.31	12	4.23	1.23	13	100.0%	0.27 [-0.73 , 1.27]
Subtotal (95% CI)			**12**			**13**	**100.0%**	**0.27 [-0.73 , 1.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.53 (P = 0.60)								
Test for subgroup differences: Chi^2 = 0.93, df = 2 (P = 0.63), I^2 = 0%								



Footnotes
(1) Clonidine versus placebo - cross-over data
(2) Naltrexone versus placebo - cross-over data
(3) Alprazolam versus placebo - cross-over data

Analysis 1.26. Comparison 1: Medications compared with placebo, Outcome 26: Secondary: Depression at end of treatment (dichotomous outcomes, RRs)

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.26.1 Omega-3 fatty acids						
Hallahan 2007 (1)	9	22	23	27	100.0%	0.48 [0.28 , 0.81]
Subtotal (95% CI)		**22**		**27**	**100.0%**	**0.48 [0.28 , 0.81]**
Total events:	9		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.73 (P = 0.006)						
Test for subgroup differences: Not applicable						

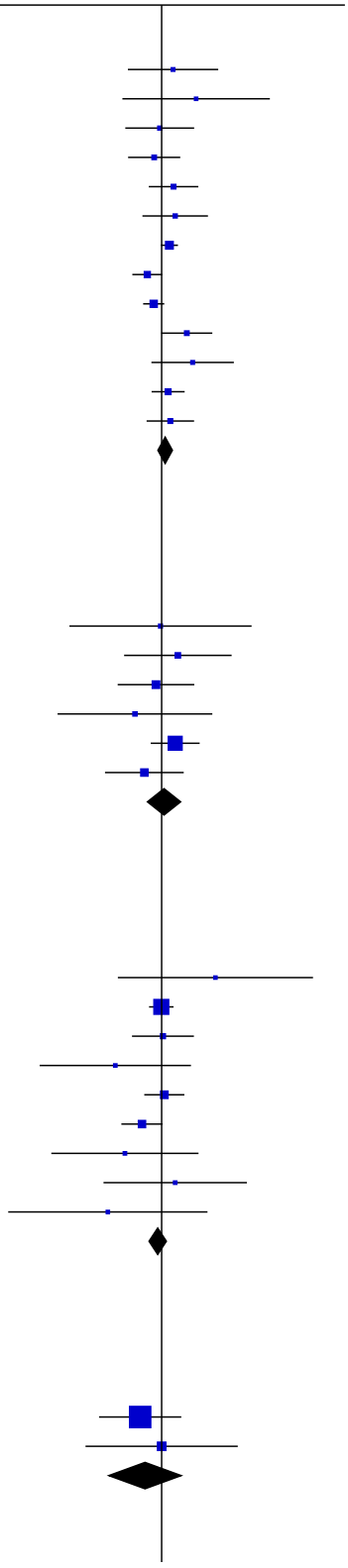


Footnotes

(1) Omega-3 fatty acid versus placebo. Event: No response (at least 50% reduction of BDI score)

Analysis 1.27. Comparison 1: Medications compared with placebo, Outcome 27: Secondary: Attrition at end of treatment (dichotomous outcomes, RRs)

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.27.1 Antipsychotics						
Montgomery 1982a (1)	4	18	3	19	2.3%	1.41 [0.36 , 5.43]
Soloff 1989 (2)	3	31	1	29	0.9%	2.81 [0.31 , 25.48]
Soloff 1993 (2)	6	36	6	34	3.8%	0.94 [0.34 , 2.65]
Soler 2005 (3)	8	30	10	30	6.0%	0.80 [0.37 , 1.74]
Bogenschutz 2004 (3)	10	20	7	20	6.5%	1.43 [0.68 , 3.00]
Linehan 2008 (3)	6	12	4	12	4.1%	1.50 [0.56 , 4.00]
Schulz 2007 (3)	75	155	61	159	19.6%	1.26 [0.98 , 1.63]
Zanarini 2001 (3)	11	19	8	9	12.5%	0.65 [0.42 , 1.02]
Zanarini 2007 (3)	45	148	59	153	17.1%	0.79 [0.58 , 1.08]
Black 2014	29	66	6	29	6.2%	2.12 [0.99 , 4.55]
Goldberg 1986 (4)	7	24	3	26	2.8%	2.53 [0.74 , 8.68]
Pascual 2008 (5)	17	30	14	30	11.2%	1.21 [0.74 , 1.99]
Grant 2022	12	37	10	40	6.9%	1.30 [0.64 , 2.64]
Subtotal (95% CI)		**626**		**590**	**100.0%**	**1.11 [0.89 , 1.38]**
Total events:	233		192			
Heterogeneity: Tau² = 0.05; Chi² = 18.33, df = 12 (P = 0.11); I² = 35%						
Test for overall effect: Z = 0.95 (P = 0.34)						
1.27.2 Antidepressants						
Soloff 1989 (6)	1	30	1	29	3.3%	0.97 [0.06 , 14.74]
Simpson 2004 (7)	3	12	2	13	9.5%	1.63 [0.33 , 8.11]
NCT00533117 (7)	4	18	5	19	18.8%	0.84 [0.27 , 2.66]
Rinne 2002 (8)	1	20	2	18	4.6%	0.45 [0.04 , 4.55]
Montgomery 1982b (9)	12	29	8	29	46.0%	1.50 [0.72 , 3.12]
Soloff 1993 (10)	4	38	6	34	17.8%	0.60 [0.18 , 1.94]
Subtotal (95% CI)		**147**		**142**	**100.0%**	**1.07 [0.65 , 1.76]**
Total events:	25		24			
Heterogeneity: Tau² = 0.00; Chi² = 2.76, df = 5 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.28 (P = 0.78)						
1.27.3 Mood stabilisers						
De la Fuente 1994 (11)	2	10	0	10	0.8%	5.00 [0.27 , 92.62]
Crawford 2018	40	137	41	139	50.1%	0.99 [0.69 , 1.43]
Reich 2009 (12)	6	15	5	13	7.8%	1.04 [0.41 , 2.62]
Tritt 2005 (12)	1	18	2	9	1.3%	0.25 [0.03 , 2.40]
Frankenburg 2002 (13)	13	20	6	10	18.7%	1.08 [0.59 , 1.97]
Hollander 2001 (13)	6	12	4	4	17.6%	0.56 [0.30 , 1.03]
Loew 2006 (14)	1	28	3	28	1.4%	0.33 [0.04 , 3.01]
Nickel 2004 (14)	3	22	1	11	1.5%	1.50 [0.18 , 12.80]
Nickel 2005 (14)	0	22	2	22	0.8%	0.20 [0.01 , 3.94]
Subtotal (95% CI)		**284**		**246**	**100.0%**	**0.89 [0.69 , 1.15]**
Total events:	72		64			
Heterogeneity: Tau² = 0.00; Chi² = 7.65, df = 8 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.89 (P = 0.37)						
1.27.4 Omega-3 fatty acids						
Hallahan 2007 (15)	3	22	7	27	77.4%	0.53 [0.15 , 1.80]
Zanarini 2003 (15)	2	20	1	10	22.6%	1.00 [0.10 , 9.75]
Subtotal (95% CI)		**42**		**37**	**100.0%**	**0.61 [0.21 , 1.79]**
Total events:	5		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.63); I² = 0%						
Test for overall effect: Z = 0.90 (P = 0.37)						



Analysis 1.27. (Continued)

Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)

1.27.5 Memantine hydrochloride

Kulkarni 2018 (16)	5	17	3	16	100.0%	1.57 [0.45 , 5.52]
Subtotal (95% CI)		**17**		**16**	**100.0%**	**1.57 [0.45 , 5.52]**
Total events:	5		3			

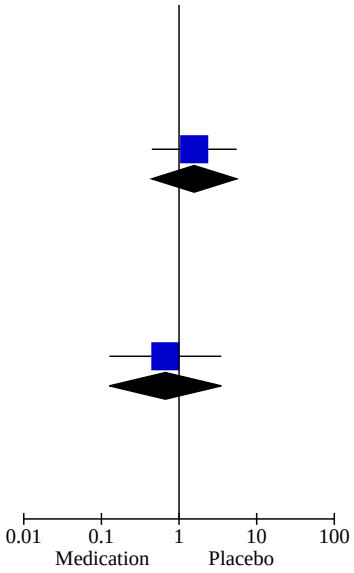
Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)

1.27.6 Clonidine

Ziegenhorn 2009 (17)	2	17	3	17	100.0%	0.67 [0.13 , 3.50]
Subtotal (95% CI)		**17**		**17**	**100.0%**	**0.67 [0.13 , 3.50]**
Total events:	2		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)

Test for subgroup differences: Chi² = 3.29, df = 5 (P = 0.66), I² = 0%

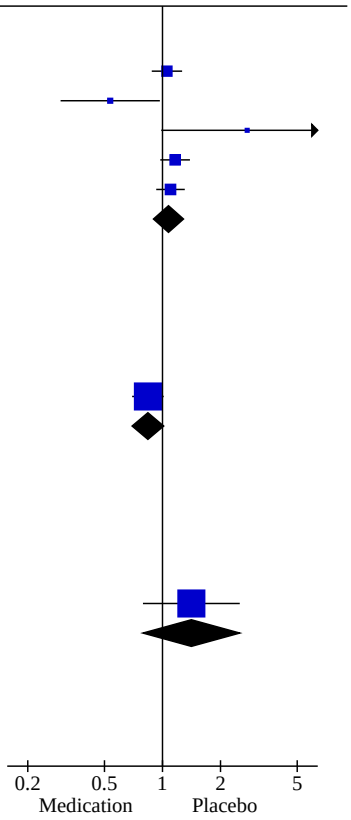


Footnotes

(1) Flupenthixol decanoate versus placebo
(2) Haloperidol versus placebo
(3) Olanzapine versus placebo
(4) Thiothixene versus placebo
(5) Ziprasidone versus placebo
(6) Amitriptyline versus placebo
(7) Fluoxetine versus placebo
(8) Fluvoxamine versus placebo
(9) Mianserin versus placebo
(10) Phenelzine sulfate versus placebo
(11) Carbamazepine versus placebo
(12) Lamotrigine versus placebo
(13) Valproate semisodium versus placebo
(14) Topiramate versus placebo
(15) Omega-3 fatty acids versus placebo
(16) Memantine hydrochloride plus TAU versus placebo plus TAU
(17) Clonidine versus placebo - cross-over data

Analysis 1.28. Comparison 1: Medications compared with placebo, Outcome 28: Secondary: Non-serious adverse events at end of treatment (dichotomous outcomes, RRs)

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.28.1 Antipsychotics						
Black 2014 (1)	30	33	25	29	29.4%	1.05 [0.88 , 1.26]
Grant 2022	11	40	19	37	7.5%	0.54 [0.30 , 0.97]
Pascual 2008 (2)	11	30	4	30	2.8%	2.75 [0.99 , 7.68]
Schulz 2007 (3)	102	155	90	159	29.8%	1.16 [0.97 , 1.39]
Zanarini 2007 (3)	99	148	93	153	30.5%	1.10 [0.93 , 1.30]
Subtotal (95% CI)		**406**		**408**	**100.0%**	**1.07 [0.90 , 1.29]**
Total events:	253		231			
Heterogeneity: Tau² = 0.02; Chi² = 9.30, df = 4 (P = 0.05); I² = 57%						
Test for overall effect: Z = 0.78 (P = 0.43)						
1.28.2 Mood stabilisers						
Crawford 2018 (4)	77	137	93	139	100.0%	0.84 [0.70 , 1.01]
Subtotal (95% CI)		**137**		**139**	**100.0%**	**0.84 [0.70 , 1.01]**
Total events:	77		93			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.81 (P = 0.07)						
1.28.3 Memantine hydrochloride						
Kulkarni 2018 (5)	12	17	8	16	100.0%	1.41 [0.79 , 2.52]
Subtotal (95% CI)		**17**		**16**	**100.0%**	**1.41 [0.79 , 2.52]**
Total events:	12		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.17 (P = 0.24)						
Test for subgroup differences: Chi² = 5.10, df = 2 (P = 0.08), I² = 60.8%						

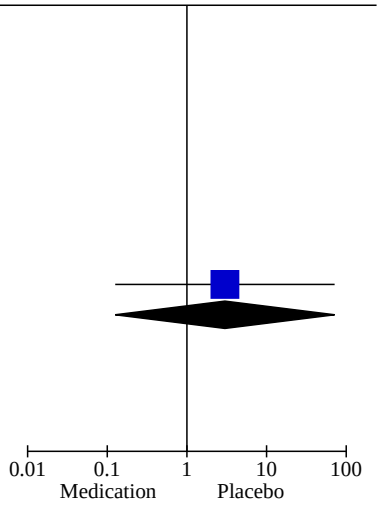


Footnotes

(1) Quetapine versus placebo
(2) Ziprasidone versus placebo
(3) Olanzapine versus placebo
(4) Lamotrigine plus TAU versus placebo plus TAU. Total number of participants with at least one adverse event
(5) Memantine hydrochloride plus TAU versus placebo plus TAU

Analysis 1.29. Comparison 1: Medications compared with placebo, Outcome 29: Secondary: Serious adverse events at end of treatment (dichotomous outcomes, RRs)

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.29.1 Memantine hydrochloride						
Kulkarni 2018 (1)	0	17	0	16		Not estimable
Subtotal (95% CI)		**17**		**16**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.29.2 Brexpiprazole						
Grant 2022	1	40	0	40	100.0%	3.00 [0.13 , 71.51]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**3.00 [0.13 , 71.51]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Memantine hydrochloride plus TAU versus placebo plus TAU

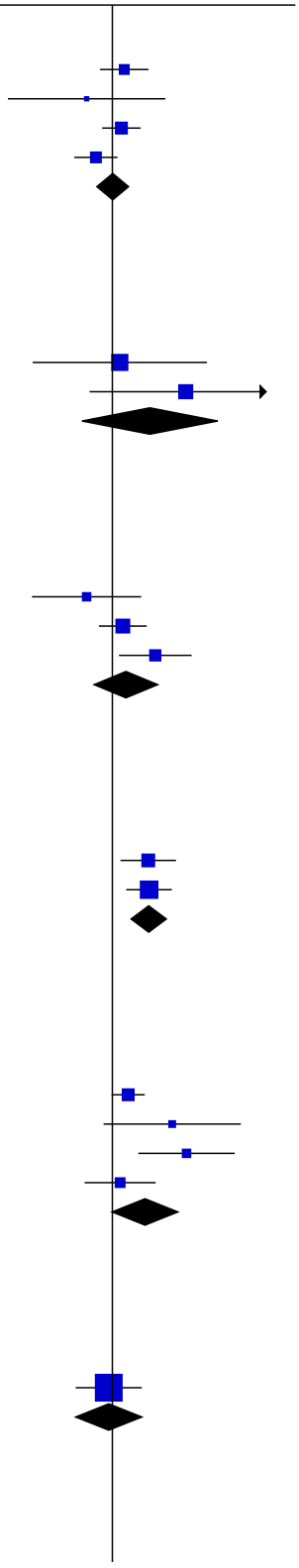
Comparison 2. Medications compared with placebo - non-serious adverse events - central nervous system

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Antipsychotics	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1.1 Headache	4	754	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.63, 1.62]
2.1.2 Dizziness	2	68	Risk Ratio (M-H, Random, 95% CI)	3.07 [0.40, 23.45]
2.1.3 Fatigue	3	692	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.58, 3.89]
2.1.4 Somnolence	2	615	Risk Ratio (M-H, Random, 95% CI)	2.97 [1.75, 5.03]
2.1.5 Sedation	4	445	Risk Ratio (M-H, Random, 95% CI)	2.66 [0.99, 7.12]
2.1.6 Anxiety	1	314	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.33, 2.42]
2.1.7 Insomnia	2	615	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.33, 1.37]
2.1.8 Hypersomnia	1	62	Risk Ratio (M-H, Random, 95% CI)	2.34 [0.69, 8.01]
2.1.9 Forgetful or confusion	1	62	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.38, 5.60]
2.1.10 Disturbance in attention	1	301	Risk Ratio (M-H, Random, 95% CI)	11.37 [0.63, 203.81]
2.1.11 Increased appetite	3	692	Risk Ratio (M-H, Random, 95% CI)	2.68 [1.71, 4.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1.12 Change in appetite	1	17	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.10, 4.06]
2.1.13 Restlessness	1	77	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.20, 4.30]
2.1.14 Hallucinations	1	77	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.01, 3.74]
2.1.15 Sleep problems	1	77	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.01, 3.74]
2.1.16 Tremor	1	77	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.01, 7.36]
2.2 Mood stabilisers	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.2.1 Paraesthesia	1	56	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.33, 27.12]
2.2.2 Headache	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.15, 6.61]
2.2.3 Dizziness	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.27, 8.30]
2.2.4 Fatigue	1	56	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.40, 10.05]
2.2.5 Memory problems	1	56	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.55, 7.22]
2.2.6 Psychiatric disorders	1	276	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.64, 1.37]
2.2.7 Nervous system disorders	1	276	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.68, 1.62]
2.3 Memantine hydrochloride	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.3.1 Somnolence	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.59, 4.57]
2.3.2 Headache	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.71, 2.36]
2.3.3 Fatigue	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.52, 3.31]
2.3.4 Dizziness	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.72, 3.98]
2.3.5 Gait/balance disturbances	1	33	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [0.53, 10.45]

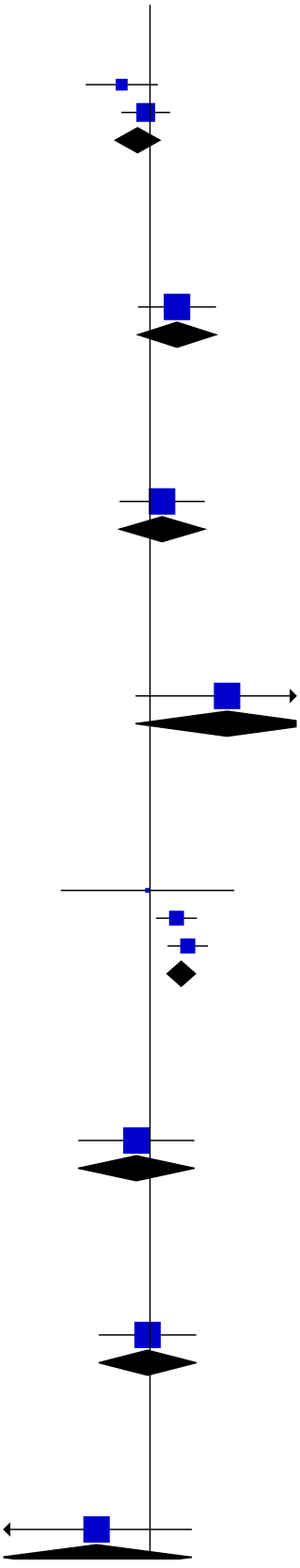
Analysis 2.1. Comparison 2: Medications compared with placebo - non-serious adverse events - central nervous system, Outcome 1: Antipsychotics

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Headache						
Black 2014 (1)	13	33	8	29	27.7%	1.43 [0.69 , 2.95]
Grant 2022 (2)	1	40	2	37	3.8%	0.46 [0.04 , 4.89]
Schulz 2007 (3)	23	155	18	159	36.5%	1.31 [0.74 , 2.33]
Zanarini 2007 (3)	13	148	22	153	32.0%	0.61 [0.32 , 1.17]
Subtotal (95% CI)		**376**		**378**	**100.0%**	**1.01 [0.63 , 1.62]**
Total events:	50		50			
Heterogeneity: Tau² = 0.07; Chi² = 4.42, df = 3 (P = 0.22); I² = 32%						
Test for overall effect: Z = 0.04 (P = 0.97)						
2.1.2 Dizziness						
Black 2014 (1)	2	7	0	1	54.4%	1.25 [0.09 , 17.02]
Pascual 2008 (4)	4	30	0	30	45.6%	9.00 [0.51 , 160.17]
Subtotal (95% CI)		**37**		**31**	**100.0%**	**3.07 [0.40 , 23.45]**
Total events:	6		0			
Heterogeneity: Tau² = 0.20; Chi² = 1.10, df = 1 (P = 0.29); I² = 9%						
Test for overall effect: Z = 1.08 (P = 0.28)						
2.1.3 Fatigue						
Grant 2022	2	40	4	37	21.6%	0.46 [0.09 , 2.38]
Schulz 2007 (3)	16	155	12	159	44.8%	1.37 [0.67 , 2.80]
Zanarini 2007 (3)	14	148	4	153	33.6%	3.62 [1.22 , 10.74]
Subtotal (95% CI)		**343**		**349**	**100.0%**	**1.50 [0.58 , 3.89]**
Total events:	32		20			
Heterogeneity: Tau² = 0.39; Chi² = 4.56, df = 2 (P = 0.10); I² = 56%						
Test for overall effect: Z = 0.84 (P = 0.40)						
2.1.4 Somnolence						
Schulz 2007 (3)	20	155	7	159	40.2%	2.93 [1.28 , 6.73]
Zanarini 2007 (3)	29	148	10	153	59.8%	3.00 [1.52 , 5.93]
Subtotal (95% CI)		**303**		**312**	**100.0%**	**2.97 [1.75 , 5.03]**
Total events:	49		17			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%						
Test for overall effect: Z = 4.05 (P < 0.0001)						
2.1.5 Sedation						
Black 2014 (1)	24	28	8	15	36.5%	1.61 [0.98 , 2.64]
Pascual 2008 (4)	6	30	1	30	14.6%	6.00 [0.77 , 46.87]
Schulz 2007 (3)	18	155	2	159	21.6%	9.23 [2.18 , 39.12]
Zanarini 2001 (3)	8	19	3	9	27.4%	1.26 [0.44 , 3.66]
Subtotal (95% CI)		**232**		**213**	**100.0%**	**2.66 [0.99 , 7.12]**
Total events:	56		14			
Heterogeneity: Tau² = 0.63; Chi² = 9.18, df = 3 (P = 0.03); I² = 67%						
Test for overall effect: Z = 1.95 (P = 0.05)						
2.1.6 Anxiety						
Schulz 2007 (3)	7	155	8	159	100.0%	0.90 [0.33 , 2.42]
Subtotal (95% CI)		**155**		**159**	**100.0%**	**0.90 [0.33 , 2.42]**
Total events:	7		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.83)						
2.1.7 Insomnia						



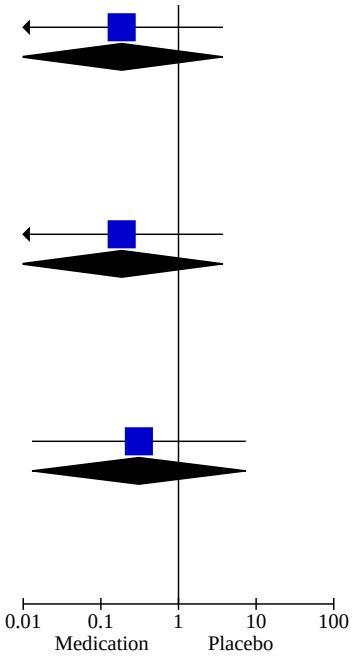
Analysis 2.1. (Continued)

2.1.7 Insomnia						
Schulz 2007 (3)	4	155	10	159	34.1%	0.41 [0.13 , 1.28]
Zanarini 2007 (3)	11	148	13	153	65.9%	0.87 [0.40 , 1.89]
Subtotal (95% CI)		**303**		**312**	**100.0%**	**0.68 [0.33 , 1.37]**
Total events:	15		23			
Heterogeneity: Tau² = 0.04; Chi² = 1.17, df = 1 (P = 0.28); I² = 15%						
Test for overall effect: Z = 1.09 (P = 0.28)						
2.1.8 Hypersomnia						
Black 2014 (1)	8	33	3	29	100.0%	2.34 [0.69 , 8.01]
Subtotal (95% CI)		**33**		**29**	**100.0%**	**2.34 [0.69 , 8.01]**
Total events:	8		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.36 (P = 0.17)						
2.1.9 Forgetful or confusion						
Black 2014 (1)	5	33	3	29	100.0%	1.46 [0.38 , 5.60]
Subtotal (95% CI)		**33**		**29**	**100.0%**	**1.46 [0.38 , 5.60]**
Total events:	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.58)						
2.1.10 Disturbance in attention						
Zanarini 2007 (3)	5	148	0	153	100.0%	11.37 [0.63 , 203.81]
Subtotal (95% CI)		**148**		**153**	**100.0%**	**11.37 [0.63 , 203.81]**
Total events:	5		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.65 (P = 0.10)						
2.1.11 Increased appetite						
Grant 2022	1	40	1	37	2.7%	0.93 [0.06 , 14.26]
Schulz 2007 (3)	27	155	12	159	48.3%	2.31 [1.21 , 4.39]
Zanarini 2007 (3)	35	148	11	153	49.0%	3.29 [1.74 , 6.23]
Subtotal (95% CI)		**343**		**349**	**100.0%**	**2.68 [1.71 , 4.19]**
Total events:	63		24			
Heterogeneity: Tau² = 0.00; Chi² = 1.18, df = 2 (P = 0.55); I² = 0%						
Test for overall effect: Z = 4.32 (P < 0.0001)						
2.1.12 Change in appetite						
Black 2014 (1)	1	4	5	13	100.0%	0.65 [0.10 , 4.06]
Subtotal (95% CI)		**4**		**13**	**100.0%**	**0.65 [0.10 , 4.06]**
Total events:	1		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.64)						
2.1.13 Restlessness						
Grant 2022 (2)	3	40	3	37	100.0%	0.93 [0.20 , 4.30]
Subtotal (95% CI)		**40**		**37**	**100.0%**	**0.93 [0.20 , 4.30]**
Total events:	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
2.1.14 Hallucinations						
Grant 2022 (2)	0	40	2	37	100.0%	0.19 [0.01 , 3.74]
Subtotal (95% CI)		**40**		**37**	**100.0%**	**0.19 [0.01 , 3.74]**



Analysis 2.1. (Continued)

Grant 2022 (2)	0	40	2	37	100.0%	0.19 [0.01 , 3.74]
Subtotal (95% CI)		**40**		**37**	**100.0%**	**0.19 [0.01 , 3.74]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
2.1.15 Sleep problems						
Grant 2022	0	40	2	37	100.0%	0.19 [0.01 , 3.74]
Subtotal (95% CI)		**40**		**37**	**100.0%**	**0.19 [0.01 , 3.74]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
2.1.16 Tremor						
Grant 2022	0	40	1	37	100.0%	0.31 [0.01 , 7.36]
Subtotal (95% CI)		**40**		**37**	**100.0%**	**0.31 [0.01 , 7.36]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
Test for subgroup differences: Chi² = 31.04, df = 15 (P = 0.009), I² = 51.7%						

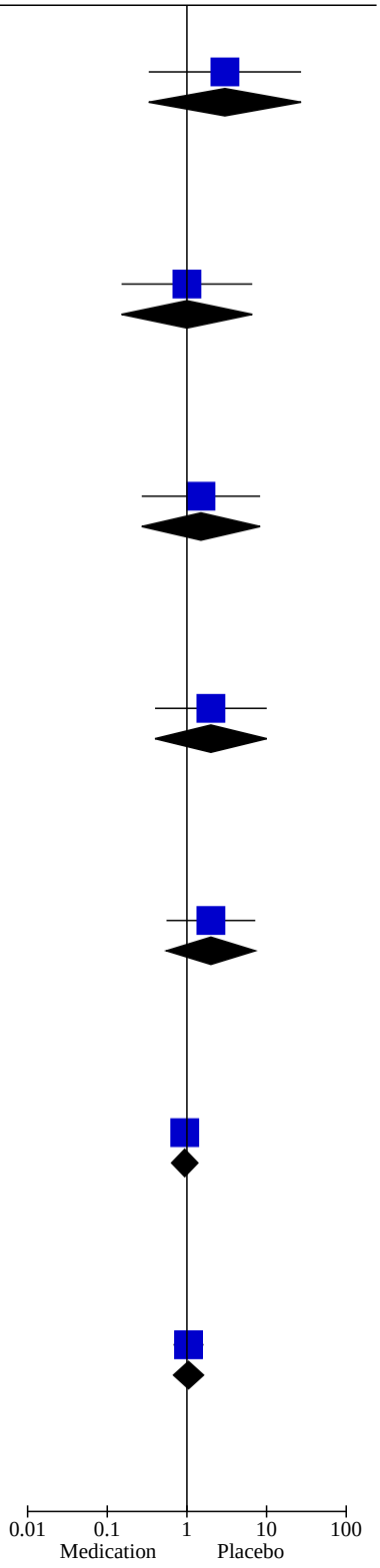


Footnotes

(1) Quetiapine versus placebo
(2) Brexpiprazole versus placebo
(3) Olanzapine versus placebo
(4) Ziprasidone versus placebo

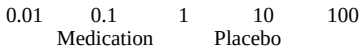
Analysis 2.2. Comparison 2: Medications compared with placebo - non-serious adverse events - central nervous system, Outcome 2: Mood stabilisers

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Paraesthesia						
Loew 2006 (1)	3	28	1	28	100.0%	3.00 [0.33 , 27.12]
Subtotal (95% CI)		**28**		**28**	**100.0%**	**3.00 [0.33 , 27.12]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
2.2.2 Headache						
Loew 2006 (1)	2	28	2	28	100.0%	1.00 [0.15 , 6.61]
Subtotal (95% CI)		**28**		**28**	**100.0%**	**1.00 [0.15 , 6.61]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
2.2.3 Dizziness						
Loew 2006 (1)	3	28	2	28	100.0%	1.50 [0.27 , 8.30]
Subtotal (95% CI)		**28**		**28**	**100.0%**	**1.50 [0.27 , 8.30]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.64)						
2.2.4 Fatigue						
Loew 2006 (1)	4	28	2	28	100.0%	2.00 [0.40 , 10.05]
Subtotal (95% CI)		**28**		**28**	**100.0%**	**2.00 [0.40 , 10.05]**
Total events:	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.84 (P = 0.40)						
2.2.5 Memory problems						
Loew 2006 (1)	6	28	3	28	100.0%	2.00 [0.55 , 7.22]
Subtotal (95% CI)		**28**		**28**	**100.0%**	**2.00 [0.55 , 7.22]**
Total events:	6		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
2.2.6 Psychiatric disorders						
Crawford 2018 (2)	37	137	40	139	100.0%	0.94 [0.64 , 1.37]
Subtotal (95% CI)		**137**		**139**	**100.0%**	**0.94 [0.64 , 1.37]**
Total events:	37		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
2.2.7 Nervous system disorders						
Crawford 2018 (2)	32	137	31	139	100.0%	1.05 [0.68 , 1.62]
Subtotal (95% CI)		**137**		**139**	**100.0%**	**1.05 [0.68 , 1.62]**
Total events:	32		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.83)						
Test for subgroup differences: Chi^2 = 2.95, df = 6 (P = 0.81), I^2 = 0%						



Analysis 2.2. (Continued)

Test for subgroup differences: Chi² = 2.95, df = 6 (P = 0.81), I² = 0%



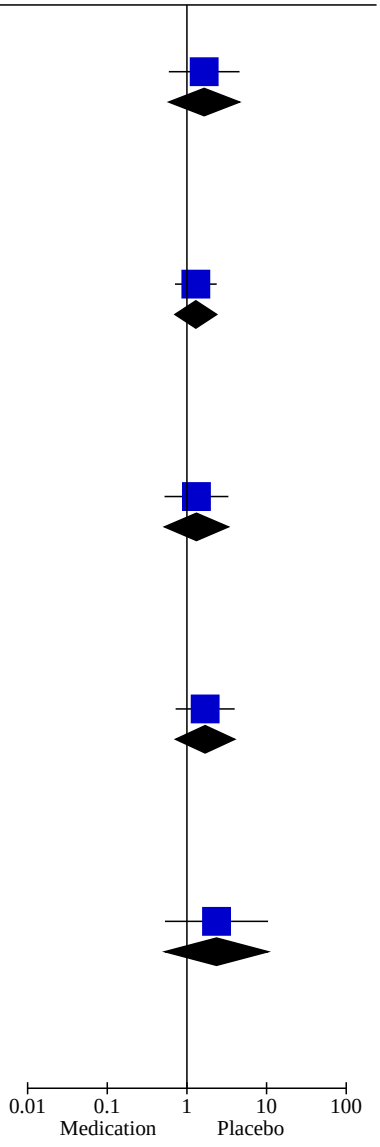
Footnotes

(1) Topiramate versus placebo

(2) Lamotrigine plus TAU versus placebo plus TAU

Analysis 2.3. Comparison 2: Medications compared with placebo - non-serious adverse events - central nervous system, Outcome 3: Memantine hydrochloride

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Somnolence						
Kulkarni 2018 (1)	7	17	4	16	100.0%	1.65 [0.59 , 4.57]
Subtotal (95% CI)		**17**		**16**	**100.0%**	**1.65 [0.59 , 4.57]**
Total events:	7		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						
2.3.2 Headache						
Kulkarni 2018 (1)	11	17	8	16	100.0%	1.29 [0.71 , 2.36]
Subtotal (95% CI)		**17**		**16**	**100.0%**	**1.29 [0.71 , 2.36]**
Total events:	11		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.84 (P = 0.40)						
2.3.3 Fatigue						
Kulkarni 2018 (1)	7	17	5	16	100.0%	1.32 [0.52 , 3.31]
Subtotal (95% CI)		**17**		**16**	**100.0%**	**1.32 [0.52 , 3.31]**
Total events:	7		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
2.3.4 Dizziness						
Kulkarni 2018 (1)	9	17	5	16	100.0%	1.69 [0.72 , 3.98]
Subtotal (95% CI)		**17**		**16**	**100.0%**	**1.69 [0.72 , 3.98]**
Total events:	9		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.21 (P = 0.23)						
2.3.5 Gait/balance disturbances						
Kulkarni 2018 (1)	5	17	2	16	100.0%	2.35 [0.53 , 10.45]
Subtotal (95% CI)		**17**		**16**	**100.0%**	**2.35 [0.53 , 10.45]**
Total events:	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
Test for subgroup differences: Chi² = 0.76, df = 4 (P = 0.94), I² = 0%						



Footnotes

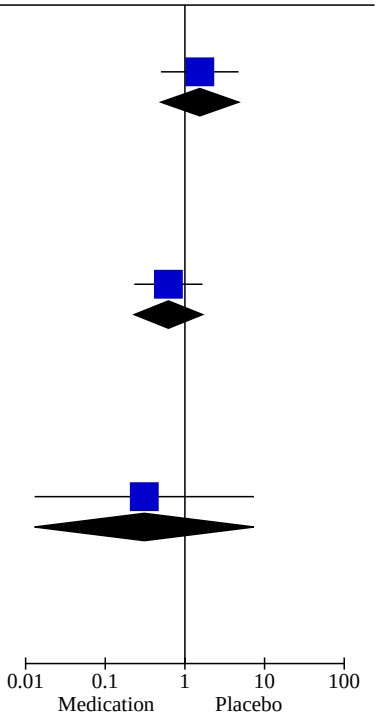
(1) Memamtine hydrochloride plus TAU versus placebo plus TAU

Comparison 3. Medications compared with placebo - non-serious adverse events - cardiovascular and respiratory system

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Antipsychotics	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1.1 Cold/flu symptoms	1	62	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.50, 4.73]
3.1.2 Nasopharyngitis	1	301	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.23, 1.66]
3.1.3 Sweating	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.36]
3.2 Antipsychotics	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.2.1 Diastolic blood pressure, standing, baseline to endpoint mean change	1	290	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-2.29, 1.73]
3.2.2 Diastolic blood pressure, supine, baseline to endpoint mean change	1	290	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-2.28, 2.06]
3.2.3 Systolic blood pressure, supine, baseline to endpoint mean change	1	290	Mean Difference (IV, Fixed, 95% CI)	-1.31 [-4.00, 1.38]
3.2.4 Systolic blood pressure, standing, baseline to endpoint mean change	1	290	Mean Difference (IV, Fixed, 95% CI)	0.35 [-2.39, 3.09]
3.2.5 Pulse, supine, baseline to endpoint mean change	1	290	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-2.28, 2.06]
3.2.6 Pulse, standing, baseline to endpoint mean change	1	290	Mean Difference (IV, Fixed, 95% CI)	0.85 [-1.65, 3.35]
3.3 Mood stabilisers	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.3.1 Blood and lymphatic system disorders	1	276	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.11, 3.99]
3.3.2 Cardiac disorders	1	276	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.23]
3.3.3 Endocrine disorders	1	276	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.23]
3.3.4 Respiratory, thoracic, and mediastinal disorders	1	276	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [0.83, 3.94]

Analysis 3.1. Comparison 3: Medications compared with placebo - non-serious adverse events - cardiovascular and respiratory system, Outcome 1: Antipsychotics

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Cold/flu symptoms						
Black 2014 (1)	7	33	4	29	100.0%	1.54 [0.50 , 4.73]
Subtotal (95% CI)		**33**		**29**	**100.0%**	**1.54 [0.50 , 4.73]**
Total events:	7		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.75 (P = 0.45)						
3.1.2 Nasopharyngitis						
Schulz 2007 (2)	6	148	10	153	100.0%	0.62 [0.23 , 1.66]
Subtotal (95% CI)		**148**		**153**	**100.0%**	**0.62 [0.23 , 1.66]**
Total events:	6		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.95 (P = 0.34)						
3.1.3 Sweating						
Grant 2022	0	40	1	37	100.0%	0.31 [0.01 , 7.36]
Subtotal (95% CI)		**40**		**37**	**100.0%**	**0.31 [0.01 , 7.36]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
Test for subgroup differences: Chi^2 = 1.85, df = 2 (P = 0.40), I^2 = 0%						



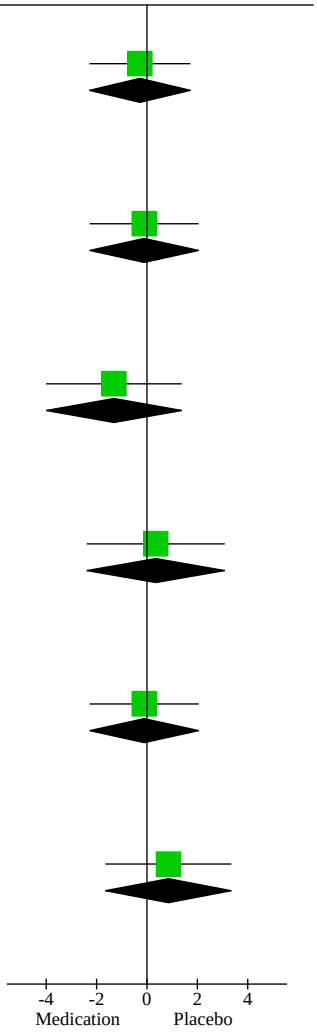
Footnotes

(1) Quetiapine plus placebo

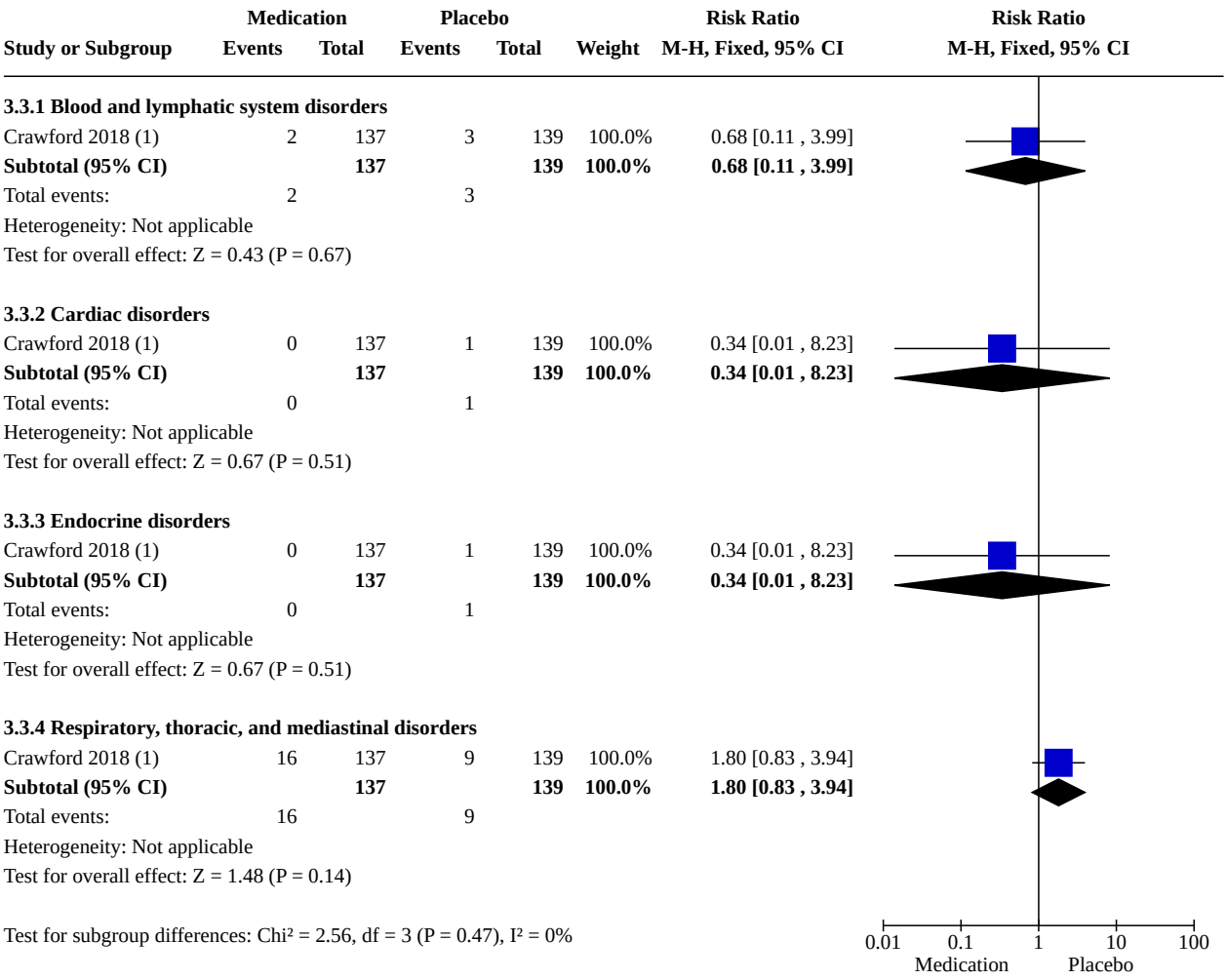
(2) Olanzapine versus placebo

Analysis 3.2. Comparison 3: Medications compared with placebo - non-serious adverse events - cardiovascular and respiratory system, Outcome 2: Antipsychotics

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
3.2.1 Diastolic blood pressure, standing, baseline to endpoint mean change								
Zanarini 2007	0.11	7.79	143	0.39	9.57	147	100.0%	-0.28 [-2.29 , 1.73]
Subtotal (95% CI)			**143**			**147**	**100.0%**	**-0.28 [-2.29 , 1.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.27 (P = 0.78)								
3.2.2 Diastolic blood pressure, supine, baseline to endpoint mean change								
Zanarini 2007	-0.21	8.61	143	-0.1	10.16	147	100.0%	-0.11 [-2.28 , 2.06]
Subtotal (95% CI)			**143**			**147**	**100.0%**	**-0.11 [-2.28 , 2.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.10 (P = 0.92)								
3.2.3 Systolic blood pressure, supine, baseline to endpoint mean change								
Zanarini 2007	-0.91	11.3	143	0.4	12.1	147	100.0%	-1.31 [-4.00 , 1.38]
Subtotal (95% CI)			**143**			**147**	**100.0%**	**-1.31 [-4.00 , 1.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.95 (P = 0.34)								
3.2.4 Systolic blood pressure, standing, baseline to endpoint mean change								
Zanarini 2007	0.69	11.37	143	0.34	12.42	147	100.0%	0.35 [-2.39 , 3.09]
Subtotal (95% CI)			**143**			**147**	**100.0%**	**0.35 [-2.39 , 3.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.25 (P = 0.80)								
3.2.5 Pulse, supine, baseline to endpoint mean change								
Zanarini 2007	-0.21	8.61	143	-0.1	10.16	147	100.0%	-0.11 [-2.28 , 2.06]
Subtotal (95% CI)			**143**			**147**	**100.0%**	**-0.11 [-2.28 , 2.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.10 (P = 0.92)								
3.2.6 Pulse, standing, baseline to endpoint mean change								
Zanarini 2007	1.5	11.5	143	0.65	10.14	147	100.0%	0.85 [-1.65 , 3.35]
Subtotal (95% CI)			**143**			**147**	**100.0%**	**0.85 [-1.65 , 3.35]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.67 (P = 0.50)								
Test for subgroup differences: Chi^2 = 1.47, df = 5 (P = 0.92), I^2 = 0%								



Analysis 3.3. Comparison 3: Medications compared with placebo - non-serious adverse events - cardiovascular and respiratory system, Outcome 3: Mood stabilisers



Footnotes

(1) Lamotrigine plus TAU versus placebo plus TAU

Comparison 4. Medications compared with placebo – non-serious adverse events - metabolic and gastro-intestinal system

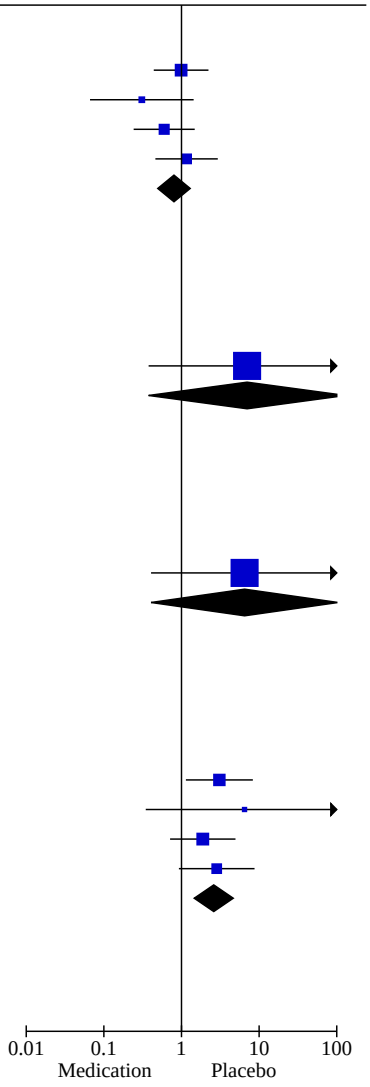
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Antipsychotics	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1.1 Nausea	4	754	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.49, 1.29]
4.1.2 Uneasy feeling	1	60	Risk Ratio (M-H, Random, 95% CI)	7.00 [0.38, 129.93]
4.1.3 Constipation	1	28	Risk Ratio (M-H, Random, 95% CI)	6.50 [0.41, 104.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1.4 Dry mouth	4	754	Risk Ratio (M-H, Random, 95% CI)	2.60 [1.46, 4.64]
4.2 Antipsychotics	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.2.1 liver function: ALT/SGPT baseline to endpoint mean change (U/L)	2	530	Std. Mean Difference (IV, Random, 95% CI)	0.46 [0.29, 0.63]
4.2.2 liver function: AST/SGOT baseline to endpoint mean change (U/L)	2	526	Std. Mean Difference (IV, Random, 95% CI)	0.35 [0.18, 0.52]
4.2.3 liver function: total bilirubin baseline to endpoint mean change (µmol/L)	1	264	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.53, -0.05]
4.2.4 liver function: direct bilirubin baseline to endpoint mean change (µmol/L)	1	258	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.60, -0.11]
4.2.5 liver function: GGT (GGPT/SGGT/YGGT) baseline to endpoint mean change	1	268	Std. Mean Difference (IV, Random, 95% CI)	0.26 [0.02, 0.50]
4.2.6 lipids: total cholesterol baseline to endpoint change (mmol/L)	2	327	Std. Mean Difference (IV, Random, 95% CI)	0.42 [0.20, 0.64]
4.2.7 lipids: LDL cholesterol baseline to endpoint mean change (mmol/L)	1	259	Std. Mean Difference (IV, Random, 95% CI)	0.35 [0.10, 0.59]
4.2.8 lipids: HDL cholesterol (dextran precip.) baseline to endpoint mean change (mmol/L)	1	269	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.52, -0.04]
4.2.9 lipids: triglycerides, fasting, baseline to endpoint mean change (mmol/L)	1	203	Std. Mean Difference (IV, Random, 95% CI)	0.37 [0.09, 0.64]
4.2.10 prolactin: baseline to endpoint mean change (µg/L)	1	259	Std. Mean Difference (IV, Random, 95% CI)	0.32 [0.07, 0.56]
4.2.11 platelet count baseline to endpoint mean change (GI/L)	2	517	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.53, 0.59]
4.2.12 erythrocyte count baseline to endpoint mean change (TI/L)	1	262	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.42, 0.06]
4.2.13 leukocyte count baseline to endpoint mean change (GI/L)	1	262	Std. Mean Difference (IV, Random, 95% CI)	-0.40 [-0.65, -0.16]
4.2.14 neutrophils, segmented, baseline to endpoint mean change (GI/L)	1	262	Std. Mean Difference (IV, Random, 95% CI)	-0.39 [-0.63, -0.14]
4.2.15 basophils baseline to endpoint mean change (GI/L)	1	262	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.53, -0.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2.16 monocytes baseline to endpoint mean change (GI/L)	1	262	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.53, -0.04]
4.2.17 haemoglobin baseline to endpoint mean change (mml/L-F)	1	262	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.45, 0.03]
4.2.18 mean cell haemoglobin concentration (MCHC) baseline to endpoint mean change (mml/L-F)	1	260	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.22, 0.27]
4.2.19 calcium baseline to endpoint mean change (mmol/L)	1	268	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.57, -0.09]
4.2.20 albumin baseline to endpoint mean change (g/L)	1	269	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.45, 0.03]
4.2.21 creatine phosphokinase baseline to endpoint mean change (U/L)	1	268	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.45, 0.03]
4.2.22 urea nitrogen baseline to endpoint mean change (mmol/L)	1	269	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.38, 0.10]
4.3 Mood stabilisers	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.3.1 gastrointestinal disorders	1	276	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.50, 0.98]
4.3.2 general disorders and administration site conditions	1	276	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.50, 2.05]
4.3.3 hepatobiliary disorders	1	276	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.13, 74.07]
4.3.4 metabolism and nutrition disorders	1	276	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.19, 22.12]
4.4 Memantine hydrochloride	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.4.1 constipation	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.59, 4.57]
4.4.2 nausea/vomiting	1	34	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.45, 2.23]

Analysis 4.1. Comparison 4: Medications compared with placebo – non-serious adverse events - metabolic and gastro-intestinal system, Outcome 1: Antipsychotics

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Nausea						
Black 2014 (1)	9	33	8	29	35.1%	0.99 [0.44 , 2.23]
Grant 2022	2	40	6	37	9.8%	0.31 [0.07 , 1.43]
Schulz 2007 (2)	7	155	12	159	28.2%	0.60 [0.24 , 1.48]
Zanarini 2007 (3)	9	148	8	153	27.0%	1.16 [0.46 , 2.93]
Subtotal (95% CI)		**376**		**378**	**100.0%**	**0.80 [0.49 , 1.29]**
Total events:	27		34			
Heterogeneity: Tau² = 0.00; Chi² = 2.79, df = 3 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.91 (P = 0.36)						
4.1.2 Uneasy feeling						
Pascual 2008 (4)	3	30	0	30	100.0%	7.00 [0.38 , 129.93]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**7.00 [0.38 , 129.93]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
4.1.3 Constipation						
Zanarini 2001 (2)	6	19	0	9	100.0%	6.50 [0.41 , 104.20]
Subtotal (95% CI)		**19**		**9**	**100.0%**	**6.50 [0.41 , 104.20]**
Total events:	6		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.32 (P = 0.19)						
4.1.4 Dry mouth						
Black 2014 (1)	14	33	4	29	33.9%	3.08 [1.14 , 8.30]
Grant 2022	3	40	0	37	3.9%	6.49 [0.35 , 121.52]
Schulz 2007 (2)	11	155	6	159	35.6%	1.88 [0.71 , 4.96]
Zanarini 2007 (2)	11	148	4	153	26.6%	2.84 [0.93 , 8.73]
Subtotal (95% CI)		**376**		**378**	**100.0%**	**2.60 [1.46 , 4.64]**
Total events:	39		14			
Heterogeneity: Tau² = 0.00; Chi² = 0.94, df = 3 (P = 0.82); I² = 0%						
Test for overall effect: Z = 3.24 (P = 0.001)						
Test for subgroup differences: Chi² = 11.95, df = 3 (P = 0.008), I² = 74.9%						



Footnotes

(1) Quetiapine versus placebo
(2) Olanzapine versus placebo
(3) Olanzpine versus placebo
(4) Ziprasidone versus placebo

Analysis 4.2. Comparison 4: Medications compared with placebo – non-serious adverse events - metabolic and gastro-intestinal system, Outcome 2: Antipsychotics

Study or Subgroup	Medication Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.2.1 liver function: ALT/SGPT baseline to endpoint mean change (U/L)								
Schulz 2007 (1)	5.33	21.14	131	-1.94	11.95	132	49.9%	0.42 [0.18 , 0.67]
Zanarini 2007	6.78	18.07	137	-0.45	9.22	130	50.1%	0.50 [0.26 , 0.74]
Subtotal (95% CI)			**268**			**262**	**100.0%**	**0.46 [0.29 , 0.63]**
Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.67); I² = 0%								
Test for overall effect: Z = 5.23 (P < 0.00001)								
4.2.2 liver function: AST/SGOT baseline to endpoint mean change (U/L)								
Schulz 2007 (1)	2.32	9.12	130	-1.07	6.91	131	49.3%	0.42 [0.17 , 0.66]
Zanarini 2007 (1)	2.83	11.59	135	0.14	6.5	130	50.7%	0.28 [0.04 , 0.53]
Subtotal (95% CI)			**265**			**261**	**100.0%**	**0.35 [0.18 , 0.52]**
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%								
Test for overall effect: Z = 3.98 (P < 0.0001)								
4.2.3 liver function: total bilirubin baseline to endpoint mean change (µmol/L)								
Schulz 2007 (1)	-0.87	3.69	132	0.11	3.06	132	100.0%	-0.29 [-0.53 , -0.05]
Subtotal (95% CI)			**132**			**132**	**100.0%**	**-0.29 [-0.53 , -0.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.33 (P = 0.02)								
4.2.4 liver function: direct bilirubin baseline to endpoint mean change (µmol/L)								
Schulz 2007 (1)	-0.27	0.94	128	0.03	0.74	130	100.0%	-0.35 [-0.60 , -0.11]
Subtotal (95% CI)			**128**			**130**	**100.0%**	**-0.35 [-0.60 , -0.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.82 (P = 0.005)								
4.2.5 liver function: GGT (GGPT/SGGT/YGGT) baseline to endpoint mean change								
Zanarini 2007	2.48	12.9	137	-0.48	9.89	131	100.0%	0.26 [0.02 , 0.50]
Subtotal (95% CI)			**137**			**131**	**100.0%**	**0.26 [0.02 , 0.50]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.09 (P = 0.04)								
4.2.6 lipids: total cholesterol baseline to endpoint change (mmol/L)								
Schulz 2007 (1)	0.17	0.74	134	-0.08	0.6	133	82.2%	0.37 [0.13 , 0.61]
Soler 2005 (1)	0.28	0.53	30	-0.1	0.65	30	17.8%	0.63 [0.11 , 1.15]
Subtotal (95% CI)			**164**			**163**	**100.0%**	**0.42 [0.20 , 0.64]**
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 1 (P = 0.37); I² = 0%								
Test for overall effect: Z = 3.72 (P = 0.0002)								
4.2.7 lipids: LDL cholesterol baseline to endpoint mean change (mmol/L)								
Schulz 2007 (1)	0.13	0.65	128	-0.08	0.55	131	100.0%	0.35 [0.10 , 0.59]
Subtotal (95% CI)			**128**			**131**	**100.0%**	**0.35 [0.10 , 0.59]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.78 (P = 0.005)								
4.2.8 lipids: HDL cholesterol (dextran precip.) baseline to endpoint mean change (mmol/L)								
Zanarini 2007 (1)	-0.04	0.2	137	0.02	0.23	132	100.0%	-0.28 [-0.52 , -0.04]
Subtotal (95% CI)			**137**			**132**	**100.0%**	**-0.28 [-0.52 , -0.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.27 (P = 0.02)								
4.2.9 lipids: triglycerides, fasting, baseline to endpoint mean change (mmol/L)								
Zanarini 2007 (1)	0.21	0.8	101	-0.06	0.66	102	100.0%	0.37 [0.09 , 0.64]
Subtotal (95% CI)			**101**			**102**	**100.0%**	**0.37 [0.09 , 0.64]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.59 (P = 0.010)								
4.2.10 prolactin: baseline to endpoint mean change (µg/L)								
Schulz 2007 (1)	7.75	27.96	129	0.65	14.82	130	100.0%	0.32 [0.07 , 0.56]
Subtotal (95% CI)			**129**			**130**	**100.0%**	**0.32 [0.07 , 0.56]**

Analysis 4.2. (Continued)

Schulz 2007 (1)	7.75	27.96	129	0.65	14.82	130	100.0%	0.32 [0.07 , 0.56]
Subtotal (95% CI)			**129**			**130**	**100.0%**	**0.32 [0.07 , 0.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.53 (P = 0.01)								
4.2.11 platelet count baseline to endpoint mean change (GI/L)								
Schulz 2007 (1)	1.04	41.99	129	-12.56	43.46	128	50.0%	0.32 [0.07 , 0.56]
Zanarini 2007 (1)	-6.44	41.1	131	4.01	40.54	129	50.0%	-0.26 [-0.50 , -0.01]
Subtotal (95% CI)			**260**			**257**	**100.0%**	**0.03 [-0.53 , 0.59]**
Heterogeneity: Tau² = 0.15; Chi² = 10.48, df = 1 (P = 0.001); I² = 90%								
Test for overall effect: Z = 0.11 (P = 0.91)								
4.2.12 erythrocyte count baseline to endpoint mean change (TI/L)								
Zanarini 2007	0.02	0.26	132	0.07	0.29	130	100.0%	-0.18 [-0.42 , 0.06]
Subtotal (95% CI)			**132**			**130**	**100.0%**	**-0.18 [-0.42 , 0.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.46 (P = 0.14)								
4.2.13 leukocyte count baseline to endpoint mean change (GI/L)								
Zanarini 2007	-0.58	1.69	132	0.12	1.77	130	100.0%	-0.40 [-0.65 , -0.16]
Subtotal (95% CI)			**132**			**130**	**100.0%**	**-0.40 [-0.65 , -0.16]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.23 (P = 0.001)								
4.2.14 neutrophils, segmented, baseline to endpoint mean change (GI/L)								
Zanarini 2007	-0.51	1.57	132	0.09	1.52	130	100.0%	-0.39 [-0.63 , -0.14]
Subtotal (95% CI)			**132**			**130**	**100.0%**	**-0.39 [-0.63 , -0.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.10 (P = 0.002)								
4.2.15 basophils baseline to endpoint mean change (GI/L)								
Zanarini 2007	-0.01	0.03	132	0	0.04	130	100.0%	-0.28 [-0.53 , -0.04]
Subtotal (95% CI)			**132**			**130**	**100.0%**	**-0.28 [-0.53 , -0.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.27 (P = 0.02)								
4.2.16 monocytes baseline to endpoint mean change (GI/L)								
Zanarini 2007	-0.03	0.16	132	0.01	0.12	130	100.0%	-0.28 [-0.53 , -0.04]
Subtotal (95% CI)			**132**			**130**	**100.0%**	**-0.28 [-0.53 , -0.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.27 (P = 0.02)								
4.2.17 haemoglobin baseline to endpoint mean change (mml/L-F)								
Zanarini 2007	-0.08	0.55	132	0.03	0.5	130	100.0%	-0.21 [-0.45 , 0.03]
Subtotal (95% CI)			**132**			**130**	**100.0%**	**-0.21 [-0.45 , 0.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.68 (P = 0.09)								
4.2.18 mean cell haemoglobin concentration (MCHC) baseline to endpoint mean change (mml/L-F)								
Zanarini 2007	-0.23	0.75	130	-0.25	0.81	130	100.0%	0.03 [-0.22 , 0.27]
Subtotal (95% CI)			**130**			**130**	**100.0%**	**0.03 [-0.22 , 0.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.21 (P = 0.84)								
4.2.19 calcium baseline to endpoint mean change (mmol/L)								
Schulz 2007 (1)	-0.03	0.09	134	0	0.09	134	100.0%	-0.33 [-0.57 , -0.09]
Subtotal (95% CI)			**134**			**134**	**100.0%**	**-0.33 [-0.57 , -0.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.70 (P = 0.007)								
4.2.20 albumin baseline to endpoint mean change (g/L)								
Zanarini 2007	-1.15	2.88	137	-0.48	3.34	132	100.0%	-0.21 [-0.45 , 0.03]
Subtotal (95% CI)			**137**			**132**	**100.0%**	**-0.21 [-0.45 , 0.03]**

Analysis 4.2. (Continued)

4.2.20 albumin baseline to endpoint mean change (g/L)

Zanarini 2007	-1.15	2.88	137	-0.48	3.34	132	100.0%	-0.21 [-0.45 , 0.03]
Subtotal (95% CI)			**137**			**132**	**100.0%**	**-0.21 [-0.45 , 0.03]**

Heterogeneity: Not applicable

Test for overall effect: Z = 1.75 (P = 0.08)

4.2.21 creatine phosphokinase baseline to endpoint mean change (U/L)

Zanarini 2007	-29.73	253.29	137	15.08	160.96	131	100.0%	-0.21 [-0.45 , 0.03]
Subtotal (95% CI)			**137**			**131**	**100.0%**	**-0.21 [-0.45 , 0.03]**

Heterogeneity: Not applicable

Test for overall effect: Z = 1.71 (P = 0.09)

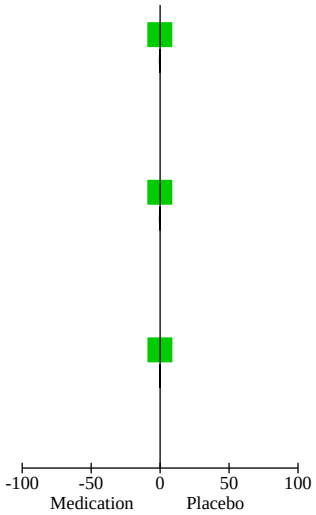
4.2.22 urea nitrogen baseline to endpoint mean change (mmol/L)

Zanarini 2007	-0.21	1.17	137	-0.04	1.24	132	100.0%	-0.14 [-0.38 , 0.10]
Subtotal (95% CI)			**137**			**132**	**100.0%**	**-0.14 [-0.38 , 0.10]**

Heterogeneity: Not applicable

Test for overall effect: Z = 1.15 (P = 0.25)

Test for subgroup differences: $Chi^2 = 150.76$, df = 21 (P < 0.00001), $I^2 = 86.1\%$

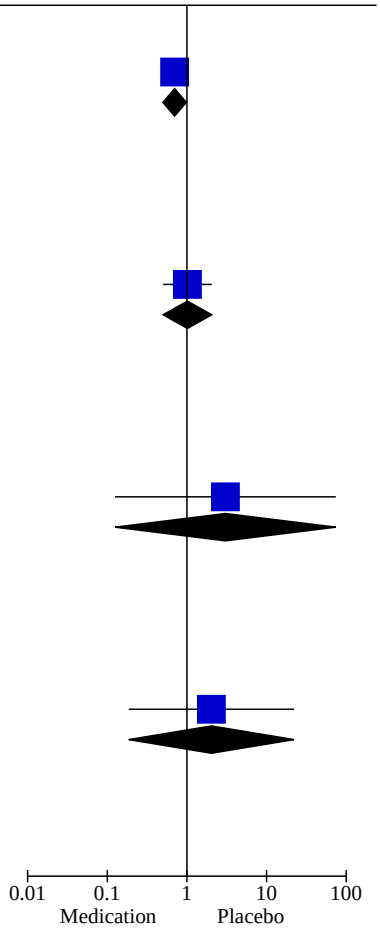


Footnotes

(1) Olanzapine versus placebo

Analysis 4.3. Comparison 4: Medications compared with placebo – non-serious adverse events - metabolic and gastro-intestinal system, Outcome 3: Mood stabilisers

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 gastrointestinal disorders						
Crawford 2018 (1)	38	137	55	139	100.0%	0.70 [0.50 , 0.98]
Subtotal (95% CI)		**137**		**139**	**100.0%**	**0.70 [0.50 , 0.98]**
Total events:	38		55			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.05 (P = 0.04)						
4.3.2 general disorders and administration site conditions						
Crawford 2018 (1)	14	137	14	139	100.0%	1.01 [0.50 , 2.05]
Subtotal (95% CI)		**137**		**139**	**100.0%**	**1.01 [0.50 , 2.05]**
Total events:	14		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.04 (P = 0.97)						
4.3.3 hepatobiliary disorders						
Crawford 2018 (1)	1	137	0	139	100.0%	3.04 [0.13 , 74.07]
Subtotal (95% CI)		**137**		**139**	**100.0%**	**3.04 [0.13 , 74.07]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.49)						
4.3.4 metabolism and nutrition disorders						
Crawford 2018 (1)	2	137	1	139	100.0%	2.03 [0.19 , 22.12]
Subtotal (95% CI)		**137**		**139**	**100.0%**	**2.03 [0.19 , 22.12]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
Test for subgroup differences: Chi² = 2.23, df = 3 (P = 0.53), I² = 0%						

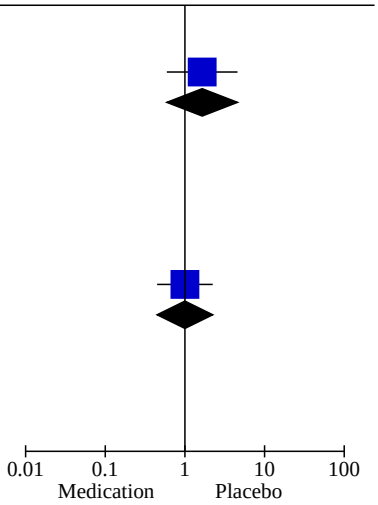


Footnotes

(1) Lamotrigine plus TAU versus placebo plus TAU

Analysis 4.4. Comparison 4: Medications compared with placebo – non-serious adverse events - metabolic and gastro-intestinal system, Outcome 4: Memantine hydrochloride

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.4.1 constipation						
Kulkarni 2018 (1)	7	17	4	16	100.0%	1.65 [0.59 , 4.57]
Subtotal (95% CI)		**17**		**16**	**100.0%**	**1.65 [0.59 , 4.57]**
Total events:	7		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						
4.4.2 nausea/vomiting						
Kulkarni 2018 (1)	7	17	7	17	100.0%	1.00 [0.45 , 2.23]
Subtotal (95% CI)		**17**		**17**	**100.0%**	**1.00 [0.45 , 2.23]**
Total events:	7		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Chi^2 = 0.57, df = 1 (P = 0.45), I^2 = 0%						



Footnotes

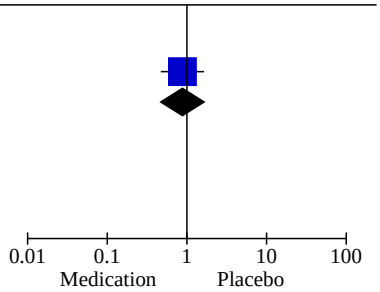
(1) Memamtine hydrochloride plus TAU versus placebo plus TAU

Comparison 5. Medications compared with placebo - non-serious adverse events - musculoskeletal system

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Antipsychotics	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1.1 Bodily pain	1	62	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.47, 1.64]
5.2 Antipsychotics	7	810	Std. Mean Difference (IV, Random, 95% CI)	0.78 [0.44, 1.12]
5.2.1 Body weight change	7	810	Std. Mean Difference (IV, Random, 95% CI)	0.78 [0.44, 1.12]
5.3 Antidepressants	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.3.1 Body weight change	1	62	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.31, 0.49]
5.4 Mood stabilisers	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.4.1 Musculoskeletal and connective tissue disorders	1	276	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.43, 3.11]
5.5 Mood stabilisers	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.5.1 Body weight change	5	184	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.72, 0.20]

Analysis 5.1. Comparison 5: Medications compared with placebo - non-serious adverse events - musculoskeletal system, Outcome 1: Antipsychotics

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.1.1 Bodily pain						
Black 2014 (1)	12	33	12	29	100.0%	0.88 [0.47 , 1.64]
Subtotal (95% CI)		**33**		**29**	**100.0%**	**0.88 [0.47 , 1.64]**
Total events:	12		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
Test for subgroup differences: Not applicable						

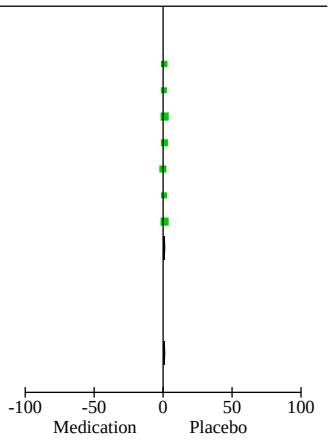


Footnotes

(1) Quetapine versus placebo

Analysis 5.2. Comparison 5: Medications compared with placebo - non-serious adverse events - musculoskeletal system, Outcome 2: Antipsychotics

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.2.1 Body weight change								
Bogenschutz 2004 (1)	3.71	3.4	16	0.08	4.8	19	11.5%	0.84 [0.14 , 1.54]
Linehan 2008 (1)	1.043	2.223	12	-1.315	4.853	12	9.6%	0.60 [-0.22 , 1.42]
Schulz 2007 (1)	2.86	3.02	155	-0.35	2.68	159	20.2%	1.12 [0.88 , 1.36]
Soler 2005 (1)	2.74	3.2	30	-0.05	2.39	30	14.3%	0.98 [0.44 , 1.51]
Soloff 1993 (2)	0.28	0.66	30	0.41	0.76	28	14.7%	-0.18 [-0.70 , 0.34]
Zanarini 2001 (1)	1.29	2.56	19	-0.35	1.17	9	9.7%	0.72 [-0.10 , 1.53]
Zanarini 2007 (1)	3.17	3.28	144	0.02	2.47	147	20.1%	1.08 [0.84 , 1.33]
Subtotal (95% CI)			**406**			**404**	**100.0%**	**0.78 [0.44 , 1.12]**
Heterogeneity: Tau² = 0.13; Chi² = 22.68, df = 6 (P = 0.0009); I² = 74%								
Test for overall effect: Z = 4.54 (P < 0.00001)								
Total (95% CI)			**406**			**404**	**100.0%**	**0.78 [0.44 , 1.12]**
Heterogeneity: Tau² = 0.13; Chi² = 22.68, df = 6 (P = 0.0009); I² = 74%								
Test for overall effect: Z = 4.54 (P < 0.00001)								
Test for subgroup differences: Not applicable								

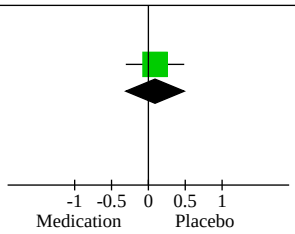


Footnotes

(1) Olanzapine versus placebo
(2) Haloperidol versus placebo

Analysis 5.3. Comparison 5: Medications compared with placebo - non-serious adverse events - musculoskeletal system, Outcome 3: Antidepressants

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
5.3.1 Body weight change								
Soloff 1993 (1)	0.5	0.83	34	0.41	0.76	28	100.0%	0.09 [-0.31 , 0.49]
Subtotal (95% CI)			**34**			**28**	**100.0%**	**0.09 [-0.31 , 0.49]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.45 (P = 0.66)								
Test for subgroup differences: Not applicable								

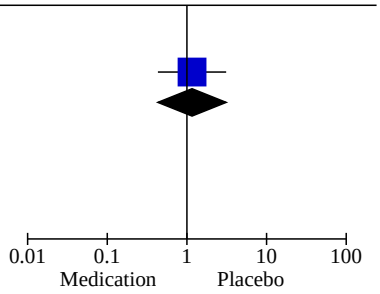


Footnotes

(1) Phenelzine sulfate versus placebo

Analysis 5.4. Comparison 5: Medications compared with placebo - non-serious adverse events - musculoskeletal system, Outcome 4: Mood stabilisers

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.4.1 Musculoskeletal and connective tissue disorders						
Crawford 2018 (1)	8	137	7	139	100.0%	1.16 [0.43 , 3.11]
Subtotal (95% CI)		**137**		**139**	**100.0%**	**1.16 [0.43 , 3.11]**
Total events:	8		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
Test for subgroup differences: Not applicable						

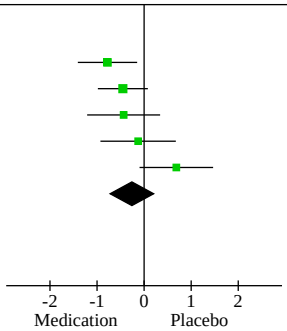


Footnotes

(1) Lamotrigine plus TAU versus placebo plus TAU

Analysis 5.5. Comparison 5: Medications compared with placebo - non-serious adverse events - musculoskeletal system, Outcome 5: Mood stabilisers

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.5.1 Body weight change								
Nickel 2005 (1)	82.3	3.9	22	86.5	6.5	20	21.8%	-0.78 [-1.41 , -0.15]
Loew 2006 (1)	72.8	11.3	28	78.5	13.5	28	24.7%	-0.45 [-0.98 , 0.08]
Nickel 2004 (1)	68.7	9.9	19	73.1	9.7	10	18.1%	-0.43 [-1.21 , 0.34]
Tritt 2005 (2)	75.3	9.2	18	76.6	11.3	9	17.5%	-0.13 [-0.93 , 0.67]
Frankenburg 2002 (3)	1.78	2.54	20	0.14	1.81	10	17.9%	0.68 [-0.10 , 1.47]
Subtotal (95% CI)			**107**			**77**	**100.0%**	**-0.26 [-0.72 , 0.20]**
Heterogeneity: Tau² = 0.15; Chi² = 8.91, df = 4 (P = 0.06); I² = 55%								
Test for overall effect: Z = 1.10 (P = 0.27)								
Test for subgroup differences: Not applicable								



Footnotes

(1) Topiramate versus placebo
(2) Lamotrigine versus placebo
(3) Valproate semisodium versus placebo

Comparison 6. Medications compared with placebo - non-serious adverse events - sensory system

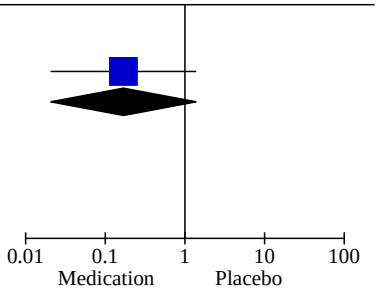
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Mood stabilisers	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1.1 Eye disorders	1	276	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.02, 1.39]

Analysis 6.1. Comparison 6: Medications compared with placebo - non-serious adverse events - sensory system, Outcome 1: Mood stabilisers

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.1.1 Eye disorders						
Crawford 2018 (1)	1	137	6	139	100.0%	0.17 [0.02 , 1.39]
Subtotal (95% CI)		**137**		**139**	**100.0%**	**0.17 [0.02 , 1.39]**
Total events:	1		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.66 (P = 0.10)

Test for subgroup differences: Not applicable

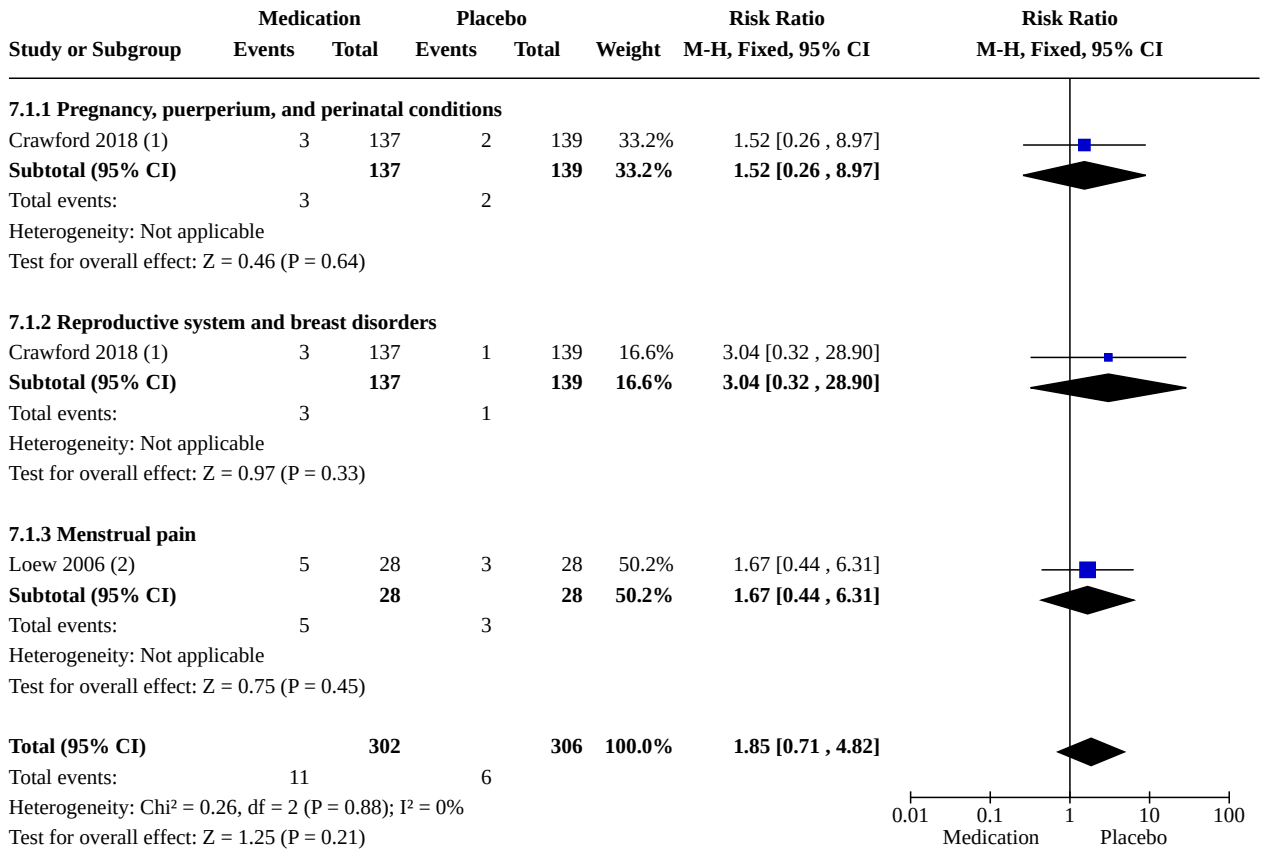


Footnotes
(1) Lamotrigine plus TAU versus placebo plus TAU

Comparison 7. Medications compared with placebo - non-serious adverse events - reproductive system

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Mood stabilisers	2	608	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [0.71, 4.82]
7.1.1 Pregnancy, puerperium, and perinatal conditions	1	276	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.26, 8.97]
7.1.2 Reproductive system and breast disorders	1	276	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.32, 28.90]
7.1.3 Menstrual pain	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.44, 6.31]

Analysis 7.1. Comparison 7: Medications compared with placebo - non-serious adverse events - reproductive system, Outcome 1: Mood stabilisers



Footnotes

(1) Lamotrigine plus TAU versus placebo plus TAU

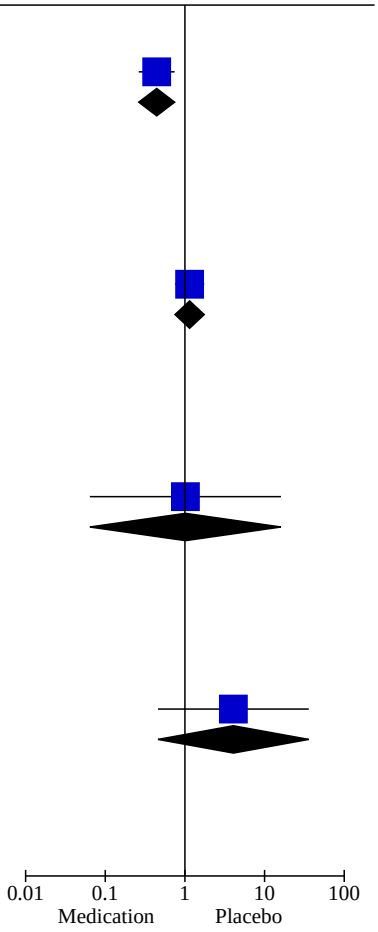
(2) Topiramate versus placebo

Comparison 8. Medications compared with placebo - non-serious adverse events - other

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Mood stabilisers	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1.1 Injury, poisoning, and procedural complications	1	276	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.26, 0.74]
8.1.2 Skin and subcutaneous tissue disorder	1	276	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.75, 1.75]
8.1.3 Social circumstances	1	276	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.06, 16.06]
8.1.4 Surgical and medical procedures	1	276	Risk Ratio (M-H, Fixed, 95% CI)	4.06 [0.46, 35.85]

Analysis 8.1. Comparison 8: Medications compared with placebo - non-serious adverse events - other, Outcome 1: Mood stabilisers

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.1.1 Injury, poisoning, and procedural complications						
Crawford 2018 (1)	17	137	39	139	100.0%	0.44 [0.26 , 0.74]
Subtotal (95% CI)		**137**		**139**	**100.0%**	**0.44 [0.26 , 0.74]**
Total events:	17		39			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.08 (P = 0.002)						
8.1.2 Skin and subcutaneous tissue disorder						
Crawford 2018 (1)	35	137	31	139	100.0%	1.15 [0.75 , 1.75]
Subtotal (95% CI)		**137**		**139**	**100.0%**	**1.15 [0.75 , 1.75]**
Total events:	35		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
8.1.3 Social circumstances						
Crawford 2018 (1)	1	137	1	139	100.0%	1.01 [0.06 , 16.06]
Subtotal (95% CI)		**137**		**139**	**100.0%**	**1.01 [0.06 , 16.06]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
8.1.4 Surgical and medical procedures						
Crawford 2018 (1)	4	137	1	139	100.0%	4.06 [0.46 , 35.85]
Subtotal (95% CI)		**137**		**139**	**100.0%**	**4.06 [0.46 , 35.85]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.26 (P = 0.21)						
Test for subgroup differences: Chi^2 = 9.95, df = 3 (P = 0.02), I^2 = 69.9%						



Footnotes

(1) Lamotrigine plus TAU versus placebo plus TAU

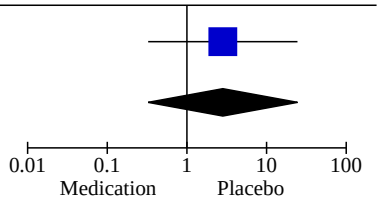
Comparison 9. Medications compared with placebo - withdrew due to adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Memantine hydrochloride	1	33	Risk Ratio (M-H, Fixed, 95% CI)	2.82 [0.33, 24.43]

Analysis 9.1. Comparison 9: Medications compared with placebo - withdrew due to adverse events, Outcome 1: Memantine hydrochloride

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kulkarni 2018 (1)	3	17	1	16	100.0%	2.82 [0.33 , 24.43]
Total (95% CI)		**17**		**16**	**100.0%**	**2.82 [0.33 , 24.43]**
Total events:	3		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable



Footnotes
(1) Memantine hydrochloride plus TAU versus placebo plus TAU

Comparison 10. Single medication compared with alternate single medication

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Primary: BPD symptom severity at end of treatment (continuous outcomes, MDs)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1.1 Olanzapine versus asenapine	1	51	Mean Difference (IV, Fixed, 95% CI)	-2.23 [-8.04, 3.58]
10.1.2 Haloperidol versus phenelzine sulfate	1	64	Mean Difference (IV, Fixed, 95% CI)	5.73 [-0.33, 11.79]
10.1.3 Alprazolam versus carbamazepine	1	27	Mean Difference (IV, Fixed, 95% CI)	-1.64 [-2.71, -0.57]
10.1.4 Alprazolam versus trifluoperazine hydrochloride	1	22	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-2.21, 0.61]
10.1.5 Alprazolam versus tranylcypromine sulfate	1	24	Mean Difference (IV, Fixed, 95% CI)	-1.58 [-2.76, -0.40]
10.1.6 Carbamazepine versus trifluoperazine hydrochloride	1	25	Mean Difference (IV, Fixed, 95% CI)	0.84 [-0.41, 2.09]
10.1.7 Carbamazepine versus tranylcypromine sulfate	1	27	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.92, 1.04]
10.1.8 Trifluoperazine hydrochloride versus tranylcypromine sulfate	1	22	Mean Difference (IV, Fixed, 95% CI)	-0.78 [-2.13, 0.57]
10.2 Primary: Self-harm at end of treatment (continuous outcomes, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.2.1 Olanzapine versus asenapine	1	51	Mean Difference (IV, Fixed, 95% CI)	0.21 [-0.58, 1.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.3 Primary: Suicide-related outcomes at end of treatment (continuous outcomes, MDs)	1	147	Mean Difference (IV, Fixed, 95% CI)	1.01 [0.54, 1.47]
10.3.1 Alprazolam versus carbamazepine	1	27	Mean Difference (IV, Fixed, 95% CI)	2.12 [1.06, 3.18]
10.3.2 Alprazolam versus trifluoperazine hydrochloride	1	22	Mean Difference (IV, Fixed, 95% CI)	1.73 [0.62, 2.84]
10.3.3 Alprazolam versus tranylcypromine sulfate	1	24	Mean Difference (IV, Fixed, 95% CI)	2.00 [0.89, 3.11]
10.3.4 Carbamazepine versus trifluoperazine hydrochloride	1	25	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-1.53, 0.75]
10.3.5 Carbamazepine versus tranylcypromine sulfate	1	27	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-1.26, 1.02]
10.3.6 Trifluoperazine hydrochloride versus tranylcypromine sulfate	1	22	Mean Difference (IV, Fixed, 95% CI)	0.27 [-1.00, 1.54]
10.4 Primary: Psychosocial functioning (continuous outcomes, MDs)	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.4.1 Olanzapine versus asenapine	1	51	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.23, 0.63]
10.4.2 Olanzapine versus haloperidol	1	28	Mean Difference (IV, Fixed, 95% CI)	0.35 [-0.45, 1.15]
10.4.3 Olanzapine versus aripiprazole	1	24	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.58, 0.82]
10.4.4 Haloperidol versus amitriptyline	1	57	Mean Difference (IV, Fixed, 95% CI)	-3.87 [-10.67, 2.93]
10.4.5 Haloperidol versus phenelzine sulfate	1	64	Mean Difference (IV, Fixed, 95% CI)	5.15 [0.29, 10.01]
10.5 Secondary: Anger at end of treatment (continuous outcomes, MDs)	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.5.1 Olanzapine versus asenapine	1	51	Mean Difference (IV, Fixed, 95% CI)	1.14 [0.31, 1.97]
10.5.2 Olanzapine versus haloperidol	1	28	Mean Difference (IV, Fixed, 95% CI)	0.21 [-8.90, 9.32]
10.5.3 Olanzapine versus aripiprazole	1	24	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-8.05, 7.25]
10.5.4 Olanzapine versus sertraline	1	120	Mean Difference (IV, Fixed, 95% CI)	-0.33 [-0.48, -0.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.5.5 Haloperidol versus amitriptyline	1	57	Mean Difference (IV, Fixed, 95% CI)	-0.34 [-0.82, 0.14]
10.5.6 Haloperidol versus phenelzine sulfate	1	64	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.31, 0.43]
10.5.7 Alprazolam versus carbamazepine	1	27	Mean Difference (IV, Fixed, 95% CI)	1.65 [0.80, 2.50]
10.5.8 Alprazolam versus trifluoperazine hydrochloride	1	22	Mean Difference (IV, Fixed, 95% CI)	0.58 [-0.77, 1.93]
10.5.9 Alprazolam versus tranylcypromine sulfate	1	24	Mean Difference (IV, Fixed, 95% CI)	1.41 [0.24, 2.58]
10.5.10 Carbamazepine versus trifluoperazine hydrochloride	1	25	Mean Difference (IV, Fixed, 95% CI)	-1.07 [-2.28, 0.14]
10.5.11 Carbamazepine versus tranylcypromine sulfate	1	27	Mean Difference (IV, Fixed, 95% CI)	-0.24 [-1.23, 0.75]
10.5.12 Trifluoperazine hydrochloride versus tranylcypromine sulfate	1	22	Mean Difference (IV, Fixed, 95% CI)	0.83 [-0.62, 2.28]
10.6 Secondary: Affective instability at end of treatment (continuous outcomes, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.6.1 Olanzapine versus asenapine	1	51	Mean Difference (IV, Fixed, 95% CI)	2.28 [1.51, 3.05]
10.7 Secondary: Chronic feelings of emptiness at end of treatment (continuous outcomes, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.7.1 Olanzapine versus asenapine	1	51	Mean Difference (IV, Fixed, 95% CI)	-0.54 [-1.29, 0.21]
10.8 Secondary: Impulsivity at end of treatment (continuous outcomes, MDs)	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.8.1 Olanzapine versus asenapine	1	51	Mean Difference (IV, Fixed, 95% CI)	-0.78 [-1.59, 0.03]
10.8.2 Haloperidol versus amitriptyline	1	57	Mean Difference (IV, Fixed, 95% CI)	3.52 [-5.52, 12.56]
10.8.3 Haloperidol versus phenelzine sulfate	1	64	Mean Difference (IV, Fixed, 95% CI)	3.29 [-14.52, 21.10]
10.8.4 Olanzapine versus fluoxetine	1	29	Mean Difference (IV, Fixed, 95% CI)	-4.31 [-19.72, 11.10]
10.8.5 Alprazolam versus carbamazepine	1	27	Mean Difference (IV, Fixed, 95% CI)	2.18 [1.20, 3.16]

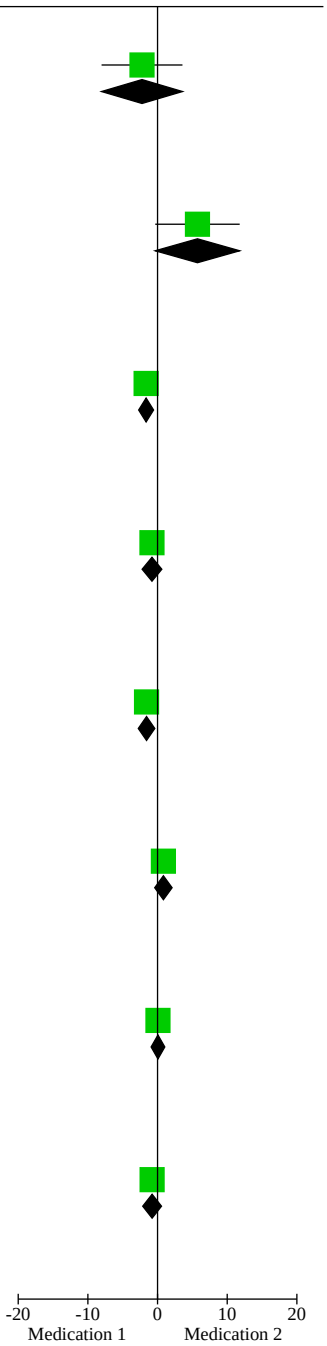
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.8.6 Alprazolam versus trifluoperazine hydrochloride	1	22	Mean Difference (IV, Fixed, 95% CI)	0.45 [-0.87, 1.77]
10.8.7 Alprazolam versus tranylcypromine sulfate	1	24	Mean Difference (IV, Fixed, 95% CI)	1.83 [0.66, 3.00]
10.8.8 Carbamazepine versus trifluoperazine hydrochloride	1	25	Mean Difference (IV, Fixed, 95% CI)	-1.73 [-2.87, -0.59]
10.8.9 Carbamazepine versus tranylcypromine sulfate	1	27	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-1.31, 0.61]
10.8.10 Trifluoperazine hydrochloride versus tranylcypromine sulfate	1	22	Mean Difference (IV, Fixed, 95% CI)	1.38 [0.08, 2.68]
10.9 Secondary: Interpersonal problems at end of treatment (continuous outcomes, MDs)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.9.1 Olanzapine versus asenapine	1	51	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.35, 1.15]
10.9.2 Haloperidol versus amitriptyline	1	57	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.62, 0.36]
10.9.3 Haloperidol versus phenelzine sulfate	1	64	Mean Difference (IV, Fixed, 95% CI)	-0.33 [-0.68, 0.02]
10.10 Secondary: Abandonment at end of treatment (continuous outcomes, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.10.1 Olanzapine versus asenapine	1	51	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.07, 0.27]
10.11 Secondary: Identity disturbance at end of treatment (continuous outcomes, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.11.1 Olanzapine versus asenapine	1	51	Mean Difference (IV, Fixed, 95% CI)	0.68 [-0.12, 1.48]
10.12 Secondary: Dissociation and psychotic-like symptoms at end of treatment (continuous outcomes, MDs)	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.12.1 Olanzapine versus asenapine	1	51	Mean Difference (IV, Fixed, 95% CI)	-0.69 [-1.53, 0.15]
10.12.2 Olanzapine versus haloperidol	1	28	Mean Difference (IV, Fixed, 95% CI)	-2.30 [-10.15, 5.55]
10.12.3 Olanzapine versus aripiprazole	1	24	Mean Difference (IV, Fixed, 95% CI)	-3.30 [-10.63, 4.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.12.4 Haloperidol versus amitriptyline	1	57	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.69, 0.13]
10.12.5 Haloperidol versus phenelzine sulfate	1	64	Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.31, 0.59]
10.13 Secondary: Depression at end of treatment (continuous outcomes, MDs)	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.13.1 Olanzapine versus asenapine	1	51	Mean Difference (IV, Fixed, 95% CI)	2.90 [0.88, 4.92]
10.13.2 Olanzapine versus sertraline	1	120	Mean Difference (IV, Fixed, 95% CI)	0.37 [0.22, 0.52]
10.13.3 Haloperidol versus amitriptyline	1	57	Mean Difference (IV, Fixed, 95% CI)	0.88 [-5.12, 6.88]
10.13.4 Haloperidol versus phenelzine sulfate	1	64	Mean Difference (IV, Fixed, 95% CI)	7.81 [2.13, 13.49]
10.13.5 Olanzapine versus fluoxetine	1	29	Mean Difference (IV, Fixed, 95% CI)	-5.40 [-10.68, -0.12]
10.13.6 Alprazolam versus carbamazepine	1	27	Mean Difference (IV, Fixed, 95% CI)	1.36 [0.37, 2.35]
10.13.7 Alprazolam versus trifluoperazine hydrochloride	1	22	Mean Difference (IV, Fixed, 95% CI)	0.90 [-0.49, 2.29]
10.13.8 Alprazolam versus tranylcypromine sulfate	1	24	Mean Difference (IV, Fixed, 95% CI)	1.67 [0.48, 2.86]
10.13.9 Carbamazepine versus trifluoperazine hydrochloride	1	25	Mean Difference (IV, Fixed, 95% CI)	-0.46 [-1.81, 0.89]
10.13.10 Carbamazepine versus tranylcypromine sulfate	1	27	Mean Difference (IV, Fixed, 95% CI)	0.31 [-0.82, 1.44]
10.13.11 Trifluoperazine hydrochloride versus tranylcypromine sulfate	1	22	Mean Difference (IV, Fixed, 95% CI)	0.77 [-0.73, 2.27]
10.14 Secondary: Attrition at end of treatment (dichotomous outcomes, RRs)	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.14.1 Olanzapine versus asenapine	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.28, 2.29]
10.14.2 Olanzapine versus haloperidol	1	28	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.14.3 Olanzapine versus aripiprazole	1	24	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.14.4 Loxapine versus chlorpromazine	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.46, 2.85]
10.14.5 Olanzapine versus sertraline	1	120	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.14.6 Olanzapine versus fluoxetine	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.01, 6.69]
10.14.7 Haloperidol versus phenelzine sulfate	1	74	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.49, 5.15]
10.14.8 Haloperidol versus amitriptyline	1	61	Risk Ratio (M-H, Fixed, 95% CI)	2.90 [0.32, 26.38]
10.15 Secondary: Adverse events at end of treatment (dichotomous outcomes, RRs)	3	132	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.64, 1.45]
10.15.1 Adverse events total: olanzapine versus haloperidol	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.35, 1.60]
10.15.2 Adverse events total: olanzapine versus aripiprazole	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.38, 1.50]
10.15.3 Adverse events total: loxapine versus chlorpromazine	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.66, 2.45]

Analysis 10.1. Comparison 10: Single medication compared with alternate single medication , Outcome 1: Primary: BPD symptom severity at end of treatment (continuous outcomes, MDs)

Study or Subgroup	Medication 1 Mean	SD	Total	Medication 2 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
10.1.1 Olanzapine versus asenapine								
Bozzatello 2017 (1)	49.12	11.73	26	51.35	9.33	25	100.0%	-2.23 [-8.04 , 3.58]
Subtotal (95% CI)			**26**			**25**	**100.0%**	**-2.23 [-8.04 , 3.58]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.75 (P = 0.45)								
10.1.2 Haloperidol versus phenelzine sulfate								
Soloff 1993 (2)	24.03	13.24	30	18.3	11.24	34	100.0%	5.73 [-0.33 , 11.79]
Subtotal (95% CI)			**30**			**34**	**100.0%**	**5.73 [-0.33 , 11.79]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.85 (P = 0.06)								
10.1.3 Alprazolam versus carbamazepine								
Cowdry 1988 (3)	3.5	1.57	12	5.14	1.17	15	100.0%	-1.64 [-2.71 , -0.57]
Subtotal (95% CI)			**12**			**15**	**100.0%**	**-1.64 [-2.71 , -0.57]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.01 (P = 0.003)								
10.1.4 Alprazolam versus trifluoperazine hydrochloride								
Cowdry 1988 (4)	3.5	1.57	12	4.3	1.77	10	100.0%	-0.80 [-2.21 , 0.61]
Subtotal (95% CI)			**12**			**10**	**100.0%**	**-0.80 [-2.21 , 0.61]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.11 (P = 0.27)								
10.1.5 Alprazolam versus tranylcypromine sulfate								
Cowdry 1988 (5)	3.5	1.57	12	5.08	1.38	12	100.0%	-1.58 [-2.76 , -0.40]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**-1.58 [-2.76 , -0.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.62 (P = 0.009)								
10.1.6 Carbamazepine versus trifluoperazine hydrochloride								
Cowdry 1988 (6)	5.14	1.17	15	4.3	1.77	10	100.0%	0.84 [-0.41 , 2.09]
Subtotal (95% CI)			**15**			**10**	**100.0%**	**0.84 [-0.41 , 2.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.32 (P = 0.19)								
10.1.7 Carbamazepine versus tranylcypromine sulfate								
Cowdry 1988 (7)	5.14	1.17	15	5.08	1.38	12	100.0%	0.06 [-0.92 , 1.04]
Subtotal (95% CI)			**15**			**12**	**100.0%**	**0.06 [-0.92 , 1.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.12 (P = 0.90)								
10.1.8 Trifluoperazine hydrochloride versus tranylcypromine sulfate								
Cowdry 1988 (8)	4.3	1.77	10	5.08	1.38	12	100.0%	-0.78 [-2.13 , 0.57]
Subtotal (95% CI)			**10**			**12**	**100.0%**	**-0.78 [-2.13 , 0.57]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.14 (P = 0.26)								

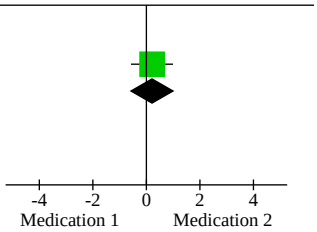


Footnotes

(1) Antipsychotic versus antipsychotic
(2) Antipsychotic versus antidepressant
(3) Benzodiazepine versus mood stabiliser - cross-over data
(4) benzodiazepine versus antipsychotic - cross-over data
(5) Benzodiazepine versus antidepressant - cross-over data
(6) Mood stabiliser versus antipsychotic - cross-over data
(7) Mood stabiliser versus antidepressant - cross-over data
(8) Antipsychotic versus antidepressant - cross-over data

Analysis 10.2. Comparison 10: Single medication compared with alternate single medication , Outcome 2: Primary: Self-harm at end of treatment (continuous outcomes, MDs)

Study or Subgroup	Medication 1 Mean	SD	Total	Medication 2 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
10.2.1 Olanzapine versus asenapine								
Bozzatello 2017 (1)	1.67	1.33	26	1.46	1.52	25	100.0%	0.21 [-0.58 , 1.00]
Subtotal (95% CI)			**26**			**25**	**100.0%**	**0.21 [-0.58 , 1.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.52 (P = 0.60)								
Test for subgroup differences: Not applicable								

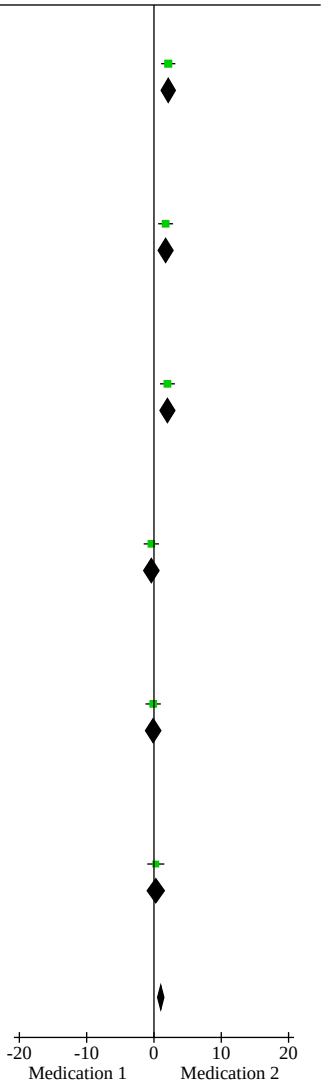


Footnotes

(1) Antipsychotic versus antipsychotic

Analysis 10.3. Comparison 10: Single medication compared with alternate single medication , Outcome 3: Primary: Suicide-related outcomes at end of treatment (continuous outcomes, MDs)

Study or Subgroup	Medication 1 Mean	SD	Total	Medication 2 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
10.3.1 Alprazolam versus carbamazepine								
Cowdry 1988 (1)	4.83	1.4	12	2.71	1.38	15	19.1%	2.12 [1.06 , 3.18]
Subtotal (95% CI)			**12**			**15**	**19.1%**	**2.12 [1.06 , 3.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.93 (P < 0.0001)								
10.3.2 Alprazolam versus trifluoperazine hydrochloride								
Cowdry 1988 (2)	4.83	1.14	12	3.1	1.45	10	17.4%	1.73 [0.62 , 2.84]
Subtotal (95% CI)			**12**			**10**	**17.4%**	**1.73 [0.62 , 2.84]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.07 (P = 0.002)								
10.3.3 Alprazolam versus tranylcypromine sulfate								
Cowdry 1988 (2)	4.83	1.14	12	2.83	1.59	12	17.4%	2.00 [0.89 , 3.11]
Subtotal (95% CI)			**12**			**12**	**17.4%**	**2.00 [0.89 , 3.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.54 (P = 0.0004)								
10.3.4 Carbamazepine versus trifluoperazine hydrochloride								
Cowdry 1988 (3)	2.71	1.38	15	3.1	1.45	10	16.5%	-0.39 [-1.53 , 0.75]
Subtotal (95% CI)			**15**			**10**	**16.5%**	**-0.39 [-1.53 , 0.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.67 (P = 0.50)								
10.3.5 Carbamazepine versus tranylcypromine sulfate								
Cowdry 1988 (4)	2.71	1.38	15	2.83	1.59	12	16.4%	-0.12 [-1.26 , 1.02]
Subtotal (95% CI)			**15**			**12**	**16.4%**	**-0.12 [-1.26 , 1.02]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.21 (P = 0.84)								
10.3.6 Trifluoperazine hydrochloride versus tranylcypromine sulfate								
Cowdry 1988 (5)	3.1	1.45	10	2.83	1.59	12	13.2%	0.27 [-1.00 , 1.54]
Subtotal (95% CI)			**10**			**12**	**13.2%**	**0.27 [-1.00 , 1.54]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.42 (P = 0.68)								
Total (95% CI)			**76**			**71**	**100.0%**	**1.01 [0.54 , 1.47]**
Heterogeneity: Chi² = 19.84, df = 5 (P = 0.001); I² = 75%								
Test for overall effect: Z = 4.27 (P < 0.0001)								
Test for subgroup differences: Chi² = 19.84, df = 5 (P = 0.001), I² = 74.8%								

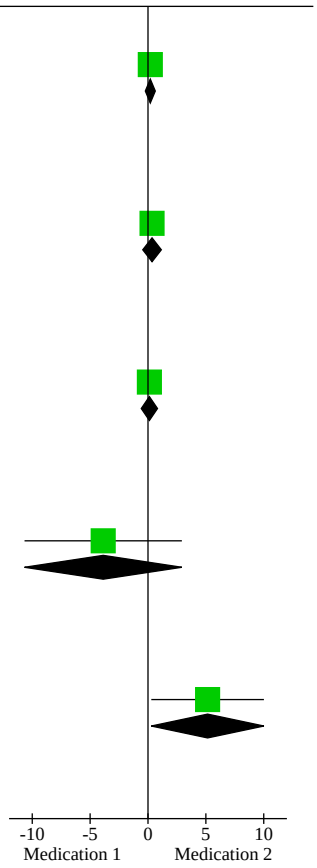


Footnotes

(1) Benzodiazepine versus mood stabiliser - cross-over data
(2) Benzodiazepine versus antidepressant - cross-over data
(3) Mood stabiliser versus antipsychotic - cross-over data
(4) Mood stabiliser versis antidepressant - cross-over data
(5) Antipsychotic versus antidepressant - cross-over data

Analysis 10.4. Comparison 10: Single medication compared with alternate single medication , Outcome 4: Primary: Psychosocial functioning (continuous outcomes, MDs)

Study or Subgroup	Medication 1 Mean	SD	Total	Medication 2 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
10.4.1 Olanzapine versus asenapine								
Bozzatello 2017 (1)	3.9	0.74	26	3.7	0.82	25	100.0%	0.20 [-0.23 , 0.63]
Subtotal (95% CI)			**26**			**25**	**100.0%**	**0.20 [-0.23 , 0.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.91 (P = 0.36)								
10.4.2 Olanzapine versus haloperidol								
Shafti 2010 (1)	2.86	1.13	14	2.51	1.03	14	100.0%	0.35 [-0.45 , 1.15]
Subtotal (95% CI)			**14**			**14**	**100.0%**	**0.35 [-0.45 , 1.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.86 (P = 0.39)								
10.4.3 Olanzapine versus aripiprazole								
Shafti 2014 (1)	2.83	0.96	12	2.71	0.78	12	100.0%	0.12 [-0.58 , 0.82]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**0.12 [-0.58 , 0.82]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.34 (P = 0.74)								
10.4.4 Haloperidol versus amitriptyline								
Soloff 1989 (2)	-55.35	12.36	28	-51.48	13.8	29	100.0%	-3.87 [-10.67 , 2.93]
Subtotal (95% CI)			**28**			**29**	**100.0%**	**-3.87 [-10.67 , 2.93]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.12 (P = 0.26)								
10.4.5 Haloperidol versus phenelzine sulfate								
Soloff 1993 (2)	-54.95	9.15	30	-60.1	10.7	34	100.0%	5.15 [0.29 , 10.01]
Subtotal (95% CI)			**30**			**34**	**100.0%**	**5.15 [0.29 , 10.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.08 (P = 0.04)								



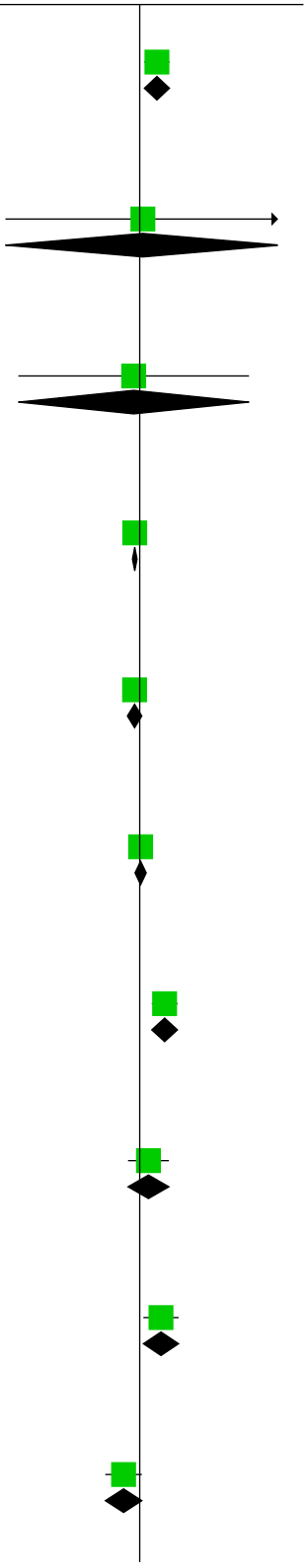
Footnotes

(1) Antipsychotic versus antipsychotic (CGI-S)

(2) Antipsychotic versus antidepressant (GAS)

Analysis 10.5. Comparison 10: Single medication compared with alternate single medication , Outcome 5: Secondary: Anger at end of treatment (continuous outcomes, MDs)

Study or Subgroup	Medication 1 Mean	SD	Total	Medication 2 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
10.5.1 Olanzapine versus asenapine								
Bozzatello 2017 (1)	7.19	1.82	26	6.05	1.15	25	100.0%	1.14 [0.31 , 1.97]
Subtotal (95% CI)			**26**			**25**	**100.0%**	**1.14 [0.31 , 1.97]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.68 (P = 0.007)								
10.5.2 Olanzapine versus haloperidol								
Shafti 2010 (1)	48.14	11.84	14	47.93	12.75	14	100.0%	0.21 [-8.90 , 9.32]
Subtotal (95% CI)			**14**			**14**	**100.0%**	**0.21 [-8.90 , 9.32]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.05 (P = 0.96)								
10.5.3 Olanzapine versus aripiprazole								
Shafti 2014 (1)	50.74	10.72	12	51.14	8.23	12	100.0%	-0.40 [-8.05 , 7.25]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**-0.40 [-8.05 , 7.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.10 (P = 0.92)								
10.5.4 Olanzapine versus sertraline								
Jariani 2010 (2)	2.05	0.39	60	2.38	0.46	60	100.0%	-0.33 [-0.48 , -0.18]
Subtotal (95% CI)			**60**			**60**	**100.0%**	**-0.33 [-0.48 , -0.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.24 (P < 0.0001)								
10.5.5 Haloperidol versus amitriptyline								
Soloff 1989 (2)	0.78	0.82	28	1.12	1.01	29	100.0%	-0.34 [-0.82 , 0.14]
Subtotal (95% CI)			**28**			**29**	**100.0%**	**-0.34 [-0.82 , 0.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.40 (P = 0.16)								
10.5.6 Haloperidol versus phenelzine sulfate								
Soloff 1993 (2)	0.79	0.66	30	0.73	0.85	34	100.0%	0.06 [-0.31 , 0.43]
Subtotal (95% CI)			**30**			**34**	**100.0%**	**0.06 [-0.31 , 0.43]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.32 (P = 0.75)								
10.5.7 Alprazolam versus carbamazepine								
Cowdry 1988 (3)	4.58	1.31	12	2.93	0.83	15	100.0%	1.65 [0.80 , 2.50]
Subtotal (95% CI)			**12**			**15**	**100.0%**	**1.65 [0.80 , 2.50]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.80 (P = 0.0001)								
10.5.8 Alprazolam versus trifluoperazine hydrochloride								
Cowdry 1988 (4)	4.58	1.31	12	4	1.83	10	100.0%	0.58 [-0.77 , 1.93]
Subtotal (95% CI)			**12**			**10**	**100.0%**	**0.58 [-0.77 , 1.93]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.84 (P = 0.40)								
10.5.9 Alprazolam versus tranylcypromine sulfate								
Cowdry 1988 (5)	4.58	1.31	12	3.17	1.59	12	100.0%	1.41 [0.24 , 2.58]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**1.41 [0.24 , 2.58]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.37 (P = 0.02)								
10.5.10 Carbamazepine versus trifluoperazine hydrochloride								
Cowdry 1988 (6)	2.93	0.83	15	4	1.83	10	100.0%	-1.07 [-2.28 , 0.14]
Subtotal (95% CI)			**15**			**10**	**100.0%**	**-1.07 [-2.28 , 0.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.73 (P = 0.08)								



Analysis 10.5. (Continued)

Heterogeneity: Not applicable
Test for overall effect: Z = 1.73 (P = 0.08)

10.5.11 Carbamazepine versus tranylcypromine sulfate

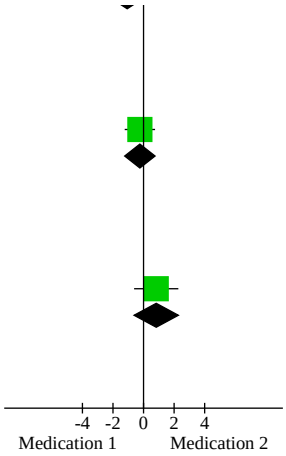
Cowdry 1988 (7)	2.93	0.83	15	3.17	1.59	12	100.0%	-0.24 [-1.23 , 0.75]
Subtotal (95% CI)			**15**			**12**	**100.0%**	**-0.24 [-1.23 , 0.75]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.47 (P = 0.64)

10.5.12 Trifluoperazine hydrochloride versus tranylcypromine sulfate

Cowdry 1988 (8)	4	1.83	10	3.17	1.59	12	100.0%	0.83 [-0.62 , 2.28]
Subtotal (95% CI)			**10**			**12**	**100.0%**	**0.83 [-0.62 , 2.28]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.12 (P = 0.26)



Footnotes

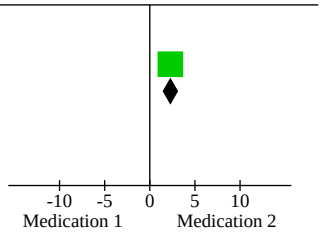
(1) Antipsychotic versus antipsychotic
(2) Antipsychotic versus antidepressant
(3) Benzodiazepine versus mood stabiliser - cross-over data
(4) Benzodiazepine versus antipsychotic - cross-over data
(5) Benzodiazepine versus antidepressant - cross-over data
(6) Mood stabiliser versus antipsychotic - cross-over data
(7) Mood stabiliser verus antidepressant - cross-over data
(8) Antipsychotic versus antidepressant - cross-over data

Analysis 10.6. Comparison 10: Single medication compared with alternate single medication , Outcome 6: Secondary: Affective instability at end of treatment (continuous outcomes, MDs)

	Medication 1			Medication 2				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
10.6.1 Olanzapine versus asenapine									
Bozzatello 2017 (1)	6.86	1.67	26	4.58	1.1	25	100.0%	2.28 [1.51 , 3.05]	
Subtotal (95% CI)			**26**			**25**	**100.0%**	**2.28 [1.51 , 3.05]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 5.78 (P < 0.00001)

Test for subgroup differences: Not applicable

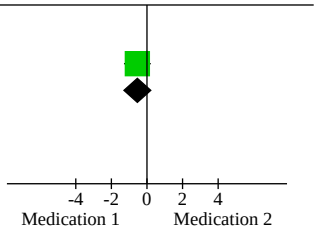


Footnotes

(1) Antipsychotic versus antipsychotic

Analysis 10.7. Comparison 10: Single medication compared with alternate single medication , Outcome 7: Secondary: Chronic feelings of emptiness at end of treatment (continuous outcomes, MDs)

Study or Subgroup	Medication 1 Mean	SD	Total	Medication 2 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
10.7.1 Olanzapine versus asenapine								
Bozzatello 2017 (1)	5.27	1.11	26	5.81	1.58	25	100.0%	-0.54 [-1.29 , 0.21]
Subtotal (95% CI)			**26**			**25**	**100.0%**	**-0.54 [-1.29 , 0.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.41 (P = 0.16)								
Test for subgroup differences: Not applicable								

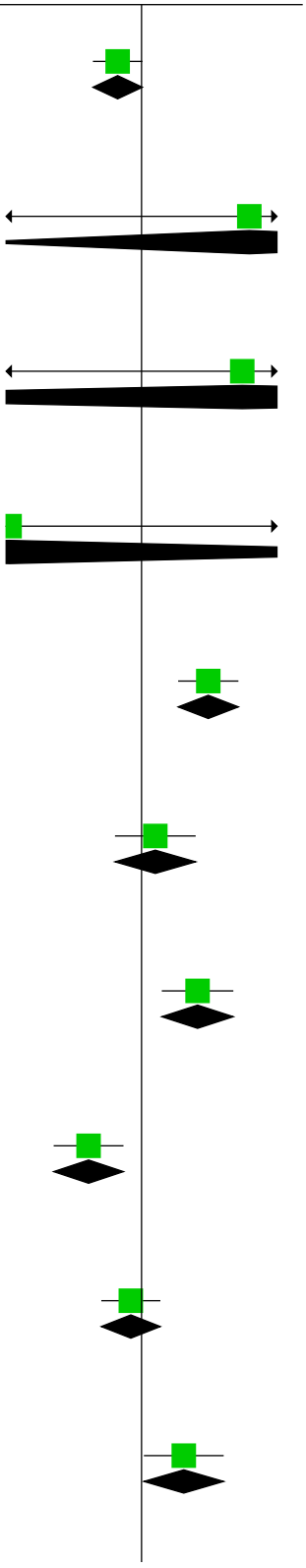


Footnotes

(1) Antipsychotic versus antipsychotic

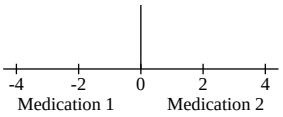
Analysis 10.8. Comparison 10: Single medication compared with alternate single medication , Outcome 8: Secondary: Impulsivity at end of treatment (continuous outcomes, MDs)

Study or Subgroup	Medication 1 Mean	SD	Total	Medication 2 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
10.8.1 Olanzapine versus asenapine								
Bozzatello 2017 (1)	7	1.58	26	7.78	1.36	25	100.0%	-0.78 [-1.59 , 0.03]
Subtotal (95% CI)			**26**			**25**	**100.0%**	**-0.78 [-1.59 , 0.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.89 (P = 0.06)								
10.8.2 Haloperidol versus amitriptyline								
Soloff 1989 (2)	104.02	15.71	28	100.5	19.01	29	100.0%	3.52 [-5.52 , 12.56]
Subtotal (95% CI)			**28**			**29**	**100.0%**	**3.52 [-5.52 , 12.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.76 (P = 0.45)								
10.8.3 Haloperidol versus phenelzine sulfate								
Soloff 1993 (2)	240.95	37.6	30	237.66	34.73	34	100.0%	3.29 [-14.52 , 21.10]
Subtotal (95% CI)			**30**			**34**	**100.0%**	**3.29 [-14.52 , 21.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.36 (P = 0.72)								
10.8.4 Olanzapine versus fluoxetine								
Zanarini 2004 (2)	-19.69	20.83	16	-15.38	21.25	13	100.0%	-4.31 [-19.72 , 11.10]
Subtotal (95% CI)			**16**			**13**	**100.0%**	**-4.31 [-19.72 , 11.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.55 (P = 0.58)								
10.8.5 Alprazolam versus carbamazepine								
Cowdry 1988 (3)	4.75	1.48	12	2.57	1.02	15	100.0%	2.18 [1.20 , 3.16]
Subtotal (95% CI)			**12**			**15**	**100.0%**	**2.18 [1.20 , 3.16]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.34 (P < 0.0001)								
10.8.6 Alprazolam versus trifluoperazine hydrochloride								
Cowdry 1988 (4)	4.75	1.48	12	4.3	1.64	10	100.0%	0.45 [-0.87 , 1.77]
Subtotal (95% CI)			**12**			**10**	**100.0%**	**0.45 [-0.87 , 1.77]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.67 (P = 0.50)								
10.8.7 Alprazolam versus tranylcypromine sulfate								
Cowdry 1988 (5)	4.75	1.48	12	2.92	1.44	12	100.0%	1.83 [0.66 , 3.00]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**1.83 [0.66 , 3.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.07 (P = 0.002)								
10.8.8 Carbamazepine versus trifluoperazine hydrochloride								
Cowdry 1988 (6)	2.57	1.02	15	4.3	1.64	10	100.0%	-1.73 [-2.87 , -0.59]
Subtotal (95% CI)			**15**			**10**	**100.0%**	**-1.73 [-2.87 , -0.59]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.97 (P = 0.003)								
10.8.9 Carbamazepine versus tranylcypromine sulfate								
Cowdry 1988 (7)	2.57	1.02	15	2.92	1.44	12	100.0%	-0.35 [-1.31 , 0.61]
Subtotal (95% CI)			**15**			**12**	**100.0%**	**-0.35 [-1.31 , 0.61]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.71 (P = 0.48)								
10.8.10 Trifluoperazine hydrochloride versus tranylcypromine sulfate								
Cowdry 1988 (8)	4.3	1.64	10	2.92	1.44	12	100.0%	1.38 [0.08 , 2.68]
Subtotal (95% CI)			**10**			**12**	**100.0%**	**1.38 [0.08 , 2.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.08 (P = 0.04)								



Analysis 10.8. (Continued)

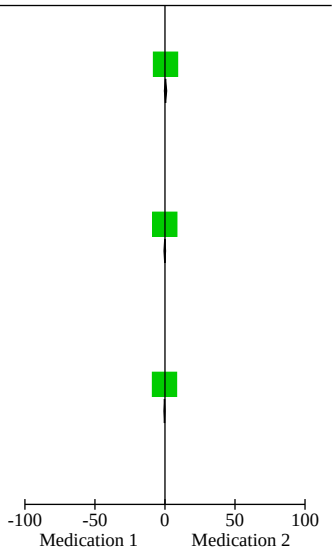
Test for overall effect: Z = 2.08 (P = 0.04)



Footnotes
(1) Antipsychotic versus antipsychotic
(2) Antipsychotic versus antidepressant
(3) Benzodiazepine versus mood stabiliser - cross-over data
(4) Benzodiazepine versus antipsychotic - cross-over data
(5) Benzodiazepine versus antidepressant - cross-over data
(6) Mood stabiliser versus antipsychotic - cross-over data
(7) Mood stabiliser versus antidepressant - cross-over data
(8) Antipsychotic versus antidepressant - cross-over data

Analysis 10.9. Comparison 10: Single medication compared with alternate single medication , Outcome 9: Secondary: Interpersonal problems at end of treatment (continuous outcomes, MDs)

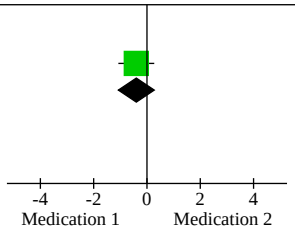
Study or Subgroup	Medication 1 Mean	SD	Total	Medication 2 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
10.9.1 Olanzapine versus asenapine								
Bozzatello 2017 (1)	7.29	1.4	26	6.89	1.32	25	100.0%	0.40 [-0.35 , 1.15]
Subtotal (95% CI)			**26**			**25**	**100.0%**	**0.40 [-0.35 , 1.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.05 (P = 0.29)								
10.9.2 Haloperidol versus amitriptyline								
Soloff 1989 (2)	1.21	0.92	28	1.34	0.95	29	100.0%	-0.13 [-0.62 , 0.36]
Subtotal (95% CI)			**28**			**29**	**100.0%**	**-0.13 [-0.62 , 0.36]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.52 (P = 0.60)								
10.9.3 Haloperidol versus phenelzine sulfate								
Soloff 1993 (2)	0.57	0.7	30	0.9	0.71	34	100.0%	-0.33 [-0.68 , 0.02]
Subtotal (95% CI)			**30**			**34**	**100.0%**	**-0.33 [-0.68 , 0.02]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.87 (P = 0.06)								



Footnotes
(1) Antipsychotic versus antipsychotic
(2) Antipsychotic versus antidepressant

Analysis 10.10. Comparison 10: Single medication compared with alternate single medication , Outcome 10: Secondary: Abandonment at end of treatment (continuous outcomes, MDs)

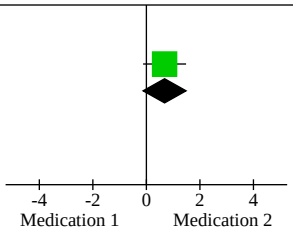
Study or Subgroup	Medication 1 Mean	SD	Total	Medication 2 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
10.10.1 Olanzapine versus asenapine								
Bozzatello 2017 (1)	6.69	1.12	26	7.09	1.32	25	100.0%	-0.40 [-1.07 , 0.27]
Subtotal (95% CI)			**26**			**25**	**100.0%**	**-0.40 [-1.07 , 0.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.16 (P = 0.24)								
Test for subgroup differences: Not applicable								



Footnotes
(1) Antipsychotic versus antipsychotic

Analysis 10.11. Comparison 10: Single medication compared with alternate single medication , Outcome 11: Secondary: Identity disturbance at end of treatment (continuous outcomes, MDs)

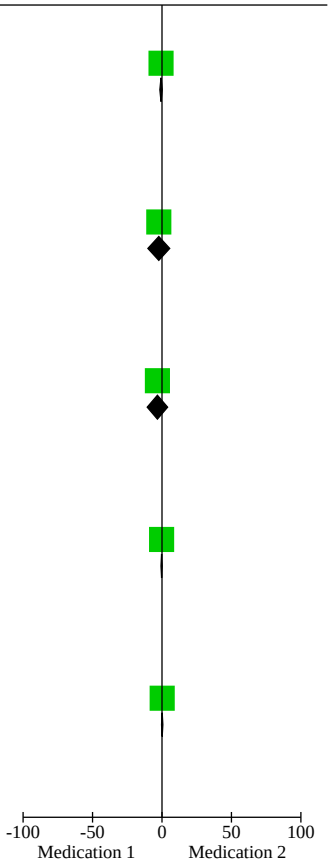
Study or Subgroup	Medication 1 Mean	SD	Total	Medication 2 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
10.11.1 Olanzapine versus asenapine								
Bozzatello 2017 (1)	5.4	1.29	26	4.72	1.61	25	100.0%	0.68 [-0.12 , 1.48]
Subtotal (95% CI)			**26**			**25**	**100.0%**	**0.68 [-0.12 , 1.48]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.66 (P = 0.10)								
Test for subgroup differences: Not applicable								



Footnotes
(1) Antipsychotic versus antipsychotic

Analysis 10.12. Comparison 10: Single medication compared with alternate single medication , Outcome 12: Secondary: Dissociation and psychotic-like symptoms at end of treatment (continuous outcomes, MDs)

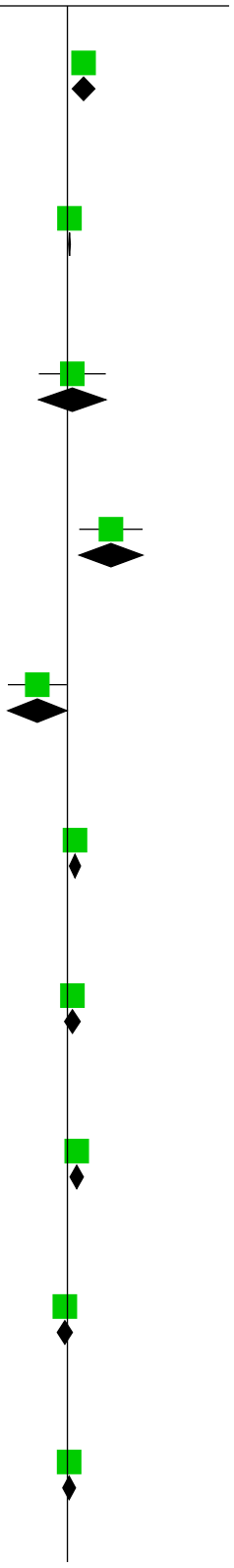
Study or Subgroup	Medication 1 Mean	SD	Total	Medication 2 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
10.12.1 Olanzapine versus asenapine								
Bozzatello 2017 (1)	1.67	1.83	26	2.36	1.15	25	100.0%	-0.69 [-1.53 , 0.15]
Subtotal (95% CI)			**26**			**25**	**100.0%**	**-0.69 [-1.53 , 0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.62 (P = 0.11)								
10.12.2 Olanzapine versus haloperidol								
Shafti 2010 (1)	20.1	12.4	14	22.4	8.4	14	100.0%	-2.30 [-10.15 , 5.55]
Subtotal (95% CI)			**14**			**14**	**100.0%**	**-2.30 [-10.15 , 5.55]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.57 (P = 0.57)								
10.12.3 Olanzapine versus aripiprazole								
Shafti 2014 (1)	32.5	9.6	12	35.8	8.7	12	100.0%	-3.30 [-10.63 , 4.03]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**-3.30 [-10.63 , 4.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.88 (P = 0.38)								
10.12.4 Haloperidol versus amitriptyline								
Soloff 1989 (2)	0.75	0.73	28	1.03	0.86	29	100.0%	-0.28 [-0.69 , 0.13]
Subtotal (95% CI)			**28**			**29**	**100.0%**	**-0.28 [-0.69 , 0.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.33 (P = 0.18)								
10.12.5 Haloperidol versus phenelzine sulfate								
Soloff 1993 (2)	1.06	0.96	30	0.92	0.87	34	100.0%	0.14 [-0.31 , 0.59]
Subtotal (95% CI)			**30**			**34**	**100.0%**	**0.14 [-0.31 , 0.59]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.61 (P = 0.54)								



Footnotes
(1) Antipsychotic versus antipsychotic
(2) Antipsychotic versus antidepressant

Analysis 10.13. Comparison 10: Single medication compared with alternate single medication , Outcome 13: Secondary: Depression at end of treatment (continuous outcomes, MDs)

Study or Subgroup	Medication 1 Mean	SD	Total	Medication 2 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
10.13.1 Olanzapine versus asenapine								
Bozzatello 2017 (1)	15.7	3.27	26	12.8	4.02	25	100.0%	2.90 [0.88 , 4.92]
Subtotal (95% CI)			**26**			**25**	**100.0%**	**2.90 [0.88 , 4.92]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.82 (P = 0.005)								
10.13.2 Olanzapine versus sertraline								
Jariani 2010 (2)	2.19	0.39	60	1.82	0.43	60	100.0%	0.37 [0.22 , 0.52]
Subtotal (95% CI)			**60**			**60**	**100.0%**	**0.37 [0.22 , 0.52]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.94 (P < 0.00001)								
10.13.3 Haloperidol versus amitriptyline								
Soloff 1989 (2)	16.22	12.32	28	15.34	10.71	29	100.0%	0.88 [-5.12 , 6.88]
Subtotal (95% CI)			**28**			**29**	**100.0%**	**0.88 [-5.12 , 6.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.29 (P = 0.77)								
10.13.4 Haloperidol versus phenelzine sulfate								
Soloff 1993 (2)	23.5	13.16	30	15.69	9.46	34	100.0%	7.81 [2.13 , 13.49]
Subtotal (95% CI)			**30**			**34**	**100.0%**	**7.81 [2.13 , 13.49]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.69 (P = 0.007)								
10.13.5 Olanzapine versus fluoxetine								
Zanarini 2004 (2)	-13.63	7.23	16	-8.23	7.19	13	100.0%	-5.40 [-10.68 , -0.12]
Subtotal (95% CI)			**16**			**13**	**100.0%**	**-5.40 [-10.68 , -0.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.01 (P = 0.04)								
10.13.6 Alprazolam versus carbamazepine								
Cowdry 1988	4.5	1.31	12	3.14	1.29	15	100.0%	1.36 [0.37 , 2.35]
Subtotal (95% CI)			**12**			**15**	**100.0%**	**1.36 [0.37 , 2.35]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.70 (P = 0.007)								
10.13.7 Alprazolam versus trifluoperazine hydrochloride								
Cowdry 1988	4.5	1.31	12	3.6	1.9	10	100.0%	0.90 [-0.49 , 2.29]
Subtotal (95% CI)			**12**			**10**	**100.0%**	**0.90 [-0.49 , 2.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.27 (P = 0.20)								
10.13.8 Alprazolam versus tranylcypromine sulfate								
Cowdry 1988	4.5	1.31	12	2.83	1.64	12	100.0%	1.67 [0.48 , 2.86]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**1.67 [0.48 , 2.86]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.76 (P = 0.006)								
10.13.9 Carbamazepine versus trifluoperazine hydrochloride								
Cowdry 1988	3.14	1.29	15	3.6	1.9	10	100.0%	-0.46 [-1.81 , 0.89]
Subtotal (95% CI)			**15**			**10**	**100.0%**	**-0.46 [-1.81 , 0.89]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.67 (P = 0.50)								
10.13.10 Carbamazepine versus tranylcypromine sulfate								
Cowdry 1988	3.14	1.29	15	2.83	1.64	12	100.0%	0.31 [-0.82 , 1.44]
Subtotal (95% CI)			**15**			**12**	**100.0%**	**0.31 [-0.82 , 1.44]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.54 (P = 0.59)								



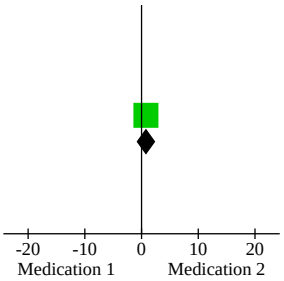
Analysis 10.13. (Continued)

Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)

10.13.11 Trifluoperazine hydrochloride versus tranylcypromine sulfate

Cowdry 1988	3.6	1.9	10	2.83	1.64	12	100.0%	0.77 [-0.73 , 2.27]
Subtotal (95% CI)			**10**			**12**	**100.0%**	**0.77 [-0.73 , 2.27]**

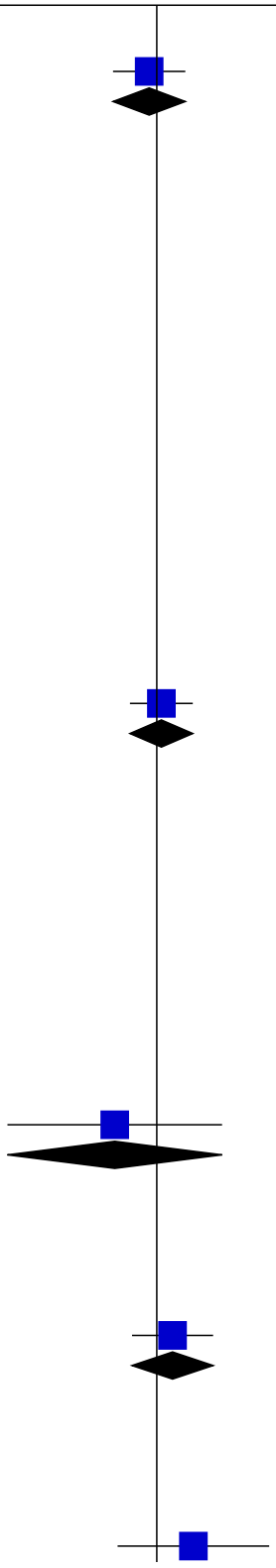
Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)



Footnotes
(1) Antipsychotic versus antipsychotic
(2) Antipsychotic versus antidepressant

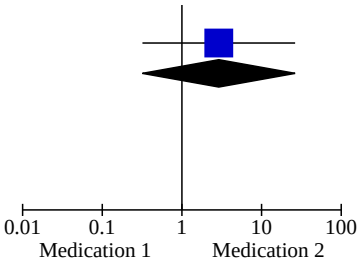
Analysis 10.14. Comparison 10: Single medication compared with alternate single medication , Outcome 14: Secondary: Attrition at end of treatment (dichotomous outcomes, RRs)

Study or Subgroup	Medication 1 Events	Medication 1 Total	Medication 2 Events	Medication 2 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.14.1 Olanzapine versus asenapine						
Bozzatello 2017 (1)	5	26	6	25	100.0%	0.80 [0.28 , 2.29]
Subtotal (95% CI)		**26**		**25**	**100.0%**	**0.80 [0.28 , 2.29]**
Total events:	5		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
10.14.2 Olanzapine versus haloperidol						
Shafti 2010 (1)	0	14	0	14		Not estimable
Subtotal (95% CI)		**14**		**14**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.14.3 Olanzapine versus aripiprazole						
Shafti 2014 (1)	0	12	0	12		Not estimable
Subtotal (95% CI)		**12**		**12**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.14.4 Loxapine versus chlorpromazine						
Leone 1982 (1)	8	40	7	40	100.0%	1.14 [0.46 , 2.85]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**1.14 [0.46 , 2.85]**
Total events:	8		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
10.14.5 Olanzapine versus sertraline						
Jariani 2010 (2)	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.14.6 Olanzapine versus fluoxetine						
Zanarini 2004 (3)	0	16	1	14	100.0%	0.29 [0.01 , 6.69]
Subtotal (95% CI)		**16**		**14**	**100.0%**	**0.29 [0.01 , 6.69]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						
10.14.7 Haloperidol versus phenelzine sulfate						
Soloff 1993 (4)	6	36	4	38	100.0%	1.58 [0.49 , 5.15]
Subtotal (95% CI)		**36**		**38**	**100.0%**	**1.58 [0.49 , 5.15]**
Total events:	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.76 (P = 0.45)						
10.14.8 Haloperidol versus amitriptyline						
Soloff 1989 (5)	3	31	1	30	100.0%	2.90 [0.32 , 26.38]



Analysis 10.14. (Continued)

10.14.8 Haloperidol versus amitriptyline						
Soloff 1989 (5)	3	31	1	30	100.0%	2.90 [0.32 , 26.38]
Subtotal (95% CI)		**31**		**30**	**100.0%**	**2.90 [0.32 , 26.38]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.95 (P = 0.34)						

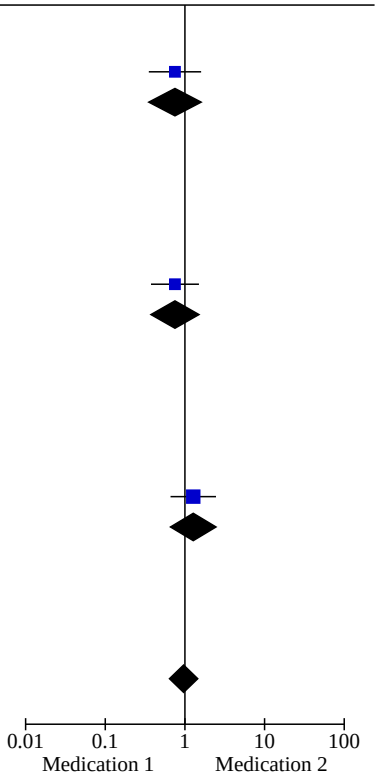


Footnotes

(1) Antipsychotic versus antipsychotic
(2) Antipsychotic versus antidepressant
(3) Olanzapine versus fluoxetine
(4) Haloperidol versus phenelzine sulfate
(5) Haloperidol versus amitriptyline

Analysis 10.15. Comparison 10: Single medication compared with alternate single medication , Outcome 15: Secondary: Adverse events at end of treatment (dichotomous outcomes, RRs)

	Medication 1		Medication 2			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
10.15.1 Adverse events total: olanzapine versus haloperidol							
Shafti 2010 (1)	6	14	8	14	29.6%	0.75 [0.35 , 1.60]	
Subtotal (95% CI)		**14**		**14**	**29.6%**	**0.75 [0.35 , 1.60]**	
Total events:	6		8				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.75 (P = 0.46)							
10.15.2 Adverse events total: olanzapine versus aripiprazole							
Shafti 2014 (1)	6	12	8	12	29.6%	0.75 [0.38 , 1.50]	
Subtotal (95% CI)		**12**		**12**	**29.6%**	**0.75 [0.38 , 1.50]**	
Total events:	6		8				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.81 (P = 0.42)							
10.15.3 Adverse events total: loxapine versus chlorpromazine							
Leone 1982 (1)	14	40	11	40	40.7%	1.27 [0.66 , 2.45]	
Subtotal (95% CI)		**40**		**40**	**40.7%**	**1.27 [0.66 , 2.45]**	
Total events:	14		11				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.72 (P = 0.47)							
Total (95% CI)		**66**		**66**	**100.0%**	**0.96 [0.64 , 1.45]**	
Total events:	26		27				
Heterogeneity: Chi² = 1.61, df = 2 (P = 0.45); I² = 0%							
Test for overall effect: Z = 0.18 (P = 0.86)							
Test for subgroup differences: Chi² = 1.55, df = 2 (P = 0.46), I² = 0%							



Footnotes

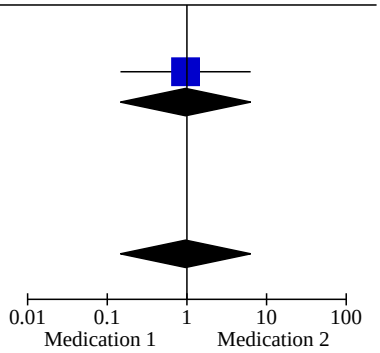
(1) Antipsychotic versus antipsychotic

Comparison 11. Single medication compared with alternate single medication - withdrew due to adverse events (AE)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Withdrew due to AE	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.15, 6.31]
11.1.1 Olanzapine[1] versus asenapine[2]	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.15, 6.31]

Analysis 11.1. Comparison 11: Single medication compared with alternate single medication - withdrew due to adverse events (AE), Outcome 1: Withdrew due to AE

Study or Subgroup	Medication 1 Events	Medication 1 Total	Medication 2 Events	Medication 2 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.1.1 Olanzapine[1] versus asenapine[2]						
Bozzatello 2017 (1)	2	26	2	25	100.0%	0.96 [0.15 , 6.31]
Subtotal (95% CI)		**26**		**25**	**100.0%**	**0.96 [0.15 , 6.31]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.04 (P = 0.97)						
Total (95% CI)		**26**		**25**	**100.0%**	**0.96 [0.15 , 6.31]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.04 (P = 0.97)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Antipsychotic versus antipsychotic

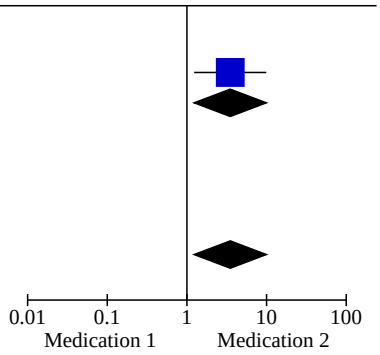
Comparison 12. Single medication compared with alternate single medication - non-serious adverse events - central nervous system

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Sedation	1	30	Risk Ratio (M-H, Fixed, 95% CI)	3.50 [1.23, 9.92]
12.1.1 Olanzapine versus fluoxetine	1	30	Risk Ratio (M-H, Fixed, 95% CI)	3.50 [1.23, 9.92]
12.2 Restlessness	2	110	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.36, 2.32]
12.2.1 Loxapine versus chlorpromazine	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.26, 8.50]
12.2.2 Olanzapine versus fluoxetine	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.23, 2.11]
12.3 Restlessness/anxiety	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.3.1 Olanzapine versus asenapine	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.82]
12.4 Sleepiness/drowsiness	2	131	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.47, 3.88]
12.4.1 Olanzapine versus asenapine	1	51	Risk Ratio (M-H, Fixed, 95% CI)	6.74 [0.37, 124.21]
12.4.2 Loxapine versus chlorpromazine	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.23, 2.76]
12.5 Fainting spells	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.68]
12.5.1 Loxapine versus chlorpromazine	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.68]
12.6 Akhatisia	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.82]
12.6.1 Olanzapine versus asenapine	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.82]
12.7 Moderate anxiety	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.53]
12.7.1 Olanzapine versus asenapine	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.53]
12.8 Fatigue	1	51	Risk Ratio (M-H, Fixed, 95% CI)	4.81 [0.24, 95.58]
12.8.1 Olanzapine versus asenapine	1	51	Risk Ratio (M-H, Fixed, 95% CI)	4.81 [0.24, 95.58]

Analysis 12.1. Comparison 12: Single medication compared with alternate single medication - non-serious adverse events - central nervous system, Outcome 1: Sedation

Study or Subgroup	Medication 1 Events	Medication 1 Total	Medication 2 Events	Medication 2 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.1.1 Olanzapine versus fluoxetine						
Zanarini 2004 (1)	12	16	3	14	100.0%	3.50 [1.23 , 9.92]
Subtotal (95% CI)		**16**		**14**	**100.0%**	**3.50 [1.23 , 9.92]**
Total events:	12		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.36 (P = 0.02)						
Total (95% CI)		**16**		**14**	**100.0%**	**3.50 [1.23 , 9.92]**
Total events:	12		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.36 (P = 0.02)						
Test for subgroup differences: Not applicable						

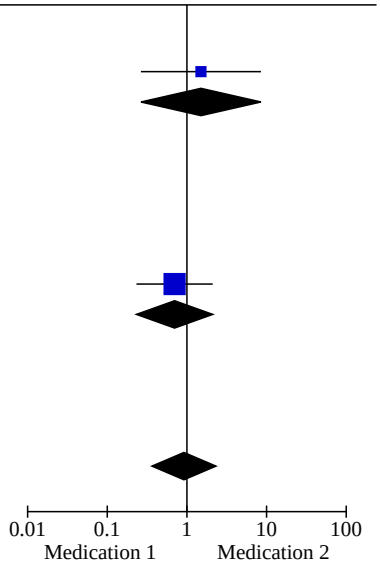


Footnotes

(1) Antipsychotic versus antidepressant

Analysis 12.2. Comparison 12: Single medication compared with alternate single medication - non-serious adverse events - central nervous system, Outcome 2: Restlessness

Study or Subgroup	Medication 1 Events	Medication 1 Total	Medication 2 Events	Medication 2 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.2.1 Loxapine versus chlorpromazine						
Leone 1982 (1)	3	40	2	40	27.3%	1.50 [0.26 , 8.50]
Subtotal (95% CI)		**40**		**40**	**27.3%**	**1.50 [0.26 , 8.50]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
12.2.2 Olanzapine versus fluoxetine						
Zanarini 2004 (2)	4	16	5	14	72.7%	0.70 [0.23 , 2.11]
Subtotal (95% CI)		**16**		**14**	**72.7%**	**0.70 [0.23 , 2.11]**
Total events:	4		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
Total (95% CI)		**56**		**54**	**100.0%**	**0.92 [0.36 , 2.32]**
Total events:	7		7			
Heterogeneity: Chi² = 0.54, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.18 (P = 0.86)						
Test for subgroup differences: Chi² = 0.53, df = 1 (P = 0.47), I² = 0%						



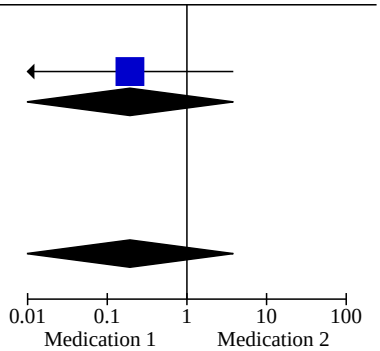
Footnotes

(1) Antipsychotic versus antipsychotic

(2) Antipsychotic versus antidepressant

Analysis 12.3. Comparison 12: Single medication compared with alternate single medication - non-serious adverse events - central nervous system, Outcome 3: Restlessness/anxiety

Study or Subgroup	Medication 1 Events	Medication 1 Total	Medication 2 Events	Medication 2 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.3.1 Olanzapine versus asenapine						
Bozzatello 2017 (1)	0	26	2	25	100.0%	0.19 [0.01 , 3.82]
Subtotal (95% CI)		**26**		**25**	**100.0%**	**0.19 [0.01 , 3.82]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						
Total (95% CI)		**26**		**25**	**100.0%**	**0.19 [0.01 , 3.82]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						
Test for subgroup differences: Not applicable						

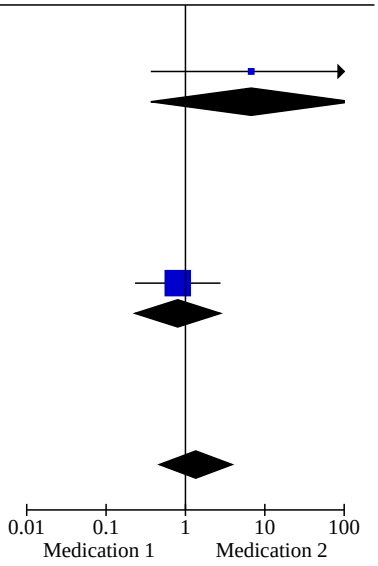


Footnotes

(1) Antipsychotic versus antipsychotic

Analysis 12.4. Comparison 12: Single medication compared with alternate single medication - non-serious adverse events - central nervous system, Outcome 4: Sleepiness/drowsiness

Study or Subgroup	Medication 1 Events	Medication 1 Total	Medication 2 Events	Medication 2 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.4.1 Olanzapine versus asenapine						
Bozzatello 2017 (1)	3	26	0	25	9.2%	6.74 [0.37 , 124.21]
Subtotal (95% CI)		**26**		**25**	**9.2%**	**6.74 [0.37 , 124.21]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.28 (P = 0.20)						
12.4.2 Loxapine versus chlorpromazine						
Leone 1982 (1)	4	40	5	40	90.8%	0.80 [0.23 , 2.76]
Subtotal (95% CI)		**40**		**40**	**90.8%**	**0.80 [0.23 , 2.76]**
Total events:	4		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.35 (P = 0.72)						
Total (95% CI)		**66**		**65**	**100.0%**	**1.35 [0.47 , 3.88]**
Total events:	7		5			
Heterogeneity: Chi^2 = 1.85, df = 1 (P = 0.17); I^2 = 46%						
Test for overall effect: Z = 0.56 (P = 0.58)						
Test for subgroup differences: Chi^2 = 1.74, df = 1 (P = 0.19), I^2 = 42.5%						

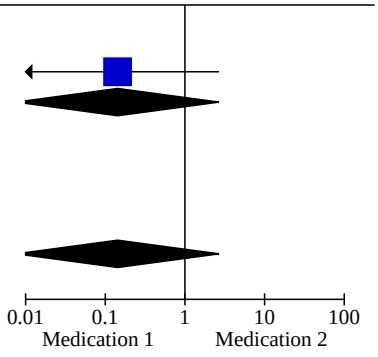


Footnotes

(1) Antipsychotic versus antipsychotic

Analysis 12.5. Comparison 12: Single medication compared with alternate single medication - non-serious adverse events - central nervous system, Outcome 5: Fainting spells

Study or Subgroup	Medication 1 Events	Medication 1 Total	Medication 2 Events	Medication 2 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.5.1 Loxapine versus chlorpromazine						
Leone 1982 (1)	0	40	3	40	100.0%	0.14 [0.01 , 2.68]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**0.14 [0.01 , 2.68]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
Total (95% CI)		**40**		**40**	**100.0%**	**0.14 [0.01 , 2.68]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
Test for subgroup differences: Not applicable						

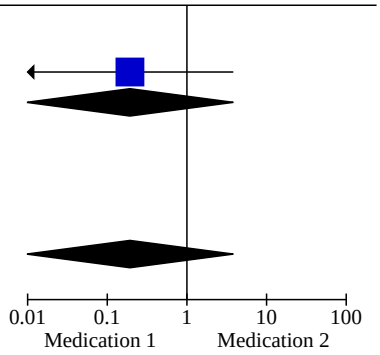


Footnotes

(1) Antipsychotic versus antipsychotic

Analysis 12.6. Comparison 12: Single medication compared with alternate single medication - non-serious adverse events - central nervous system, Outcome 6: Akhatisia

Study or Subgroup	Medication 1 Events	Medication 1 Total	Medication 2 Events	Medication 2 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.6.1 Olanzapine versus asenapine						
Bozzatello 2017 (1)	0	26	2	25	100.0%	0.19 [0.01 , 3.82]
Subtotal (95% CI)		**26**		**25**	**100.0%**	**0.19 [0.01 , 3.82]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						
Total (95% CI)		**26**		**25**	**100.0%**	**0.19 [0.01 , 3.82]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						
Test for subgroup differences: Not applicable						

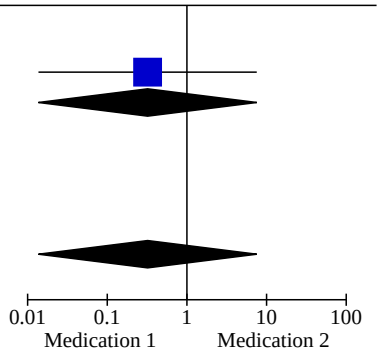


Footnotes

(1) Antipsychotic versus antipsychotic

Analysis 12.7. Comparison 12: Single medication compared with alternate single medication - non-serious adverse events - central nervous system, Outcome 7: Moderate anxiety

Study or Subgroup	Medication 1 Events	Medication 1 Total	Medication 2 Events	Medication 2 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.7.1 Olanzapine versus asenapine						
Bozzatello 2017 (1)	0	26	1	25	100.0%	0.32 [0.01 , 7.53]
Subtotal (95% CI)		**26**		**25**	**100.0%**	**0.32 [0.01 , 7.53]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
Total (95% CI)		**26**		**25**	**100.0%**	**0.32 [0.01 , 7.53]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
Test for subgroup differences: Not applicable						

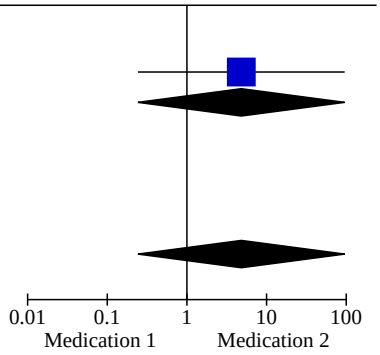


Footnotes

(1) Antipsychotic versus antipsychotic

Analysis 12.8. Comparison 12: Single medication compared with alternate single medication - non-serious adverse events - central nervous system, Outcome 8: Fatigue

Study or Subgroup	Medication 1 Events	Medication 1 Total	Medication 2 Events	Medication 2 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.8.1 Olanzapine versus asenapine						
Bozzatello 2017 (1)	2	26	0	25	100.0%	4.81 [0.24 , 95.58]
Subtotal (95% CI)		**26**		**25**	**100.0%**	**4.81 [0.24 , 95.58]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						
Total (95% CI)		**26**		**25**	**100.0%**	**4.81 [0.24 , 95.58]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						
Test for subgroup differences: Not applicable						



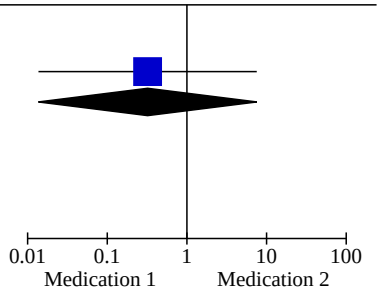
Footnotes
(1) Antipsychotic versus antipsychotic

Comparison 13. Single medication compared with alternate single medication - cardiovascular and respiratory system

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Oral hypoaesthesia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1.1 Olanzapine versus asenapine	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.53]

Analysis 13.1. Comparison 13: Single medication compared with alternate single medication - cardiovascular and respiratory system, Outcome 1: Oral hypoaesthesia

Study or Subgroup	Medication 1 Events	Medication 1 Total	Medication 2 Events	Medication 2 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
13.1.1 Olanzapine versus asenapine						
Bozzatello 2017 (1)	0	26	1	25	100.0%	0.32 [0.01 , 7.53]
Subtotal (95% CI)		**26**		**25**	**100.0%**	**0.32 [0.01 , 7.53]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
Test for subgroup differences: Not applicable						



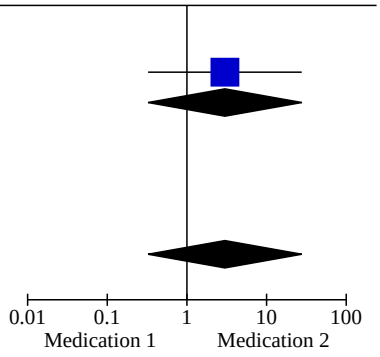
Footnotes
(1) Antipsychotic versus antipsychotic

Comparison 14. Single medication compared with alternate single medication - non-serious adverse events - musculoskeletal system

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Muscle spasm	1	80	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.33, 27.63]
14.1.1 Loxapine (medication 1) versus chlorpromazine (medication 2)	1	80	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.33, 27.63]
14.2 Body weight change	2	93	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.47, 0.25]
14.2.1 Haloperidol versus phenelzine sulfate	1	64	Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.59, 0.15]
14.2.2 Olanzapine versus fluoxetine	1	29	Mean Difference (IV, Fixed, 95% CI)	2.50 [0.72, 4.28]
14.3 Weight gain (3 or more kg within 4 weeks)	1	51	Risk Ratio (M-H, Fixed, 95% CI)	4.81 [0.24, 95.58]
14.3.1 Olanzapine versus asenapine	1	51	Risk Ratio (M-H, Fixed, 95% CI)	4.81 [0.24, 95.58]

Analysis 14.1. Comparison 14: Single medication compared with alternate single medication - non-serious adverse events - musculoskeletal system, Outcome 1: Muscle spasm

Study or Subgroup	Medication 1 Events	Medication 1 Total	Medication 2 Events	Medication 2 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
14.1.1 Loxapine (medication 1) versus chlorpromazine (medication 2)						
Leone 1982 (1)	3	40	1	40	100.0%	3.00 [0.33 , 27.63]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**3.00 [0.33 , 27.63]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
Total (95% CI)		**40**		**40**	**100.0%**	**3.00 [0.33 , 27.63]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Not applicable						

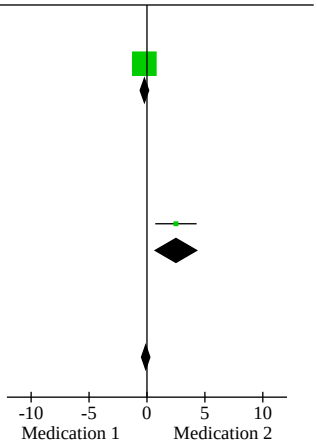


Footnotes

(1) Antipsychotic versus antipsychotic

Analysis 14.2. Comparison 14: Single medication compared with alternate single medication - non-serious adverse events - musculoskeletal system, Outcome 2: Body weight change

Study or Subgroup	Medication 1 Mean	SD	Total	Medication 2 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
14.2.1 Haloperidol versus phenelzine sulfate								
Soloff 1993 (1)	0.28	0.66	30	0.5	0.83	34	96.0%	-0.22 [-0.59 , 0.15]
Subtotal (95% CI)			**30**			**34**	**96.0%**	**-0.22 [-0.59 , 0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.18 (P = 0.24)								
14.2.2 Olanzapine versus fluoxetine								
Zanarini 2004 (1)	2.9	2.6	16	0.4	2.3	13	4.0%	2.50 [0.72 , 4.28]
Subtotal (95% CI)			**16**			**13**	**4.0%**	**2.50 [0.72 , 4.28]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.75 (P = 0.006)								
Total (95% CI)			**46**			**47**	**100.0%**	**-0.11 [-0.47 , 0.25]**
Heterogeneity: Chi² = 8.56, df = 1 (P = 0.003); I² = 88%								
Test for overall effect: Z = 0.60 (P = 0.55)								
Test for subgroup differences: Chi² = 8.56, df = 1 (P = 0.003), I² = 88.3%								

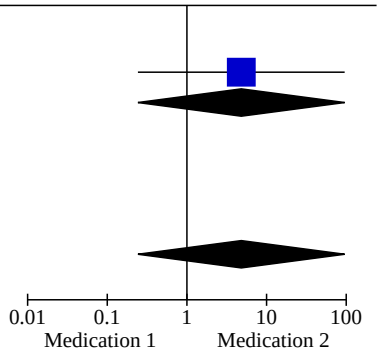


Footnotes

(1) Antipsychotic versus antidepressant

Analysis 14.3. Comparison 14: Single medication compared with alternate single medication - non-serious adverse events - musculoskeletal system, Outcome 3: Weight gain (3 or more kg within 4 weeks)

Study or Subgroup	Medication 1 Events	Total	Medication 2 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
14.3.1 Olanzapine versus asenapine						
Bozzatello 2017 (1)	2	26	0	25	100.0%	4.81 [0.24 , 95.58]
Subtotal (95% CI)		**26**		**25**	**100.0%**	**4.81 [0.24 , 95.58]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						
Total (95% CI)		**26**		**25**	**100.0%**	**4.81 [0.24 , 95.58]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Antipsychotic versus antipsychotic

Comparison 15. Single medication compared with combination of medications

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Primary: BPD symptom severity at end of treatment (continuous outcome, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

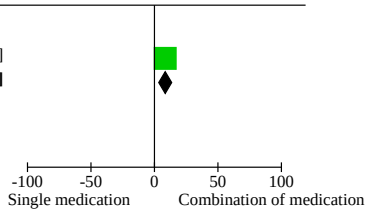
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid	1	34	Mean Difference (IV, Fixed, 95% CI)	8.48 [3.39, 13.57]
15.2 Primary: Self-harm at end of treatment (continuous outcome, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.2.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid	1	34	Mean Difference (IV, Fixed, 95% CI)	2.55 [0.98, 4.12]
15.3 Primary: Suicide-related outcomes at end of treatment (continuous outcome, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.3.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid	1	34	Mean Difference (IV, Fixed, 95% CI)	0.23 [-0.74, 1.20]
15.4 Primary: Psychosocial functioning at end of treatment (continuous outcome, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.4.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid	1	34	Mean Difference (IV, Fixed, 95% CI)	0.88 [-6.21, 7.97]
15.5 Secondary: Anger at end of treatment (continuous outcome, MDs)	2	89	Mean Difference (IV, Fixed, 95% CI)	0.64 [-0.77, 2.04]
15.5.1 Olanzapine versus olanzapine plus fluoxetine	1	29	Mean Difference (IV, Fixed, 95% CI)	0.46 [-12.93, 13.85]
15.5.2 Fluoxetine versus fluoxetine plus olanzapine	1	26	Mean Difference (IV, Fixed, 95% CI)	4.77 [-9.67, 19.21]
15.5.3 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid	1	34	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.82, 2.02]
15.6 Secondary: Affective instability at end of treatment (continuous outcome, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.6.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid	1	34	Mean Difference (IV, Fixed, 95% CI)	1.72 [0.68, 2.76]
15.7 Secondary: Chronic feelings of emptiness at end of treatment (continuous outcome, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.7.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid	1	34	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.97, 1.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.8 Secondary: Impulsivity at end of treatment (continuous outcome, MDs)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.8.1 Olanzapine versus olanzapine plus fluoxetine	1	29	Mean Difference (IV, Fixed, 95% CI)	0.46 [-12.93, 13.85]
15.8.2 Fluoxetinge versus fluoxetine plus olanzapine	1	26	Mean Difference (IV, Fixed, 95% CI)	4.77 [-9.67, 19.21]
15.8.3 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid	1	34	Mean Difference (IV, Fixed, 95% CI)	12.59 [6.11, 19.07]
15.9 Secondary: Interpersonal problems at end of treatment (continuous outcome, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.9.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid	1	34	Mean Difference (IV, Fixed, 95% CI)	0.47 [-0.41, 1.35]
15.10 Secondary: Abandonment at end of treatment (continuous outcome, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.10.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid	1	34	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.83, 0.85]
15.11 Secondary: Identity disturbance at end of treatment (continuous outcome, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.11.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid	1	34	Mean Difference (IV, Fixed, 95% CI)	0.70 [-0.34, 1.74]
15.12 Secondary: Dissociation and psychotic-like symptoms at end of treatment (continuous outcome, MDs)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.12.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid	1	34	Mean Difference (IV, Fixed, 95% CI)	0.03 [-1.09, 1.15]
15.13 Secondary: Depression at end of treatment (continuous outcome, MDs)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.13.1 Olanzapine versus olanzapine plus fluoxetine	1	29	Mean Difference (IV, Fixed, 95% CI)	-1.78 [-6.48, 2.92]
15.13.2 Fluoxetine versus fluoxetine plus olanzapine	1	26	Mean Difference (IV, Fixed, 95% CI)	3.62 [-1.36, 8.60]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.13.3 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid	1	34	Mean Difference (IV, Fixed, 95% CI)	1.30 [0.00, 2.60]
15.14 Secondary: Attrition at end of treatment (dichotomous outcomes, RRs)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.14.1 Olanzapine versus olanzapine plus fluoxetine	1	31	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.63]
15.14.2 Fluoxetine versus fluoxetine plus olanzapine	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.05, 5.28]
15.14.3 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid	1	43	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.29, 2.97]

Analysis 15.1. Comparison 15: Single medication compared with combination of medications, Outcome 1: Primary: BPD symptom severity at end of treatment (continuous outcome, MDs)

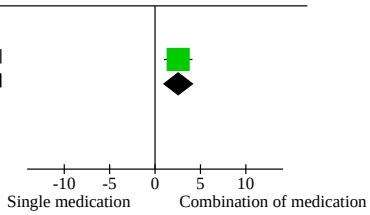
Study or Subgroup	Single medication Mean	SD	Total	Combination of medication Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
15.1.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid								
Bellino 2014 (1)	44.57	6.53	16	36.09	8.57	18	100.0%	8.48 [3.39 , 13.57]
Subtotal (95% CI)			**16**			**18**	**100.0%**	**8.48 [3.39 , 13.57]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.27 (P = 0.001)								
Test for subgroup differences: Not applicable								



Footnotes
(1) Mood stabiliser versus mood stabiliser plus omega-3 fatty acids

Analysis 15.2. Comparison 15: Single medication compared with combination of medications, Outcome 2: Primary: Self-harm at end of treatment (continuous outcome, MDs)

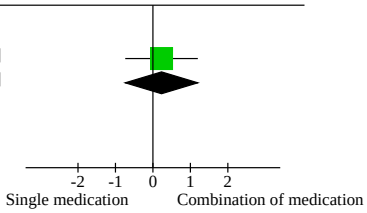
Study or Subgroup	Single medication Mean	SD	Total	Combination of medication Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
15.2.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid								
Bellino 2014 (1)	5.88	1.89	16	3.33	2.74	18	100.0%	2.55 [0.98 , 4.12]
Subtotal (95% CI)			**16**			**18**	**100.0%**	**2.55 [0.98 , 4.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.19 (P = 0.001)								
Test for subgroup differences: Not applicable								



Footnotes
(1) Mood stabiliser versus mood stabiliser plus omega-3 fatty acids

Analysis 15.3. Comparison 15: Single medication compared with combination of medications, Outcome 3: Primary: Suicide-related outcomes at end of treatment (continuous outcome, MDs)

	Single medication			Combination of medication				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
15.3.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid									
Bellino 2014 (1)	1.12	1.31	16	0.89	1.57	18	100.0%	0.23 [-0.74 , 1.20]	
Subtotal (95% CI)			**16**			**18**	**100.0%**	**0.23 [-0.74 , 1.20]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.47 (P = 0.64)									
Test for subgroup differences: Not applicable									

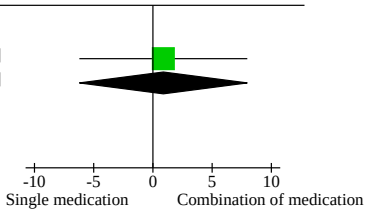


Footnotes

(1) Mood stabiliser versus mood stabiliser plus omega-3 fatty acids

Analysis 15.4. Comparison 15: Single medication compared with combination of medications, Outcome 4: Primary: Psychosocial functioning at end of treatment (continuous outcome, MDs)

	Single medication			Combination of medication				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
15.4.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid									
Bellino 2014 (1)	-70.25	9.98	16	-71.13	11.11	18	100.0%	0.88 [-6.21 , 7.97]	
Subtotal (95% CI)			**16**			**18**	**100.0%**	**0.88 [-6.21 , 7.97]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.24 (P = 0.81)									
Test for subgroup differences: Not applicable									

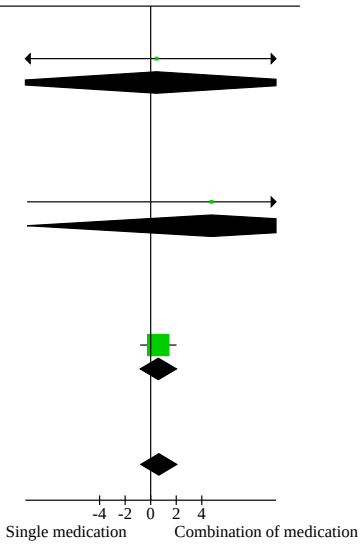


Footnotes

(1) Mood stabiliser versus mood stabiliser plus omega-3 fatty acids (CGI-S)

Analysis 15.5. Comparison 15: Single medication compared with combination of medications, Outcome 5: Secondary: Anger at end of treatment (continuous outcome, MDs)

Study or Subgroup	Single medication Mean	SD	Total	Combination of medication Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
15.5.1 Olanzapine versus olanzapine plus fluoxetine								
Zanarini 2004 (1)	-19.69	20.83	16	-20.15	15.95	13	1.1%	0.46 [-12.93 , 13.85]
Subtotal (95% CI)			**16**			**13**	**1.1%**	**0.46 [-12.93 , 13.85]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.07 (P = 0.95)								
15.5.2 Fluoxetine versus fluoxetine plus olanzapine								
Zanarini 2004 (2)	-15.38	21.25	13	-20.15	15.95	13	0.9%	4.77 [-9.67 , 19.21]
Subtotal (95% CI)			**13**			**13**	**0.9%**	**4.77 [-9.67 , 19.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.65 (P = 0.52)								
15.5.3 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid								
Bellino 2014 (3)	3.38	2.12	16	2.78	2.1	18	97.9%	0.60 [-0.82 , 2.02]
Subtotal (95% CI)			**16**			**18**	**97.9%**	**0.60 [-0.82 , 2.02]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.83 (P = 0.41)								
Total (95% CI)			**45**			**44**	**100.0%**	**0.64 [-0.77 , 2.04]**
Heterogeneity: Chi² = 0.32, df = 2 (P = 0.85); I² = 0%								
Test for overall effect: Z = 0.89 (P = 0.37)								
Test for subgroup differences: Chi² = 0.32, df = 2 (P = 0.85), I² = 0%								

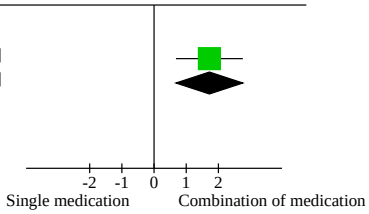


Footnotes

(1) Antipsychotic versus antipsychotic plus antidepressant
(2) Antidepressant versus antidepressant plus antipsychotic
(3) Mood stabiliser versus mood stabiliser plus omega-3 fatty acids

Analysis 15.6. Comparison 15: Single medication compared with combination of medications, Outcome 6: Secondary: Affective instability at end of treatment (continuous outcome, MDs)

Study or Subgroup	Single medication Mean	SD	Total	Combination of medication Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
15.6.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid								
Bellino 2014 (1)	6.5	1.63	16	4.78	1.44	18	100.0%	1.72 [0.68 , 2.76]
Subtotal (95% CI)			**16**			**18**	**100.0%**	**1.72 [0.68 , 2.76]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.24 (P = 0.001)								
Test for subgroup differences: Not applicable								

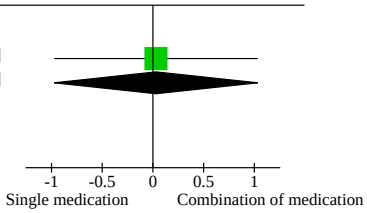


Footnotes

(1) Mood stabiliser versus mood stabiliser plus omega-3 fatty acids

Analysis 15.7. Comparison 15: Single medication compared with combination of medications, Outcome 7: Secondary: Chronic feelings of emptiness at end of treatment (continuous outcome, MDs)

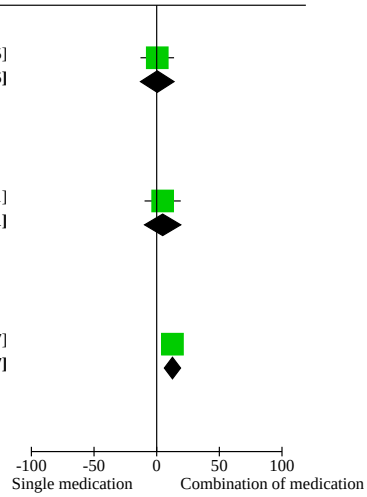
Study or Subgroup	Single medication Mean	SD	Total	Combination of medication Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
15.7.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid								
Bellino 2014 (1)	5.25	1.24	16	5.22	1.73	18	100.0%	0.03 [-0.97 , 1.03]
Subtotal (95% CI)			**16**			**18**	**100.0%**	**0.03 [-0.97 , 1.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.06 (P = 0.95)								
Test for subgroup differences: Not applicable								



Footnotes
(1) Mood stabiliser versus mood stabiliser plus omega-3 fatty acids

Analysis 15.8. Comparison 15: Single medication compared with combination of medications, Outcome 8: Secondary: Impulsivity at end of treatment (continuous outcome, MDs)

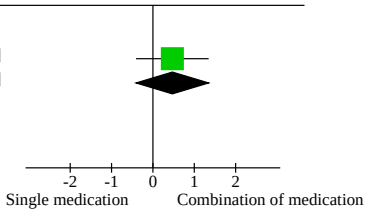
Study or Subgroup	Single medication Mean	SD	Total	Combination of medication Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
15.8.1 Olanzapine versus olanzapine plus fluoxetine								
Zanarini 2004 (1)	-19.69	20.83	16	-20.15	15.95	13	100.0%	0.46 [-12.93 , 13.85]
Subtotal (95% CI)			**16**			**13**	**100.0%**	**0.46 [-12.93 , 13.85]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.07 (P = 0.95)								
15.8.2 Fluoxetinge versus fluoxetine plus olanzapine								
Zanarini 2004 (2)	-15.38	21.25	13	-20.15	15.95	13	100.0%	4.77 [-9.67 , 19.21]
Subtotal (95% CI)			**13**			**13**	**100.0%**	**4.77 [-9.67 , 19.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.65 (P = 0.52)								
15.8.3 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid								
Bellino 2014 (3)	77.37	5.51	16	64.78	12.74	18	100.0%	12.59 [6.11 , 19.07]
Subtotal (95% CI)			**16**			**18**	**100.0%**	**12.59 [6.11 , 19.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.81 (P = 0.0001)								



Footnotes
(1) Antipsychotic versus antipsychotic plus antidepressant
(2) Antidepressant versus antidepressant plus antipsychotic
(3) Mood stabiliser versus mood stabiliser plus omega-3 fatty acids

Analysis 15.9. Comparison 15: Single medication compared with combination of medications, Outcome 9: Secondary: Interpersonal problems at end of treatment (continuous outcome, MDs)

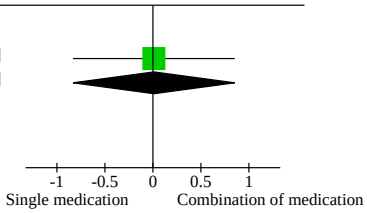
Study or Subgroup	Single medication Mean	SD	Total	Combination of medication Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
15.9.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid								
Bellino 2014 (1)	6.25	1.34	16	5.78	1.26	18	100.0%	0.47 [-0.41 , 1.35]
Subtotal (95% CI)			**16**			**18**	**100.0%**	**0.47 [-0.41 , 1.35]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.05 (P = 0.29)								
Test for subgroup differences: Not applicable								



Footnotes
(1) Mood stabiliser versus mood stabiliser plus omega-3 fatty acids

Analysis 15.10. Comparison 15: Single medication compared with combination of medications, Outcome 10: Secondary: Abandonment at end of treatment (continuous outcome, MDs)

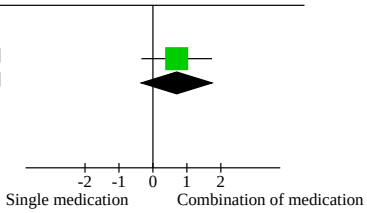
Study or Subgroup	Single medication Mean	SD	Total	Combination of medication Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
15.10.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid								
Bellino 2014 (1)	6.12	1.09	16	6.11	1.41	18	100.0%	0.01 [-0.83 , 0.85]
Subtotal (95% CI)			**16**			**18**	**100.0%**	**0.01 [-0.83 , 0.85]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.02 (P = 0.98)								
Test for subgroup differences: Not applicable								



Footnotes
(1) Mood stabiliser versus mood stabiliser plus omega-3 fatty acids

Analysis 15.11. Comparison 15: Single medication compared with combination of medications, Outcome 11: Secondary: Identity disturbance at end of treatment (continuous outcome, MDs)

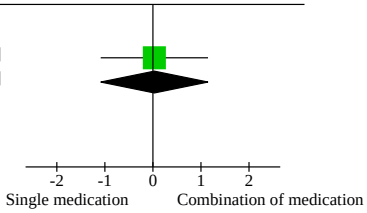
Study or Subgroup	Single medication Mean	SD	Total	Combination of medication Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
15.11.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid								
Bellino 2014 (1)	4.9	1.53	16	4.2	1.56	18	100.0%	0.70 [-0.34 , 1.74]
Subtotal (95% CI)			**16**			**18**	**100.0%**	**0.70 [-0.34 , 1.74]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.32 (P = 0.19)								
Test for subgroup differences: Not applicable								



Footnotes
(1) Mood stabiliser versus mood stabiliser plus omega-3 fatty acids

Analysis 15.12. Comparison 15: Single medication compared with combination of medications, Outcome 12: Secondary: Dissociation and psychotic-like symptoms at end of treatment (continuous outcome, MDs)

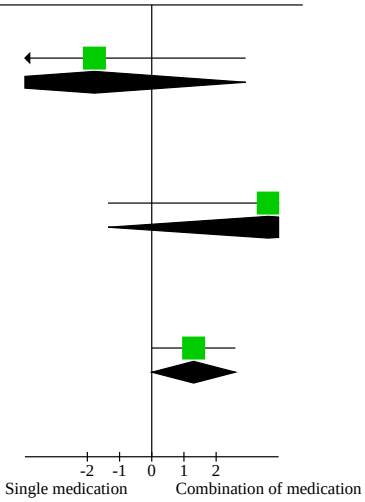
Study or Subgroup	Single medication Mean	SD	Total	Combination of medication Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
15.12.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid								
Bellino 2014 (1)	1.36	1.28	16	1.33	2	18	100.0%	0.03 [-1.09 , 1.15]
Subtotal (95% CI)			**16**			**18**	**100.0%**	**0.03 [-1.09 , 1.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.05 (P = 0.96)								
Test for subgroup differences: Not applicable								



Footnotes
(1) Mood stabiliser versus mood stabiliser plus omega-3 fatty acids

Analysis 15.13. Comparison 15: Single medication compared with combination of medications, Outcome 13: Secondary: Depression at end of treatment (continuous outcome, MDs)

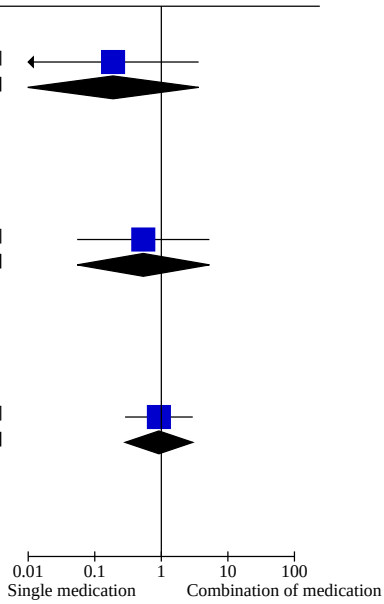
Study or Subgroup	Single medication Mean	SD	Total	Combination of medication Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
15.13.1 Olanzapine versus olanzapine plus fluoxetine								
Zanarini 2004 (1)	-13.63	7.23	16	-11.85	5.67	13	100.0%	-1.78 [-6.48 , 2.92]
Subtotal (95% CI)			**16**			**13**	**100.0%**	**-1.78 [-6.48 , 2.92]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.74 (P = 0.46)								
15.13.2 Fluoxetine versus fluoxetine plus olanzapine								
Zanarini 2004 (2)	-8.23	7.19	13	-11.85	5.67	13	100.0%	3.62 [-1.36 , 8.60]
Subtotal (95% CI)			**13**			**13**	**100.0%**	**3.62 [-1.36 , 8.60]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.43 (P = 0.15)								
15.13.3 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid								
Bellino 2014 (3)	13.63	1.26	16	12.33	2.47	18	100.0%	1.30 [0.00 , 2.60]
Subtotal (95% CI)			**16**			**18**	**100.0%**	**1.30 [0.00 , 2.60]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.96 (P = 0.05)								



Footnotes
(1) Antipsychotic versus antipsychotic plus antidepressant
(2) Antidepressant versus antidepressant plus antipsychotic
(3) Mood stabiliser versus mood stabiliser plus omega-3 fatty acids

Analysis 15.14. Comparison 15: Single medication compared with combination of medications, Outcome 14: Secondary: Attrition at end of treatment (dichotomous outcomes, RRs)

Study or Subgroup	Single medication Events	Total	Combination of medication Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
15.14.1 Olanzapine versus olanzapine plus fluoxetine						
Zanarini 2004 (1)	0	16	2	15	100.0%	0.19 [0.01 , 3.63]
Subtotal (95% CI)		**16**		**15**	**100.0%**	**0.19 [0.01 , 3.63]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						
15.14.2 Fluoxetine versus fluoxetine plus olanzapine						
Zanarini 2004 (2)	1	14	2	15	100.0%	0.54 [0.05 , 5.28]
Subtotal (95% CI)		**14**		**15**	**100.0%**	**0.54 [0.05 , 5.28]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.59)						
15.14.3 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid						
Bellino 2014 (3)	4	20	5	23	100.0%	0.92 [0.29 , 2.97]
Subtotal (95% CI)		**20**		**23**	**100.0%**	**0.92 [0.29 , 2.97]**
Total events:	4		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						
Test for subgroup differences: Chi² = 1.02, df = 2 (P = 0.60), I² = 0%						

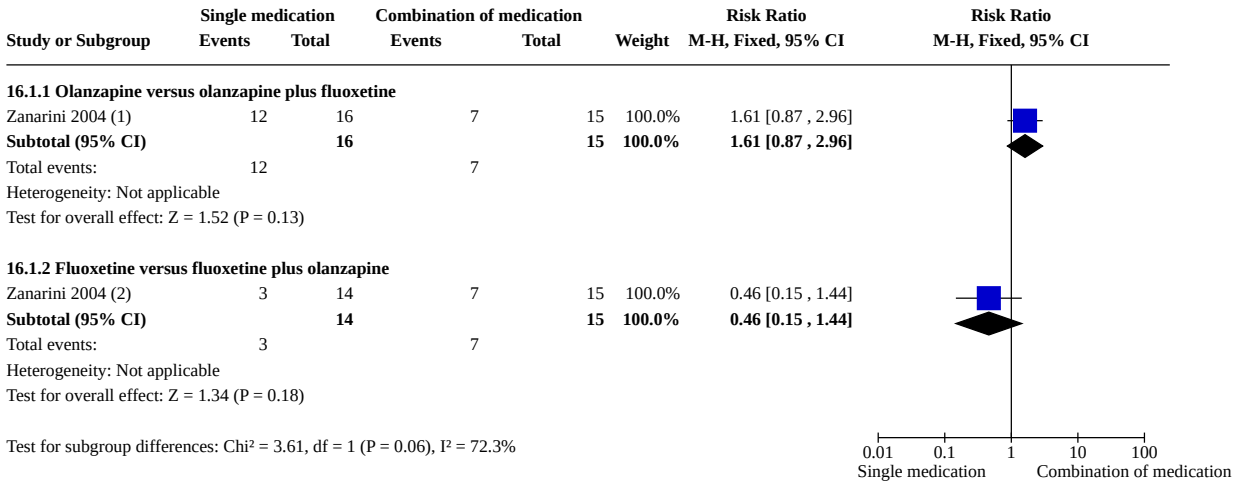


Footnotes
(1) Antipsychotic versus antipsychotic plus antidepressant
(2) Antidepressant versus antidepressant plus antipsychotic
(3) Mood stabiliser versus mood stabiliser plus omega-3 fatty acids

Comparison 16. Single medication compared with combination of medications - non-serious adverse events - central nervous system

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Sedation	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1.1 Olanzapine versus olanzapine plus fluoxetine	1	31	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [0.87, 2.96]
16.1.2 Fluoxetine versus fluoxetine plus olanzapine	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.15, 1.44]

Analysis 16.1. Comparison 16: Single medication compared with combination of medications - non-serious adverse events - central nervous system, Outcome 1: Sedation



Footnotes

(1) Antipsychotic versus antipsychotic plus antidepressant

(2) Antidepressant versus antidepressant plus antipsychotic

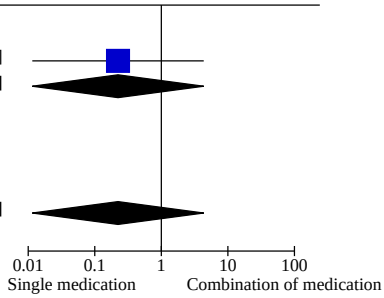
Comparison 17. Single medication compared with combination of medications - non-serious adverse events - gastro-intestinal system

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Nausea	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.01, 4.34]
17.1.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.01, 4.34]
17.2 Dyspepsia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.2.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid	1	34	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.08, 16.55]

Analysis 17.1. Comparison 17: Single medication compared with combination of medications - non-serious adverse events - gastro-intestinal system, Outcome 1: Nausea

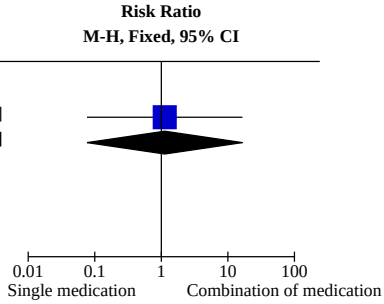
Study or Subgroup	Single medication Events	Total	Combination of medication Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
17.1.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid						
Bellino 2014 (1)	0	16	2	18	100.0%	0.22 [0.01 , 4.34]
Subtotal (95% CI)		**16**		**18**	**100.0%**	**0.22 [0.01 , 4.34]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
Total (95% CI)		**16**		**18**	**100.0%**	**0.22 [0.01 , 4.34]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
Test for subgroup differences: Not applicable						



Footnotes
(1) Mood stabiliser versus mood stabiliser plus omega-3 fatty acids

Analysis 17.2. Comparison 17: Single medication compared with combination of medications - non-serious adverse events - gastro-intestinal system, Outcome 2: Dyspepsia

Study or Subgroup	Single medication Events	Total	Combination of medication Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
17.2.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid						
Bellino 2014 (1)	1	16	1	18	100.0%	1.13 [0.08 , 16.55]
Subtotal (95% CI)		**16**		**18**	**100.0%**	**1.13 [0.08 , 16.55]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.09 (P = 0.93)						
Test for subgroup differences: Not applicable						



Footnotes
(1) Mood stabiliser versus mood stabiliser plus omega-3 fatty acids

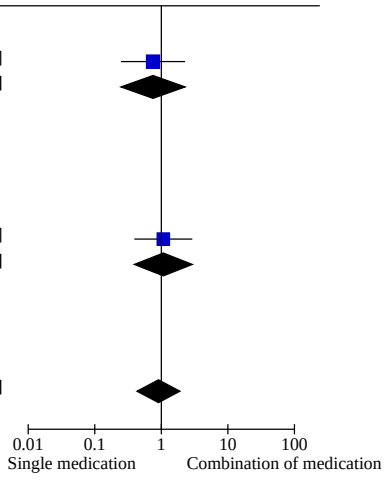
Comparison 18. Single medication compared with combination of medications - musculoskeletal system

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 Akathisia	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.43, 1.90]
18.1.1 Olanzapine versus olanzapine plus fluoxetine	1	31	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.25, 2.28]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1.2 Fluoxetine versus fluoxetine plus olanzapine	1	29	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.39, 2.92]
18.2 Body weight change	1	34	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.26, 4.80]
18.2.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid	1	34	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.26, 4.80]
18.3 Body weight change	1	55	Mean Difference (IV, Fixed, 95% CI)	0.23 [-0.76, 1.22]
18.3.1 Olanzapine versus olanzapine plus fluoxetine	1	29	Mean Difference (IV, Fixed, 95% CI)	1.50 [0.09, 2.91]
18.3.2 Fluoxetine versus fluoxetine plus olanzapine	1	26	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-2.39, 0.39]

Analysis 18.1. Comparison 18: Single medication compared with combination of medications - musculoskeletal system, Outcome 1: Akathisia

Study or Subgroup	Single medication Events	Total	Combination of medication Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
18.1.1 Olanzapine versus olanzapine plus fluoxetine						
Zanarini 2004 (1)	4	16	5	15	51.7%	0.75 [0.25 , 2.28]
Subtotal (95% CI)		**16**		**15**	**51.7%**	**0.75 [0.25 , 2.28]**
Total events:	4		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
18.1.2 Fluoxetine versus fluoxetine plus olanzapine						
Zanarini 2004 (2)	5	14	5	15	48.3%	1.07 [0.39 , 2.92]
Subtotal (95% CI)		**14**		**15**	**48.3%**	**1.07 [0.39 , 2.92]**
Total events:	5		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.89)						
Total (95% CI)		**30**		**30**	**100.0%**	**0.91 [0.43 , 1.90]**
Total events:	9		10			
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.26 (P = 0.79)						
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² = 0%						



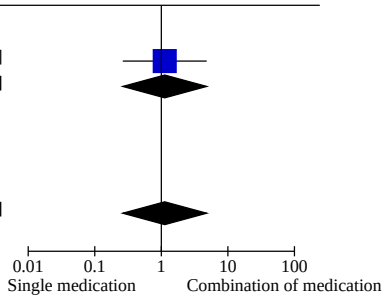
Footnotes

(1) Antipsychotic versus antipsychotic plus antidepressant

(2) Antidepressant versus antidepressant plus antipsychotic

Analysis 18.2. Comparison 18: Single medication compared with combination of medications - musculoskeletal system, Outcome 2: Body weight change

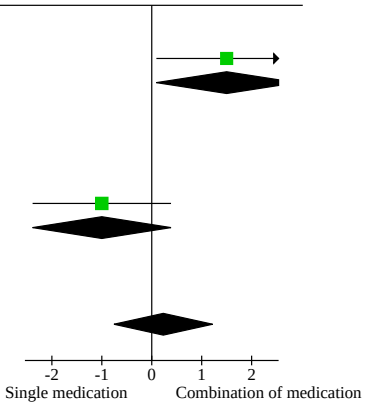
Study or Subgroup	Single medication Events	Total	Combination of medication Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
18.2.1 Valproic acid versus valproic acid plus eicosapentaenoic acid and docosahexaenoic acid						
Bellino 2014 (1)	3	16	3	18	100.0%	1.13 [0.26 , 4.80]
Subtotal (95% CI)		**16**		**18**	**100.0%**	**1.13 [0.26 , 4.80]**
Total events:	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.87)						
Total (95% CI)		**16**		**18**	**100.0%**	**1.13 [0.26 , 4.80]**
Total events:	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.87)						
Test for subgroup differences: Not applicable						



Footnotes
(1) Mood stabiliser versus mood stabiliser plus omega-3 fatty acids

Analysis 18.3. Comparison 18: Single medication compared with combination of medications - musculoskeletal system, Outcome 3: Body weight change

Study or Subgroup	Single medication Mean	SD	Total	Combination of medication Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
18.3.1 Olanzapine versus olanzapine plus fluoxetine								
Zanarini 2004 (1)	2.9	2.6	16	1.4	1.1	13	49.2%	1.50 [0.09 , 2.91]
Subtotal (95% CI)			**16**			**13**	**49.2%**	**1.50 [0.09 , 2.91]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.09 (P = 0.04)								
18.3.2 Fluoxetine versus fluoxetine plus olanzapine								
Zanarini 2004 (2)	0.4	2.3	13	1.4	1.1	13	50.8%	-1.00 [-2.39 , 0.39]
Subtotal (95% CI)			**13**			**13**	**50.8%**	**-1.00 [-2.39 , 0.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.41 (P = 0.16)								
Total (95% CI)			**29**			**26**	**100.0%**	**0.23 [-0.76 , 1.22]**
Heterogeneity: Chi² = 6.15, df = 1 (P = 0.01); I² = 84%								
Test for overall effect: Z = 0.46 (P = 0.65)								
Test for subgroup differences: Chi² = 6.15, df = 1 (P = 0.01), I² = 83.8%								



Footnotes
(1) Antipsychotic versus antipsychotic plus antidepressant
(2) Antidepressant versus antidepressant plus antipsychotic

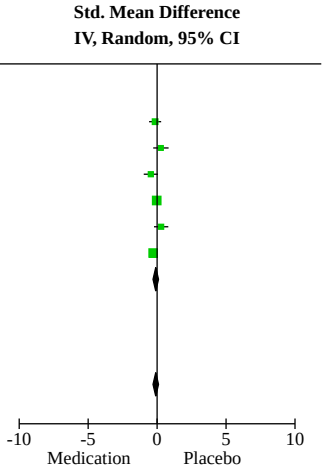
Comparison 19. Medication compared with placebo - TSA sensitivity analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.1 BPD symptom severity at end of treatment	6	859	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.30, 0.10]
19.1.1 Antipsychotics	6	859	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.30, 0.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.2 Secondary: interpersonal problems at end of treatment	7	616	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.38, -0.05]
19.2.1 Antipsychotics	7	616	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.38, -0.05]
19.3 Attrition at end of treatment	22	1550	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.84, 1.17]
19.3.1 Antipsychotics	11	1044	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.84, 1.30]
19.3.2 Antidepressants	5	252	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.65, 1.97]
19.3.3 Mood stabiliser	8	254	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.55, 1.15]

Analysis 19.1. Comparison 19: Medication compared with placebo - TSA sensitivity analyses, Outcome 1: BPD symptom severity at end of treatment

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
19.1.1 Antipsychotics								
Black 2014 (1)	7.9	4.8151	66	8.6	4.8	29	13.9%	-0.14 [-0.58 , 0.29]
Goldberg 1986 (2)	6	6.3589	24	4.22	6.3589	26	9.8%	0.28 [-0.28 , 0.83]
Pascual 2008 (3)	12	6.4679	30	14.99	6.4679	30	11.1%	-0.46 [-0.97 , 0.06]
Schulz 2007 (4)	3	6.3736	150	3.19	6.3736	155	27.5%	-0.03 [-0.25 , 0.19]
Soloff 1993 (5)	4	6.4315	30	2.09	6.4315	28	10.9%	0.29 [-0.22 , 0.81]
Zanarini 2007 (4)	5	6.3967	144	6.85	6.3967	147	26.9%	-0.29 [-0.52 , -0.06]
Subtotal (95% CI)			**444**			**415**	**100.0%**	**-0.10 [-0.30 , 0.10]**
Heterogeneity: Tau² = 0.02; Chi² = 8.70, df = 5 (P = 0.12); I² = 43%								
Test for overall effect: Z = 0.96 (P = 0.34)								
Total (95% CI)			**444**			**415**	**100.0%**	**-0.10 [-0.30 , 0.10]**
Heterogeneity: Tau² = 0.02; Chi² = 8.70, df = 5 (P = 0.12); I² = 43%								
Test for overall effect: Z = 0.96 (P = 0.34)								
Test for subgroup differences: Not applicable								

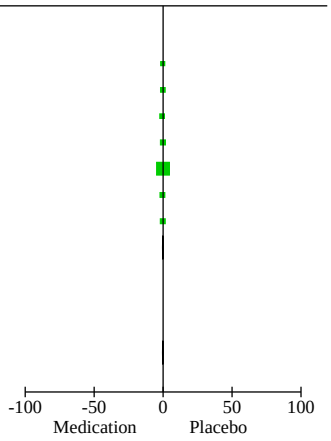


Footnotes

(1) Quetiapine versus placebo (both active groups pooled into one), final scores (Tab. 4 + text p. 1179), baseline SDs (Tab. 4)
(2) Thiothixine versus placebo
(3) Ziprasidone versus placebo
(4) Olanzapine versus placebo
(5) Haloperidol versus placebo

Analysis 19.2. Comparison 19: Medication compared with placebo - TSA sensitivity analyses, Outcome 2: Secondary: interpersonal problems at end of treatment

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
19.2.1 Antipsychotics								
Bogenschutz 2004 (1)	2	1.2378	16	2.37	1.2378	19	6.0%	-0.29 [-0.96 , 0.38]
Goldberg 1986 (2)	1	1.2364	24	1.22	1.2364	26	8.6%	-0.18 [-0.73 , 0.38]
Nickel 2006 (3)	3	1.2619	26	3.95	1.2619	26	8.4%	-0.74 [-1.30 , -0.18]
Pascual 2008 (4)	4	1.2394	30	4.15	1.2394	30	10.3%	-0.12 [-0.63 , 0.39]
Schulz 2007 (1)	2	1.2223	150	2.09	1.2223	155	47.3%	-0.07 [-0.30 , 0.15]
Soloff 1989 (5)	5	1.2722	28	5.65	1.2722	28	9.4%	-0.50 [-1.04 , 0.03]
Soloff 1993 (5)	8	1.2178	30	8.28	1.2178	28	9.9%	-0.23 [-0.74 , 0.29]
Subtotal (95% CI)			**304**			**312**	**100.0%**	**-0.21 [-0.38 , -0.05]**
Heterogeneity: Tau² = 0.00; Chi² = 6.20, df = 6 (P = 0.40); I² = 3%								
Test for overall effect: Z = 2.51 (P = 0.01)								
Total (95% CI)			**304**			**312**	**100.0%**	**-0.21 [-0.38 , -0.05]**
Heterogeneity: Tau² = 0.00; Chi² = 6.20, df = 6 (P = 0.40); I² = 3%								
Test for overall effect: Z = 2.51 (P = 0.01)								
Test for subgroup differences: Not applicable								

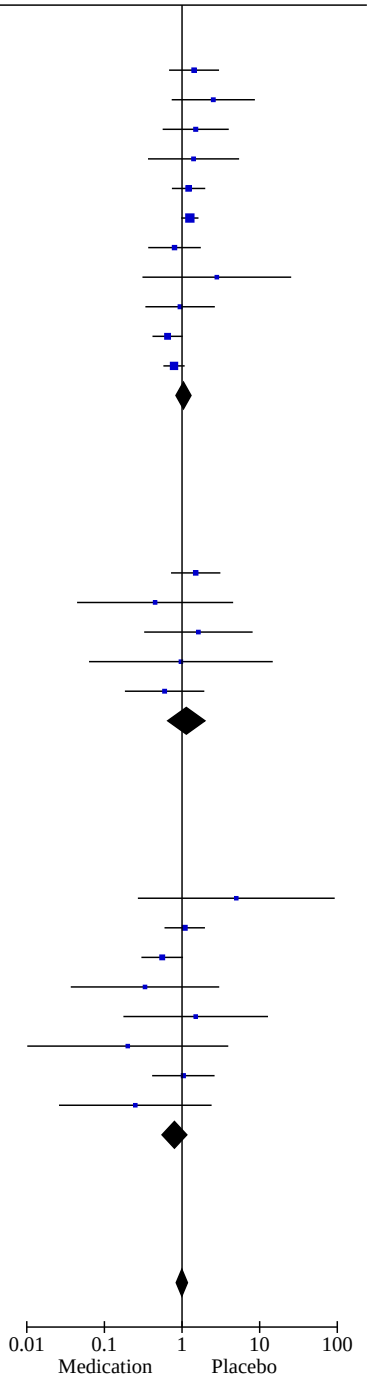


Footnotes

(1) Olanzapine versus placebo
(2) Thiothixene versus placebo
(3) Aripiprazole versus placebo
(4) Ziprasidone versus placebo
(5) Haloperidol versus placebo

Analysis 19.3. Comparison 19: Medication compared with placebo - TSA sensitivity analyses, Outcome 3: Attrition at end of treatment

Study or Subgroup	Medication Events	Medication Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
19.3.1 Antipsychotics						
Bogenschutz 2004 (1)	10	20	7	20	4.5%	1.43 [0.68 , 3.00]
Goldberg 1986 (2)	7	24	3	26	1.7%	2.53 [0.74 , 8.68]
Linehan 2008 (1)	6	12	4	12	2.7%	1.50 [0.56 , 4.00]
Montgomery 1982a (3)	4	18	3	19	1.5%	1.41 [0.36 , 5.43]
Pascual 2008 (4)	17	30	14	30	8.8%	1.21 [0.74 , 1.99]
Schulz 2007 (1)	75	155	61	159	20.8%	1.26 [0.98 , 1.63]
Soler 2005 (1)	8	30	10	30	4.1%	0.80 [0.37 , 1.74]
Soloff 1989 (5)	3	31	1	29	0.6%	2.81 [0.31 , 25.48]
Soloff 1993 (5)	6	36	6	34	2.4%	0.94 [0.34 , 2.65]
Zanarini 2001 (1)	11	19	8	9	10.3%	0.65 [0.42 , 1.02]
Zanarini 2007 (1)	45	148	59	153	16.5%	0.79 [0.58 , 1.08]
Subtotal (95% CI)		**523**		**521**	**73.8%**	**1.04 [0.84 , 1.30]**
Total events:	192		176			
Heterogeneity: Tau² = 0.04; Chi² = 14.58, df = 10 (P = 0.15); I² = 31%						
Test for overall effect: Z = 0.38 (P = 0.71)						
19.3.2 Antidepressants						
Montgomery 1982b (6)	12	29	8	29	4.6%	1.50 [0.72 , 3.12]
Rinne 2002 (7)	1	20	2	18	0.5%	0.45 [0.04 , 4.55]
Simpson 2004 (8)	3	12	2	13	1.0%	1.63 [0.33 , 8.11]
Soloff 1989 (9)	1	30	1	29	0.4%	0.97 [0.06 , 14.74]
Soloff 1993 (10)	4	38	6	34	1.9%	0.60 [0.18 , 1.94]
Subtotal (95% CI)		**129**		**123**	**8.4%**	**1.14 [0.65 , 1.97]**
Total events:	21		19			
Heterogeneity: Tau² = 0.00; Chi² = 2.56, df = 4 (P = 0.63); I² = 0%						
Test for overall effect: Z = 0.45 (P = 0.65)						
19.3.3 Mood stabiliser						
De la Fuente 1994 (11)	2	10	0	10	0.3%	5.00 [0.27 , 92.62]
Frankenburg 2002 (12)	13	20	6	10	6.4%	1.08 [0.59 , 1.97]
Hollander 2001 (12)	6	12	4	4	6.1%	0.56 [0.30 , 1.03]
Loew 2006 (13)	1	28	3	28	0.6%	0.33 [0.04 , 3.01]
Nickel 2004 (13)	3	22	1	11	0.6%	1.50 [0.18 , 12.80]
Nickel 2005 (13)	0	22	2	22	0.3%	0.20 [0.01 , 3.94]
Reich 2009 (14)	6	15	5	13	3.0%	1.04 [0.41 , 2.62]
Tritt 2005 (14)	1	18	2	9	0.5%	0.25 [0.03 , 2.40]
Subtotal (95% CI)		**147**		**107**	**17.8%**	**0.80 [0.55 , 1.15]**
Total events:	32		23			
Heterogeneity: Tau² = 0.00; Chi² = 6.95, df = 7 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.21 (P = 0.23)						
Total (95% CI)		**799**		**751**	**100.0%**	**0.99 [0.84 , 1.17]**
Total events:	245		218			
Heterogeneity: Tau² = 0.02; Chi² = 25.94, df = 23 (P = 0.30); I² = 11%						
Test for overall effect: Z = 0.07 (P = 0.94)						
Test for subgroup differences: Chi² = 1.78, df = 2 (P = 0.41), I² = 0%						



Footnotes

(1) Olanzapine versus placebo
(2) Thiothixene versus placebo
(3) Flupenthixol decanoate versus placebo
(4) Ziprasidone versus placebo

Analysis 19.3. (Continued)

(3) Flupenthixol decanoate versus placebo
(4) Ziprasidone versus placebo
(5) Haloperidol versus placebo
(6) Mianserin versus placebo
(7) Fluvoxamine versus placebo
(8) Fluoxetine versus placebo
(9) Amitriptyline versus placebo
(10) Phenelzine sulfate versus placebo
(11) Carbamazepine versus placebo
(12) Valproate semisodium versus placebo
(13) Topiramate versus placebo
(14) Lamotrigine versus placebo

Comparison 20. Subgroup analysis: types of medication

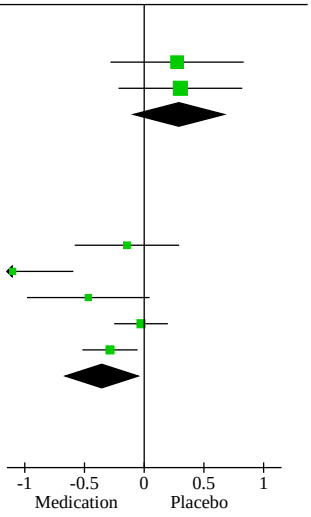
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.1 BPD symptom severity - antipsychotics vs placebo by class (1st vs 2nd generation)	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
20.1.1 1st generation	2	108	Std. Mean Difference (IV, Random, 95% CI)	0.29 [-0.09, 0.67]
20.1.2 2nd generation	5	820	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-0.66, -0.05]
20.2 Suicide-related outcomes - antipsychotics vs placebo by class (1st vs 2nd generation)	7	854	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.18, 0.29]
20.2.1 1st generation	2	103	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-1.26, 0.86]
20.2.2 2nd generation	5	751	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.17, 0.31]
20.3 Psychosocial functioning - antipsychotics vs placebo by class (1st vs 2nd generation)	7	904	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.33, -0.00]
20.3.1 1st generation	3	164	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.67, 0.42]
20.3.2 2nd generation	4	740	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.32, -0.03]
20.4 BPD symptom severity - antipsychotics vs placebo by substance	7	928	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.49, 0.08]
20.4.1 Haloperidol	1	58	Std. Mean Difference (IV, Random, 95% CI)	0.30 [-0.22, 0.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.4.2 Olanzapine	2	596	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.41, 0.10]
20.4.3 Thiothixene	1	50	Std. Mean Difference (IV, Random, 95% CI)	0.28 [-0.28, 0.83]
20.4.4 Quetiapine	1	95	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.58, 0.29]
20.4.5 Ziprasidone	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.47 [-0.98, 0.05]
20.4.6 Brexpiprazole	1	69	Std. Mean Difference (IV, Random, 95% CI)	-1.10 [-1.61, -0.59]
20.5 BPD symptom severity - mood stabiliser vs placebo by substance	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
20.5.1 Divalproex semisodium	1	15	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-1.22, 0.93]
20.5.2 Lamotrigine	2	222	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.34, 0.19]
20.6 Suicide-related outcomes - antipsychotics vs placebo by substance	7	856	Std. Mean Difference (IV, Random, 95% CI)	0.13 [-0.08, 0.34]
20.6.1 Olanzapine	4	691	Std. Mean Difference (IV, Random, 95% CI)	0.13 [-0.13, 0.39]
20.6.2 Ziprasidone	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.78, 0.23]
20.6.3 Brexpiprazole	1	80	Std. Mean Difference (IV, Random, 95% CI)	0.28 [-0.16, 0.72]
20.6.4 Alprazolam	1	25	Std. Mean Difference (IV, Random, 95% CI)	0.62 [-0.18, 1.43]
20.7 Psychosocial functioning - antipsychotics vs placebo by substance	7	904	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.33, -0.00]
20.7.1 Haloperidol	2	114	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-1.08, 0.77]
20.7.2 Olanzapine	3	645	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.30, 0.01]
20.7.3 Quetiapine	1	95	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.81, 0.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.7.4 Thiothixene	1	50	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.61, 0.50]
20.8 Psychosocial functioning - antidepressants vs placebo by class/substance	4	161	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.57, 0.06]
20.8.1 Tricyclic antidepressants (TCA)/amitriptyline	2	119	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.56, 0.16]
20.8.2 Selective serotonin reuptake inhibitors (SSRIs)/fluoxetine	2	42	Std. Mean Difference (IV, Random, 95% CI)	-0.40 [-1.07, 0.27]

Analysis 20.1. Comparison 20: Subgroup analysis: types of medication, Outcome 1: BPD symptom severity - antipsychotics vs placebo by class (1st vs 2nd generation)

	Medication			Placebo				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
20.1.1 1st generation									
Goldberg 1986 (1)	15.2859	4.4436	24	14.0812	4.1812	26	46.3%	0.28 [-0.28 , 0.83]	
Soloff 1993 (2)	24.03	13.24	30	20.08	12.44	28	53.7%	0.30 [-0.22 , 0.82]	
Subtotal (95% CI)			**54**			**54**	**100.0%**	**0.29 [-0.09 , 0.67]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%									
Test for overall effect: Z = 1.50 (P = 0.13)									
20.1.2 2nd generation									
Black 2014 (3)	7.9	4.8151	66	8.6	4.8	29	18.2%	-0.14 [-0.58 , 0.29]	
Grant 2022 (4)	3.1	3.9	35	8.4	5.5	34	16.1%	-1.10 [-1.61 , -0.59]	
Pascual 2008 (5)	3.88	0.6	30	4.3	1.1	30	15.9%	-0.47 [-0.98 , 0.05]	
Schulz 2007 (6)	-6.37	6.73	150	-6.19	6.89	155	25.0%	-0.03 [-0.25 , 0.20]	
Zanarini 2007 (6)	-8.52	6.15	144	-6.69	6.58	147	24.8%	-0.29 [-0.52 , -0.06]	
Subtotal (95% CI)			**425**			**395**	**100.0%**	**-0.36 [-0.66 , -0.05]**	
Heterogeneity: Tau² = 0.08; Chi² = 15.60, df = 4 (P = 0.004); I² = 74%									
Test for overall effect: Z = 2.28 (P = 0.02)									
Test for subgroup differences: Chi² = 6.74, df = 1 (P = 0.009), I² = 85.2%									

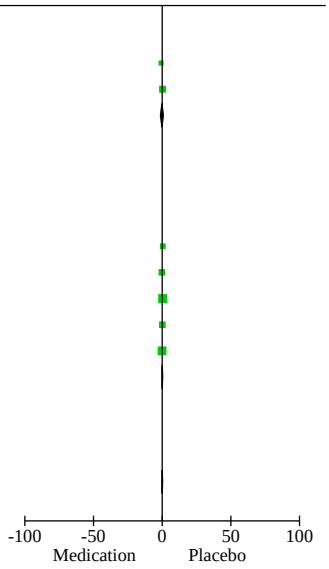


Footnotes

(1) Thiothixine versus placebo
(2) Haloperidol versus placebo
(3) Quetiapine versus placebo (both active groups pooled into one), final scores (Tab. 4 + text p. 1179), baseline SDs (Tab. 4)
(4) Brexpiprazole versus placebo
(5) Ziprasidone versus placebo
(6) Olanzapine versus placebo

Analysis 20.2. Comparison 20: Subgroup analysis: types of medication, Outcome 2: Suicide-related outcomes - antipsychotics vs placebo by class (1st vs 2nd generation)

	Medication			Placebo				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
20.2.1 1st generation									
Cowdry 1988 (1)	3.1	1.45	10	4.08	0.9	13	5.9%	-0.81 [-1.67 , 0.05]	
Grant 2022	0.23	0.66	40	0.08	0.35	40	14.5%	0.28 [-0.16 , 0.72]	
Subtotal (95% CI)			**50**			**53**	**20.4%**	**-0.20 [-1.26 , 0.86]**	
Heterogeneity: Tau² = 0.47; Chi² = 4.86, df = 1 (P = 0.03); I² = 79%									
Test for overall effect: Z = 0.37 (P = 0.71)									
20.2.2 2nd generation									
Bogenschutz 2004 (2)	-0.125	0.34157	16	-0.5263	1.17229	19	8.6%	0.44 [-0.24 , 1.11]	
Pascual 2008 (3)	2.7	1.6	30	3.13	1.5	30	12.4%	-0.27 [-0.78 , 0.23]	
Schulz 2007 (2)	-0.28	1.21	150	-0.61	1.21	155	23.2%	0.27 [0.05 , 0.50]	
Soler 2005 (2)	1.23	2.87	30	0.88	1.68	30	12.4%	0.15 [-0.36 , 0.65]	
Zanarini 2007 (2)	-0.3	0.8	144	-0.2	0.9	147	23.0%	-0.12 [-0.35 , 0.11]	
Subtotal (95% CI)			**370**			**381**	**79.6%**	**0.07 [-0.17 , 0.31]**	
Heterogeneity: Tau² = 0.04; Chi² = 8.61, df = 4 (P = 0.07); I² = 54%									
Test for overall effect: Z = 0.58 (P = 0.56)									
Total (95% CI)			**420**			**434**	**100.0%**	**0.05 [-0.18 , 0.29]**	
Heterogeneity: Tau² = 0.05; Chi² = 13.47, df = 6 (P = 0.04); I² = 55%									
Test for overall effect: Z = 0.43 (P = 0.67)									
Test for subgroup differences: Chi² = 0.24, df = 1 (P = 0.63), I² = 0%									

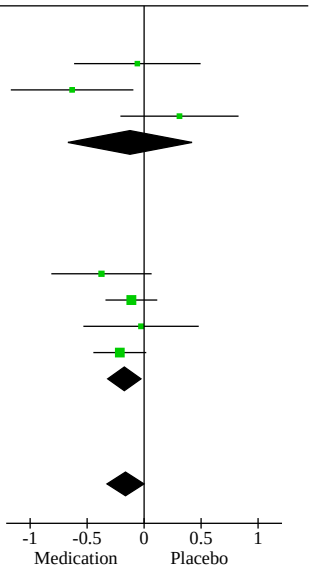


Footnotes

(1) Trifluoperazine hydrochloride versus placebo - cross-over data
(2) Olanzapine versus placebo
(3) Ziprasidone versus placebo

Analysis 20.3. Comparison 20: Subgroup analysis: types of medication, Outcome 3: Psychosocial functioning - antipsychotics vs placebo by class (1st vs 2nd generation)

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
20.3.1 1st generation								
Goldberg 1986 (1)	-72.42	9.25	24	-71.92	7.32	26	7.5%	-0.06 [-0.61 , 0.50]
Soloff 1989 (2)	-55.35	12.36	28	-48.16	9.95	28	8.0%	-0.63 [-1.17 , -0.09]
Soloff 1993 (2)	-54.95	9.15	30	-58.43	12.8	28	8.5%	0.31 [-0.21 , 0.83]
Subtotal (95% CI)			**82**			**82**	**24.0%**	**-0.12 [-0.67 , 0.42]**
Heterogeneity: Tau² = 0.16; Chi² = 6.18, df = 2 (P = 0.05); I² = 68%								
Test for overall effect: Z = 0.45 (P = 0.66)								
20.3.2 2nd generation								
Black 2014 (3)	-1.045	1.1689	66	-0.62	1.0232	29	11.2%	-0.37 [-0.81 , 0.07]
Schulz 2007 (4)	-5.89	8.87	147	-4.92	8.44	151	28.3%	-0.11 [-0.34 , 0.12]
Soler 2005 (5)	3.93	1.5	30	3.97	1.45	30	8.8%	-0.03 [-0.53 , 0.48]
Zanarini 2007 (6)	-7.74	8.09	144	-6	8.19	143	27.7%	-0.21 [-0.45 , 0.02]
Subtotal (95% CI)			**387**			**353**	**76.0%**	**-0.17 [-0.32 , -0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 1.52, df = 3 (P = 0.68); I² = 0%								
Test for overall effect: Z = 2.33 (P = 0.02)								
Total (95% CI)			**469**			**435**	**100.0%**	**-0.16 [-0.33 , -0.00]**
Heterogeneity: Tau² = 0.01; Chi² = 7.80, df = 6 (P = 0.25); I² = 23%								
Test for overall effect: Z = 1.97 (P = 0.05)								
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%								

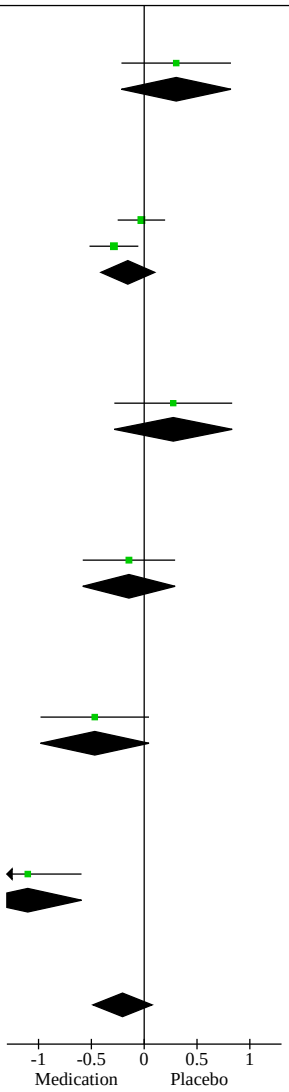


Footnotes

(1) Thiothixene versus placebo - GAS
(2) Haloperidol versus placebo - GAS
(3) Quetiapine vs. placebo (GAF). Active groups pooled. SDs calculated from SEs. Multiplied by (-1), neg. ES indicating beneficial effects
(4) Olanzapine versus placebo - SDS, mean change from baseline to endpoint
(5) Olanzapine versus placebo - CGI-S
(6) Olanzapine 5-10 mg/d - SDS, mean change from baseline to endpoint

Analysis 20.4. Comparison 20: Subgroup analysis: types of medication, Outcome 4: BPD symptom severity - antipsychotics vs placebo by substance

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
20.4.1 Haloperidol								
Soloff 1993 (1)	24.03	13.24	30	20.08	12.44	28	12.3%	0.30 [-0.22 , 0.82]
Subtotal (95% CI)			**30**			**28**	**12.3%**	**0.30 [-0.22 , 0.82]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.15 (P = 0.25)								
20.4.2 Olanzapine								
Schulz 2007 (2)	-6.37	6.73	150	-6.19	6.89	155	18.7%	-0.03 [-0.25 , 0.20]
Zanarini 2007 (2)	-8.52	6.15	144	-6.69	6.58	147	18.6%	-0.29 [-0.52 , -0.06]
Subtotal (95% CI)			**294**			**302**	**37.3%**	**-0.15 [-0.41 , 0.10]**
Heterogeneity: Tau² = 0.02; Chi² = 2.51, df = 1 (P = 0.11); I² = 60%								
Test for overall effect: Z = 1.19 (P = 0.23)								
20.4.3 Thiothixene								
Goldberg 1986 (3)	15.2859	4.4436	24	14.0812	4.1812	26	11.5%	0.28 [-0.28 , 0.83]
Subtotal (95% CI)			**24**			**26**	**11.5%**	**0.28 [-0.28 , 0.83]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.97 (P = 0.33)								
20.4.4 Quetiapine								
Black 2014 (4)	7.9	4.8151	66	8.6	4.8	29	14.0%	-0.14 [-0.58 , 0.29]
Subtotal (95% CI)			**66**			**29**	**14.0%**	**-0.14 [-0.58 , 0.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.65 (P = 0.52)								
20.4.5 Ziprasidone								
Pascual 2008 (5)	3.88	0.6	30	4.3	1.1	30	12.4%	-0.47 [-0.98 , 0.05]
Subtotal (95% CI)			**30**			**30**	**12.4%**	**-0.47 [-0.98 , 0.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.79 (P = 0.07)								
20.4.6 Brexpiprazole								
Grant 2022 (6)	3.1	3.9	35	8.4	5.5	34	12.5%	-1.10 [-1.61 , -0.59]
Subtotal (95% CI)			**35**			**34**	**12.5%**	**-1.10 [-1.61 , -0.59]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.25 (P < 0.0001)								
Total (95% CI)			**479**			**449**	**100.0%**	**-0.21 [-0.49 , 0.08]**
Heterogeneity: Tau² = 0.10; Chi² = 22.37, df = 6 (P = 0.001); I² = 73%								
Test for overall effect: Z = 1.43 (P = 0.15)								
Test for subgroup differences: Chi² = 19.72, df = 5 (P = 0.001), I² = 74.6%								

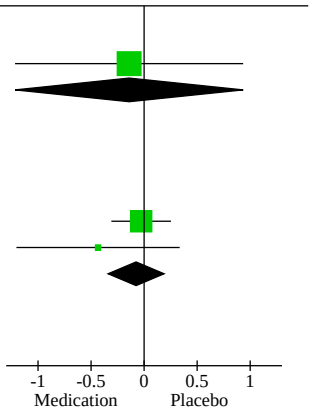


Footnotes

(1) Haloperidol versus placebo
(2) Olanzapine versus placebo
(3) Thiothixine versus placebo
(4) Quetiapine versus placebo (both active groups pooled into one), final scores (Tab. 4 + text p. 1179), baseline SDs (Tab. 4)
(5) Ziprasidone versus placebo
(6) Brexpiprazole versus placebo

Analysis 20.5. Comparison 20: Subgroup analysis: types of medication, Outcome 5: BPD symptom severity - mood stabiliser vs placebo by substance

Study or Subgroup	Medication Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
20.5.1 Divalproex semisodium								
Moen 2012 (1)	28.7	7.1	10	30	11.4	5	100.0%	-0.14 [-1.22 , 0.93]
Subtotal (95% CI)			**10**			**5**	**100.0%**	**-0.14 [-1.22 , 0.93]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.26 (P = 0.80)								
20.5.2 Lamotrigine								
Crawford 2018 (2)	11.3	6.6	97	11.5	7.7	98	88.3%	-0.03 [-0.31 , 0.25]
Reich 2009 (3)	-8.8	5	15	-6.6	4.8	12	11.7%	-0.43 [-1.20 , 0.34]
Subtotal (95% CI)			**112**			**110**	**100.0%**	**-0.08 [-0.34 , 0.19]**
Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 1 (P = 0.33); I² = 0%								
Test for overall effect: Z = 0.56 (P = 0.57)								
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%								

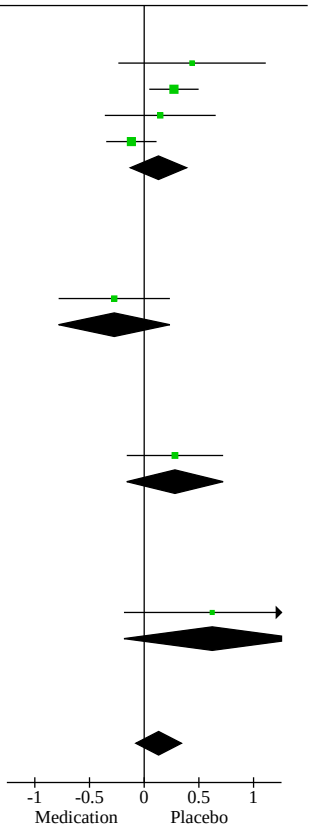


Footnotes

(1) Divalproex versus placebo
(2) Lamotrigine plus TAU versus placebo plus TAU
(3) Lamotrigine versus placebo

Analysis 20.6. Comparison 20: Subgroup analysis: types of medication, Outcome 6: Suicide-related outcomes - antipsychotics vs placebo by substance

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
20.6.1 Olanzapine								
Bogenschutz 2004 (1)	-0.125	0.34157	16	-0.5263	1.17229	19	7.6%	0.44 [-0.24 , 1.11]
Schulz 2007 (1)	-0.28	1.21	150	-0.61	1.21	155	25.2%	0.27 [0.05 , 0.50]
Soler 2005 (1)	1.23	2.87	30	0.88	1.68	30	11.5%	0.15 [-0.36 , 0.65]
Zanarini 2007	-0.3	0.8	144	-0.2	0.9	147	24.9%	-0.12 [-0.35 , 0.11]
Subtotal (95% CI)			**340**			**351**	**69.1%**	**0.13 [-0.13 , 0.39]**
Heterogeneity: Tau² = 0.03; Chi² = 6.65, df = 3 (P = 0.08); I² = 55%								
Test for overall effect: Z = 1.00 (P = 0.32)								
20.6.2 Ziprasidone								
Pascual 2008 (2)	2.7	1.6	30	3.13	1.5	30	11.4%	-0.27 [-0.78 , 0.23]
Subtotal (95% CI)			**30**			**30**	**11.4%**	**-0.27 [-0.78 , 0.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.05 (P = 0.29)								
20.6.3 Brexpiprazole								
Grant 2022	0.23	0.66	40	0.08	0.35	40	13.8%	0.28 [-0.16 , 0.72]
Subtotal (95% CI)			**40**			**40**	**13.8%**	**0.28 [-0.16 , 0.72]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.25 (P = 0.21)								
20.6.4 Alprazolam								
Cowdry 1988 (3)	4.83	1.4	12	4.08	0.9	13	5.6%	0.62 [-0.18 , 1.43]
Subtotal (95% CI)			**12**			**13**	**5.6%**	**0.62 [-0.18 , 1.43]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.51 (P = 0.13)								
Total (95% CI)			**422**			**434**	**100.0%**	**0.13 [-0.08 , 0.34]**
Heterogeneity: Tau² = 0.03; Chi² = 10.97, df = 6 (P = 0.09); I² = 45%								
Test for overall effect: Z = 1.24 (P = 0.22)								
Test for subgroup differences: Chi² = 4.30, df = 3 (P = 0.23), I² = 30.2%								

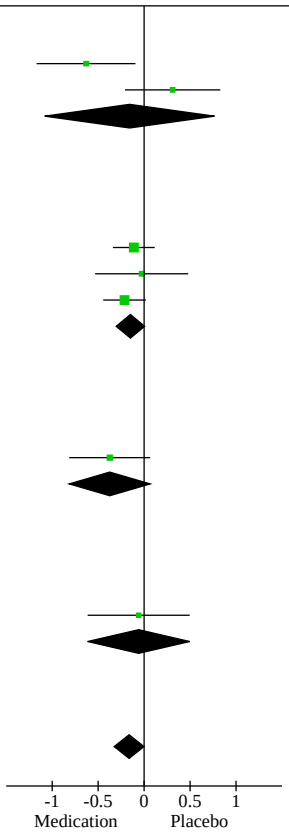


Footnotes

(1) Olanzapine versus placebo
(2) Ziprasidone versus placebo
(3) Alprazolam versus placebo - cross-over data

Analysis 20.7. Comparison 20: Subgroup analysis: types of medication, Outcome 7: Psychosocial functioning - antipsychotics vs placebo by substance

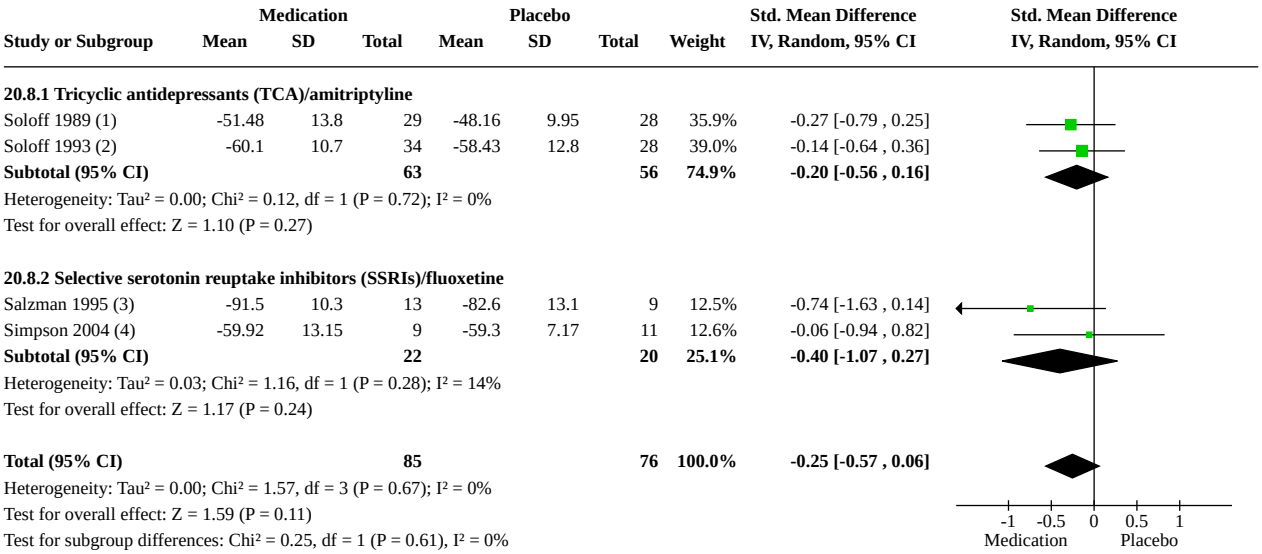
Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
20.7.1 Haloperidol								
Soloff 1989 (1)	-55.35	12.36	28	-48.16	9.95	28	8.0%	-0.63 [-1.17 , -0.09]
Soloff 1993 (1)	-54.95	9.15	30	-58.43	12.8	28	8.5%	0.31 [-0.21 , 0.83]
Subtotal (95% CI)			**58**			**56**	**16.5%**	**-0.16 [-1.08 , 0.77]**
Heterogeneity: Tau² = 0.37; Chi² = 6.11, df = 1 (P = 0.01); I² = 84%								
Test for overall effect: Z = 0.34 (P = 0.74)								
20.7.2 Olanzapine								
Schulz 2007 (2)	-5.89	8.87	147	-4.92	8.44	151	28.3%	-0.11 [-0.34 , 0.12]
Soler 2005 (3)	3.93	1.5	30	3.97	1.45	30	8.8%	-0.03 [-0.53 , 0.48]
Zanarini 2007 (4)	-7.74	8.09	144	-6	8.19	143	27.7%	-0.21 [-0.45 , 0.02]
Subtotal (95% CI)			**321**			**324**	**64.8%**	**-0.15 [-0.30 , 0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 2 (P = 0.73); I² = 0%								
Test for overall effect: Z = 1.89 (P = 0.06)								
20.7.3 Quetiapine								
Black 2014 (5)	-1.045	1.1689	66	-0.62	1.0232	29	11.2%	-0.37 [-0.81 , 0.07]
Subtotal (95% CI)			**66**			**29**	**11.2%**	**-0.37 [-0.81 , 0.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.67 (P = 0.10)								
20.7.4 Thiothixene								
Goldberg 1986 (6)	-72.42	9.25	24	-71.92	7.32	26	7.5%	-0.06 [-0.61 , 0.50]
Subtotal (95% CI)			**24**			**26**	**7.5%**	**-0.06 [-0.61 , 0.50]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.21 (P = 0.83)								
Total (95% CI)			**469**			**435**	**100.0%**	**-0.16 [-0.33 , -0.00]**
Heterogeneity: Tau² = 0.01; Chi² = 7.80, df = 6 (P = 0.25); I² = 23%								
Test for overall effect: Z = 1.97 (P = 0.05)								
Test for subgroup differences: Chi² = 1.05, df = 3 (P = 0.79), I² = 0%								



Footnotes

(1) Haloperidol versus placebo - GAS
(2) Olanzapine versus placebo - SDS, mean change from baseline to endpoint
(3) Olanzapine versus placebo - CGI-S
(4) Olanzapine 5-10 mg/d - SDS, mean change from baseline to endpoint
(5) Quetiapine vs. placebo (GAF). Active groups pooled. SDs calculated from SEs. Multiplied by (-1), neg. ES indicating beneficial effects
(6) Thiothixene versus placebo - GAS

Analysis 20.8. Comparison 20: Subgroup analysis: types of medication, Outcome 8: Psychosocial functioning - antidepressants vs placebo by class/substance



Footnotes

(1) Amitriptyline versus placebo - GAS
(2) Amitriptyline versus placebo GAS
(3) Fluoxetine versus placebo (GAS)
(4) Fluoxetine versus placebo - GAF

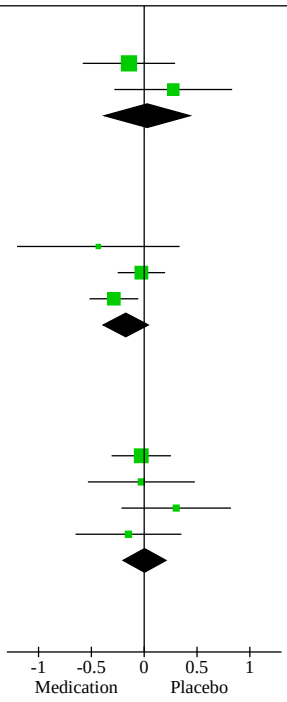
Comparison 21. Subgroup analysis: psychosocial functioning at baseline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.1 Primary: BPD symptom severity by severity of impairment at baseline	8		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1.1 Mild or slightly impaired (GAS/GAF 61 to 80)	2	145	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.38, 0.43]
21.1.2 Moderate severity of illness (GAS/GAF 51-60, CGI 4)	3	623	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.39, 0.04]
21.1.3 Marked or serious severity of illness (GAS/GAF 41-50, CGI 5), SFQ 15	3	375	Std. Mean Difference (IV, Random, 95% CI)	0.00 [-0.20, 0.21]
21.2 Primary: Suicide-related outcomes by severity of impairment at baseline	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
21.2.1 Moderate severity of illness (GAS/GAF 51-60, CGI 4)	4	647	Std. Mean Difference (IV, Random, 95% CI)	0.16 [-0.14, 0.46]
21.2.2 Marked or serious severity of illness (GAS/GAF 41-50, CGI 5), SFQ 15	2	80	Std. Mean Difference (IV, Random, 95% CI)	0.22 [-0.22, 0.66]
21.3 Primary: Psychosocial functioning by severity of impairment at baseline	12	1294	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.31, -0.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.3.1 Mild or slightly impaired	3	167	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.64, 0.00]
21.3.2 Moderate severity of illness (GAS/GAF 51-60, CGI 4)	4	619	Std. Mean Difference (IV, Random, 95% CI)	-0.24 [-0.50, 0.03]
21.3.3 Marked or serious severity of illness (GAS/GAF 41-50, CGI 5), SFQ 15	5	508	Std. Mean Difference (IV, Random, 95% CI)	-0.09 [-0.29, 0.11]

Analysis 21.1. Comparison 21: Subgroup analysis: psychosocial functioning at baseline, Outcome 1: Primary: BPD symptom severity by severity of impairment at baseline

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
21.1.1 Mild or slightly impaired (GAS/GAF 61 to 80)								
Black 2014 (1)	7.9	4.8151	66	8.6	4.8	29	58.9%	-0.14 [-0.58 , 0.29]
Goldberg 1986 (2)	15.2859	4.4436	24	14.0812	4.1812	26	41.1%	0.28 [-0.28 , 0.83]
Subtotal (95% CI)			**90**			**55**	**100.0%**	**0.03 [-0.38 , 0.43]**
Heterogeneity: Tau² = 0.02; Chi² = 1.35, df = 1 (P = 0.25); I² = 26%								
Test for overall effect: Z = 0.14 (P = 0.89)								
21.1.2 Moderate severity of illness (GAS/GAF 51-60, CGI 4)								
Reich 2009 (3)	-8.8	5	15	-6.6	4.8	12	7.1%	-0.43 [-1.20 , 0.34]
Schulz 2007 (4)	-6.37	6.73	150	-6.19	6.89	155	47.1%	-0.03 [-0.25 , 0.20]
Zanarini 2007 (4)	-8.52	6.15	144	-6.69	6.58	147	45.7%	-0.29 [-0.52 , -0.06]
Subtotal (95% CI)			**309**			**314**	**100.0%**	**-0.17 [-0.39 , 0.04]**
Heterogeneity: Tau² = 0.01; Chi² = 3.00, df = 2 (P = 0.22); I² = 33%								
Test for overall effect: Z = 1.60 (P = 0.11)								
21.1.3 Marked or serious severity of illness (GAS/GAF 41-50, CGI 5), SFQ 15								
Crawford 2018 (5)	11.3	6.6	97	11.5	7.7	98	52.2%	-0.03 [-0.31 , 0.25]
Soler 2005 (6)	3.93	1.5	30	3.97	1.45	30	16.1%	-0.03 [-0.53 , 0.48]
Soloff 1993 (7)	24.03	13.24	30	20.08	12.44	28	15.3%	0.30 [-0.22 , 0.82]
Soloff 1993 (8)	18.3	11.24	34	20.08	12.44	28	16.4%	-0.15 [-0.65 , 0.35]
Subtotal (95% CI)			**191**			**184**	**100.0%**	**0.00 [-0.20 , 0.21]**
Heterogeneity: Tau² = 0.00; Chi² = 1.70, df = 3 (P = 0.64); I² = 0%								
Test for overall effect: Z = 0.03 (P = 0.98)								
Test for subgroup differences: Chi² = 1.65, df = 2 (P = 0.44), I² = 0%								

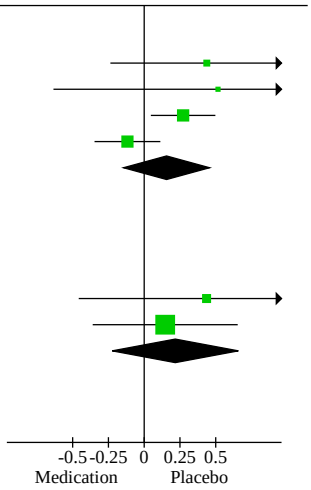


Footnotes

(1) Quetiapine versus placebo (both active groups pooled into one), final scores (Tab. 4 + text p. 1179), baseline SDs (Tab. 4)
(2) Thiothixine versus placebo
(3) Lamotrigine versus placebo
(4) Olanzapine versus placebo
(5) Lamotrigine plus TAU versus placebo plus TAU
(6) Olanzapine versus placebo - CGI-S
(7) Haloperidol versus placebo
(8) Phenelzine sulfate versus placebo

Analysis 21.2. Comparison 21: Subgroup analysis: psychosocial functioning at baseline, Outcome 2: Primary: Suicide-related outcomes by severity of impairment at baseline

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
21.2.1 Moderate severity of illness (GAS/GAF 51-60, CGI 4)								
Bogenschutz 2004 (1)	-0.125	0.34157	16	-0.5263	1.17229	19	14.4%	0.44 [-0.24 , 1.11]
Hollander 2001 (2)	0.9	1.2	12	0.3	0.6	4	6.0%	0.52 [-0.63 , 1.67]
Schulz 2007 (1)	-0.28	1.21	150	-0.61	1.21	155	40.0%	0.27 [0.05 , 0.50]
Zanarini 2007 (1)	-0.3	0.8	144	-0.2	0.9	147	39.6%	-0.12 [-0.35 , 0.11]
Subtotal (95% CI)			**322**			**325**	**100.0%**	**0.16 [-0.14 , 0.46]**
Heterogeneity: Tau² = 0.05; Chi² = 7.11, df = 3 (P = 0.07); I² = 58%								
Test for overall effect: Z = 1.02 (P = 0.31)								
21.2.2 Marked or serious severity of illness (GAS/GAF 41-50, CGI 5), SFQ 15								
Simpson 2004 (3)	2.13	3.48	9	1	1.18	11	24.3%	0.44 [-0.46 , 1.33]
Soler 2005 (1)	1.23	2.87	30	0.88	1.68	30	75.7%	0.15 [-0.36 , 0.65]
Subtotal (95% CI)			**39**			**41**	**100.0%**	**0.22 [-0.22 , 0.66]**
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.58); I² = 0%								
Test for overall effect: Z = 0.97 (P = 0.33)								
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%								

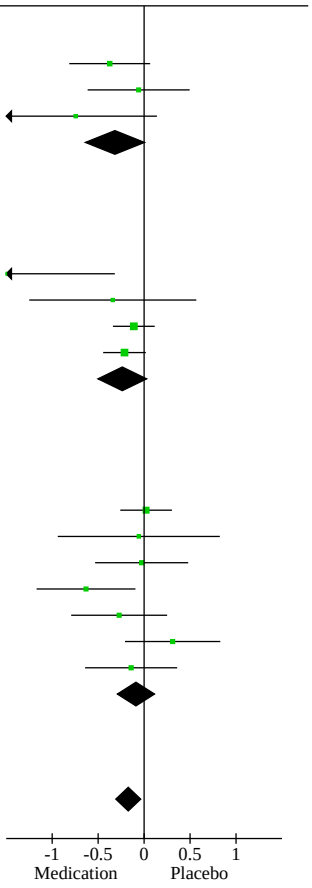


Footnotes

(1) Olanzapine versus placebo
(2) Valproate semisodium versus placebo
(3) Fluoxetine versus placebo

Analysis 21.3. Comparison 21: Subgroup analysis: psychosocial functioning at baseline, Outcome 3: Primary: Psychosocial functioning by severity of impairment at baseline

Study or Subgroup	Medication Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
21.3.1 Mild or slightly impaired								
Black 2014 (1)	-1.045	1.1689	66	-0.62	1.0232	29	7.6%	-0.37 [-0.81 , 0.07]
Goldberg 1986 (2)	-72.42	9.25	24	-71.92	7.32	26	5.1%	-0.06 [-0.61 , 0.50]
Salzman 1995 (3)	-91.5	10.3	13	-82.6	13.1	9	2.2%	-0.74 [-1.63 , 0.14]
Subtotal (95% CI)			**103**			**64**	**14.9%**	**-0.32 [-0.64 , 0.00]**
Heterogeneity: Tau² = 0.00; Chi² = 1.79, df = 2 (P = 0.41); I² = 0%								
Test for overall effect: Z = 1.94 (P = 0.05)								
21.3.2 Moderate severity of illness (GAS/GAF 51-60, CGI 4)								
Amminger 2013 (4)	-75.6	10.8	8	-55.7	14	7	1.2%	-1.51 [-2.71 , -0.32]
De la Fuente 1994 (5)	-67.12	16.17	9	-60.1	22.33	10	2.1%	-0.34 [-1.25 , 0.57]
Schulz 2007 (6)	-5.89	8.87	147	-4.92	8.44	151	18.3%	-0.11 [-0.34 , 0.12]
Zanarini 2007 (7)	-7.74	8.09	144	-6	8.19	143	17.9%	-0.21 [-0.45 , 0.02]
Subtotal (95% CI)			**308**			**311**	**39.5%**	**-0.24 [-0.50 , 0.03]**
Heterogeneity: Tau² = 0.03; Chi² = 5.31, df = 3 (P = 0.15); I² = 44%								
Test for overall effect: Z = 1.76 (P = 0.08)								
21.3.3 Marked or serious severity of illness (GAS/GAF 41-50, CGI 5), SFQ 15								
Crawford 2018 (8)	12.4	4.3	97	12.3	4.9	98	14.4%	0.02 [-0.26 , 0.30]
Simpson 2004 (9)	-59.92	13.15	9	-59.3	7.17	11	2.2%	-0.06 [-0.94 , 0.82]
Soler 2005 (10)	3.93	1.5	30	3.97	1.45	30	6.0%	-0.03 [-0.53 , 0.48]
Soloff 1989 (11)	-55.35	12.36	28	-48.16	9.95	28	5.4%	-0.63 [-1.17 , -0.09]
Soloff 1989 (12)	-51.48	13.8	29	-48.16	9.95	28	5.7%	-0.27 [-0.79 , 0.25]
Soloff 1993 (11)	-54.95	9.15	30	-58.43	12.8	28	5.8%	0.31 [-0.21 , 0.83]
Soloff 1993 (13)	-60.1	10.7	34	-58.43	12.8	28	6.1%	-0.14 [-0.64 , 0.36]
Subtotal (95% CI)			**257**			**251**	**45.6%**	**-0.09 [-0.29 , 0.11]**
Heterogeneity: Tau² = 0.01; Chi² = 7.35, df = 6 (P = 0.29); I² = 18%								
Test for overall effect: Z = 0.86 (P = 0.39)								
Total (95% CI)			**668**			**626**	**100.0%**	**-0.17 [-0.31 , -0.04]**
Heterogeneity: Tau² = 0.01; Chi² = 16.40, df = 13 (P = 0.23); I² = 21%								
Test for overall effect: Z = 2.50 (P = 0.01)								
Test for subgroup differences: Chi² = 1.66, df = 2 (P = 0.44), I² = 0%								



Footnotes

(1) Quetiapine vs. placebo (GAF). Active groups pooled. SDs calculated from SEs. Multiplied by (-1), neg. ES indicating beneficial effects
(2) Thiothixene versus placebo - GAS
(3) Fluoxetine versus placebo (GAS)
(4) Long-chain omega-3 polyunsaturated fatty acids versus placebo GAF
(5) Carbamazepine versus placebo - GAS
(6) Olanzapine versus placebo - SDS, mean change from baseline to endpoint
(7) Olanzapine 5-10 mg/d - SDS, mean change from baseline to endpoint
(8) Lamotrigine plus TAU versus placebo plus TAU - SFQ
(9) Fluoxetine versus placebo - GAF
(10) Olanzapine versus placebo - CGI-S
(11) Haloperidol versus placebo - GAS
(12) Amitriptyline versus placebo - GAS
(13) Amitriptyline versus placebo GAS

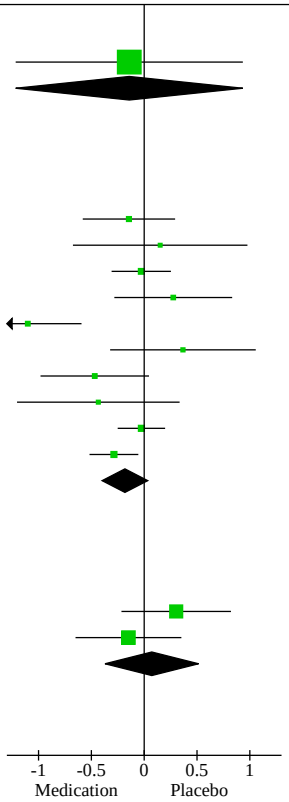
Comparison 22. Subgroup analysis: setting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.1 BPD symptom severity by setting	12		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.1.1 Inpatient	1	15	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-1.22, 0.93]
22.1.2 Outpatient	10	1148	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.40, 0.03]
22.1.3 Mixed	1	120	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.37, 0.51]
22.2 Primary: Suicide-related outcomes at end of treatment	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
22.2.1 Inpatient	1	20	Std. Mean Difference (IV, Random, 95% CI)	0.44 [-0.46, 1.33]
22.2.2 Outpatient	6	767	Std. Mean Difference (IV, Random, 95% CI)	0.09 [-0.14, 0.32]
22.3 Primary: Psychosocial functioning at end of treatment	12		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
22.3.1 Inpatient	2	39	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.83, 0.44]
22.3.2 Outpatient	8	1022	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.34, -0.01]
22.3.3 Mixed	2	233	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.56, 0.20]

Analysis 22.1. Comparison 22: Subgroup analysis: setting, Outcome 1: BPD symptom severity by setting

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
22.1.1 Inpatient								
Moen 2012 (1)	28.7	7.1	10	30	11.4	5	100.0%	-0.14 [-1.22 , 0.93]
Subtotal (95% CI)			**10**			**5**	**100.0%**	**-0.14 [-1.22 , 0.93]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.26 (P = 0.80)								
22.1.2 Outpatient								
Black 2014 (2)	7.9	4.8151	66	8.6	4.8	29	10.7%	-0.14 [-0.58 , 0.29]
Cowdry 1988 (3)	4.3	1.77	10	4.08	1.04	13	5.0%	0.15 [-0.67 , 0.98]
Crawford 2018 (4)	11.3	6.6	97	11.5	7.7	98	14.3%	-0.03 [-0.31 , 0.25]
Goldberg 1986 (5)	15.2859	4.4436	24	14.0812	4.1812	26	8.4%	0.28 [-0.28 , 0.83]
Grant 2022 (6)	3.1	3.9	35	8.4	5.5	34	9.2%	-1.10 [-1.61 , -0.59]
Kulkarni 2018 (7)	9.2	5.6	17	7.2	5	16	6.5%	0.37 [-0.32 , 1.06]
Pascual 2008 (8)	3.88	0.6	30	4.3	1.1	30	9.1%	-0.47 [-0.98 , 0.05]
Reich 2009 (9)	-8.8	5	15	-6.6	4.8	12	5.6%	-0.43 [-1.20 , 0.34]
Schulz 2007 (10)	-6.37	6.73	150	-6.19	6.89	155	15.7%	-0.03 [-0.25 , 0.20]
Zanarini 2007 (10)	-8.52	6.15	144	-6.69	6.58	147	15.6%	-0.29 [-0.52 , -0.06]
Subtotal (95% CI)			**588**			**560**	**100.0%**	**-0.18 [-0.40 , 0.03]**
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 23.55$, df = 9 (P = 0.005); $I^2 = 62\%$								
Test for overall effect: Z = 1.66 (P = 0.10)								
22.1.3 Mixed								
Soloff 1993 (11)	24.03	13.24	30	20.08	12.44	28	48.9%	0.30 [-0.22 , 0.82]
Soloff 1993 (12)	18.3	11.24	34	20.08	12.44	28	51.1%	-0.15 [-0.65 , 0.35]
Subtotal (95% CI)			**64**			**56**	**100.0%**	**0.07 [-0.37 , 0.51]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 1.51$, df = 1 (P = 0.22); $I^2 = 34\%$								
Test for overall effect: Z = 0.32 (P = 0.75)								
Test for subgroup differences: $Chi^2 = 1.02$, df = 2 (P = 0.60), $I^2 = 0\%$								

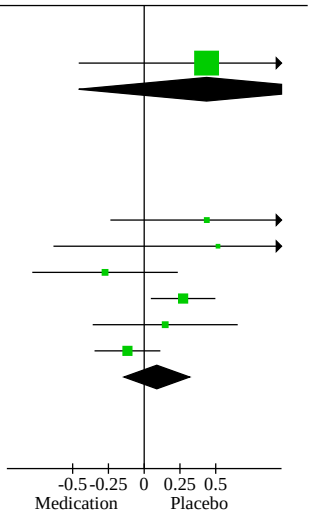


Footnotes

(1) Divalproex versus placebo
(2) Quetiapine versus placebo (both active groups pooled into one), final scores (Tab. 4 + text p. 1179), baseline SDs (Tab. 4)
(3) Trifluoperazine hydrochloride versus placebo - cross-over data
(4) Lamotrigine plus TAU versus placebo plus TAU
(5) Thiothixine versus placebo
(6) Brexpiprazole versus placebo
(7) Memantine hydrochloride plus TAU versus placebo plus TAU
(8) Ziprasidone versus placebo
(9) Lamotrigine versus placebo
(10) Olanzapine versus placebo
(11) Haloperidol versus placebo
(12) Phenelzine sulfate versus placebo

Analysis 22.2. Comparison 22: Subgroup analysis: setting, Outcome 2: Primary: Suicide-related outcomes at end of treatment

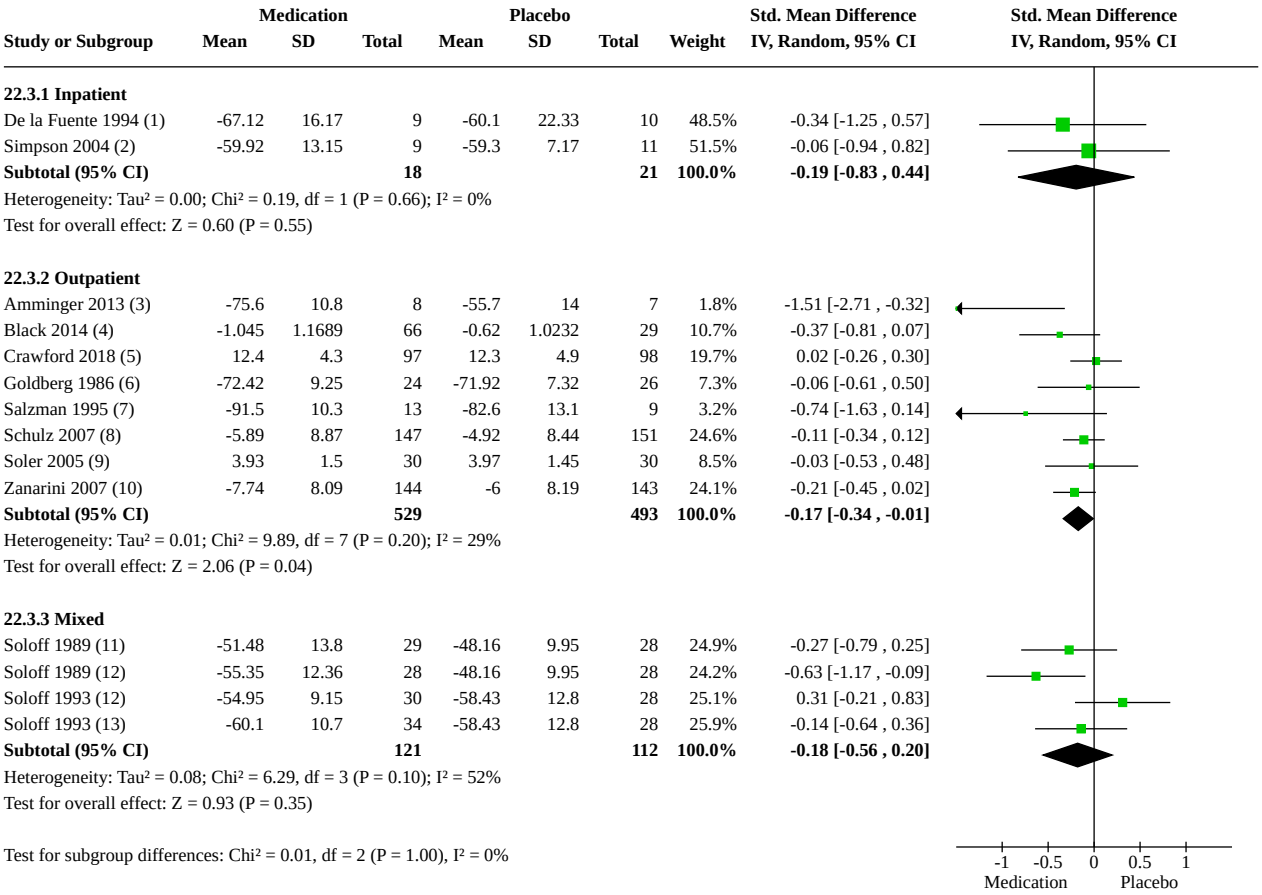
Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
22.2.1 Inpatient								
Simpson 2004 (1)	2.13	3.48	9	1	1.18	11	100.0%	0.44 [-0.46 , 1.33]
Subtotal (95% CI)			**9**			**11**	**100.0%**	**0.44 [-0.46 , 1.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.96 (P = 0.34)								
22.2.2 Outpatient								
Bogenschutz 2004 (2)	-0.125	0.34157	16	-0.5263	1.17229	19	9.1%	0.44 [-0.24 , 1.11]
Hollander 2001 (3)	0.9	1.2	12	0.3	0.6	4	3.6%	0.52 [-0.63 , 1.67]
Pascual 2008 (4)	2.7	1.6	30	3.13	1.5	30	13.7%	-0.27 [-0.78 , 0.23]
Schulz 2007 (2)	-0.28	1.21	150	-0.61	1.21	155	30.0%	0.27 [0.05 , 0.50]
Soler 2005 (2)	1.23	2.87	30	0.88	1.68	30	13.8%	0.15 [-0.36 , 0.65]
Zanarini 2007 (2)	-0.3	0.8	144	-0.2	0.9	147	29.7%	-0.12 [-0.35 , 0.11]
Subtotal (95% CI)			**382**			**385**	**100.0%**	**0.09 [-0.14 , 0.32]**
Heterogeneity: Tau² = 0.03; Chi² = 9.16, df = 5 (P = 0.10); I² = 45%								
Test for overall effect: Z = 0.75 (P = 0.45)								
Test for subgroup differences: Chi² = 0.55, df = 1 (P = 0.46), I² = 0%								



Footnotes

(1) Fluoxetine versus placebo
(2) Olanzapine versus placebo
(3) Valproate semisodium versus placebo
(4) Ziprasidone versus placebo

Analysis 22.3. Comparison 22: Subgroup analysis: setting, Outcome 3: Primary: Psychosocial functioning at end of treatment



Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
22.3.1 Inpatient								
De la Fuente 1994 (1)	-67.12	16.17	9	-60.1	22.33	10	48.5%	-0.34 [-1.25 , 0.57]
Simpson 2004 (2)	-59.92	13.15	9	-59.3	7.17	11	51.5%	-0.06 [-0.94 , 0.82]
Subtotal (95% CI)			**18**			**21**	**100.0%**	**-0.19 [-0.83 , 0.44]**
Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%								
Test for overall effect: Z = 0.60 (P = 0.55)								
22.3.2 Outpatient								
Amminger 2013 (3)	-75.6	10.8	8	-55.7	14	7	1.8%	-1.51 [-2.71 , -0.32]
Black 2014 (4)	-1.045	1.1689	66	-0.62	1.0232	29	10.7%	-0.37 [-0.81 , 0.07]
Crawford 2018 (5)	12.4	4.3	97	12.3	4.9	98	19.7%	0.02 [-0.26 , 0.30]
Goldberg 1986 (6)	-72.42	9.25	24	-71.92	7.32	26	7.3%	-0.06 [-0.61 , 0.50]
Salzman 1995 (7)	-91.5	10.3	13	-82.6	13.1	9	3.2%	-0.74 [-1.63 , 0.14]
Schulz 2007 (8)	-5.89	8.87	147	-4.92	8.44	151	24.6%	-0.11 [-0.34 , 0.12]
Soler 2005 (9)	3.93	1.5	30	3.97	1.45	30	8.5%	-0.03 [-0.53 , 0.48]
Zanarini 2007 (10)	-7.74	8.09	144	-6	8.19	143	24.1%	-0.21 [-0.45 , 0.02]
Subtotal (95% CI)			**529**			**493**	**100.0%**	**-0.17 [-0.34 , -0.01]**
Heterogeneity: Tau² = 0.01; Chi² = 9.89, df = 7 (P = 0.20); I² = 29%								
Test for overall effect: Z = 2.06 (P = 0.04)								
22.3.3 Mixed								
Soloff 1989 (11)	-51.48	13.8	29	-48.16	9.95	28	24.9%	-0.27 [-0.79 , 0.25]
Soloff 1989 (12)	-55.35	12.36	28	-48.16	9.95	28	24.2%	-0.63 [-1.17 , -0.09]
Soloff 1993 (12)	-54.95	9.15	30	-58.43	12.8	28	25.1%	0.31 [-0.21 , 0.83]
Soloff 1993 (13)	-60.1	10.7	34	-58.43	12.8	28	25.9%	-0.14 [-0.64 , 0.36]
Subtotal (95% CI)			**121**			**112**	**100.0%**	**-0.18 [-0.56 , 0.20]**
Heterogeneity: Tau² = 0.08; Chi² = 6.29, df = 3 (P = 0.10); I² = 52%								
Test for overall effect: Z = 0.93 (P = 0.35)								
Test for subgroup differences: Chi² = 0.01, df = 2 (P = 1.00), I² = 0%								

Footnotes

(1) Carbamazepine versus placebo - GAS
(2) Fluoxetine versus placebo - GAF
(3) Long-chain omega-3 polyunsaturated fatty acids versus placebo GAF
(4) Quetiapine vs. placebo (GAF). Active groups pooled. SDs calculated from SEs. Multiplied by (-1), neg. ES indicating beneficial effects
(5) Lamotrigine plus TAU versus placebo plus TAU - SFQ
(6) Thiothixene versus placebo - GAS
(7) Fluoxetine versus placebo (GAS)
(8) Olanzapine versus placebo - SDS, mean change from baseline to endpoint
(9) Olanzapine versus placebo - CGI-S
(10) Olanzapine 5-10 mg/d - SDS, mean change from baseline to endpoint
(11) Amitriptyline versus placebo - GAS
(12) Haloperidol versus placebo - GAS
(13) Amitriptyline versus placebo GAS

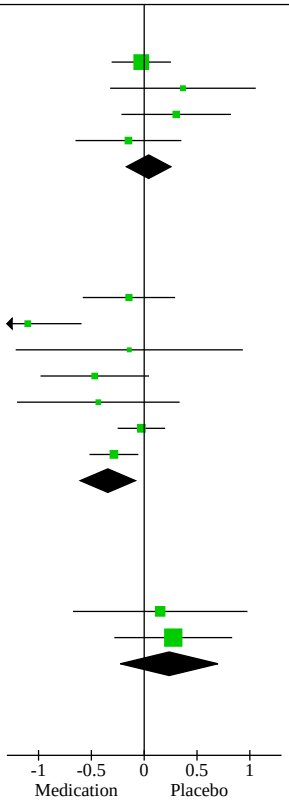
Comparison 23. Subgroup analysis: funding

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23.1 BPD symptom severity by funding	12		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
23.1.1 Publicly (grants from universities, authorities, research foundations)	3	348	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.17, 0.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23.1.2 Funded or partially funded by pharmaceutical industry	7	862	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.61, -0.08]
23.1.3 Unclear funding	2	73	Std. Mean Difference (IV, Random, 95% CI)	0.24 [-0.23, 0.70]
23.2 Primary: Psychosocial functioning at end of treatment	12		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
23.2.1 Publicly (grants from universities, authorities, research foundations)	4	443	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.55, 0.12]
23.2.2 Funded or partially funded by pharmaceutical industry	5	760	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.31, -0.03]
23.2.3 Unclear funding	3	91	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.69, 0.15]

Analysis 23.1. Comparison 23: Subgroup analysis: funding, Outcome 1: BPD symptom severity by funding

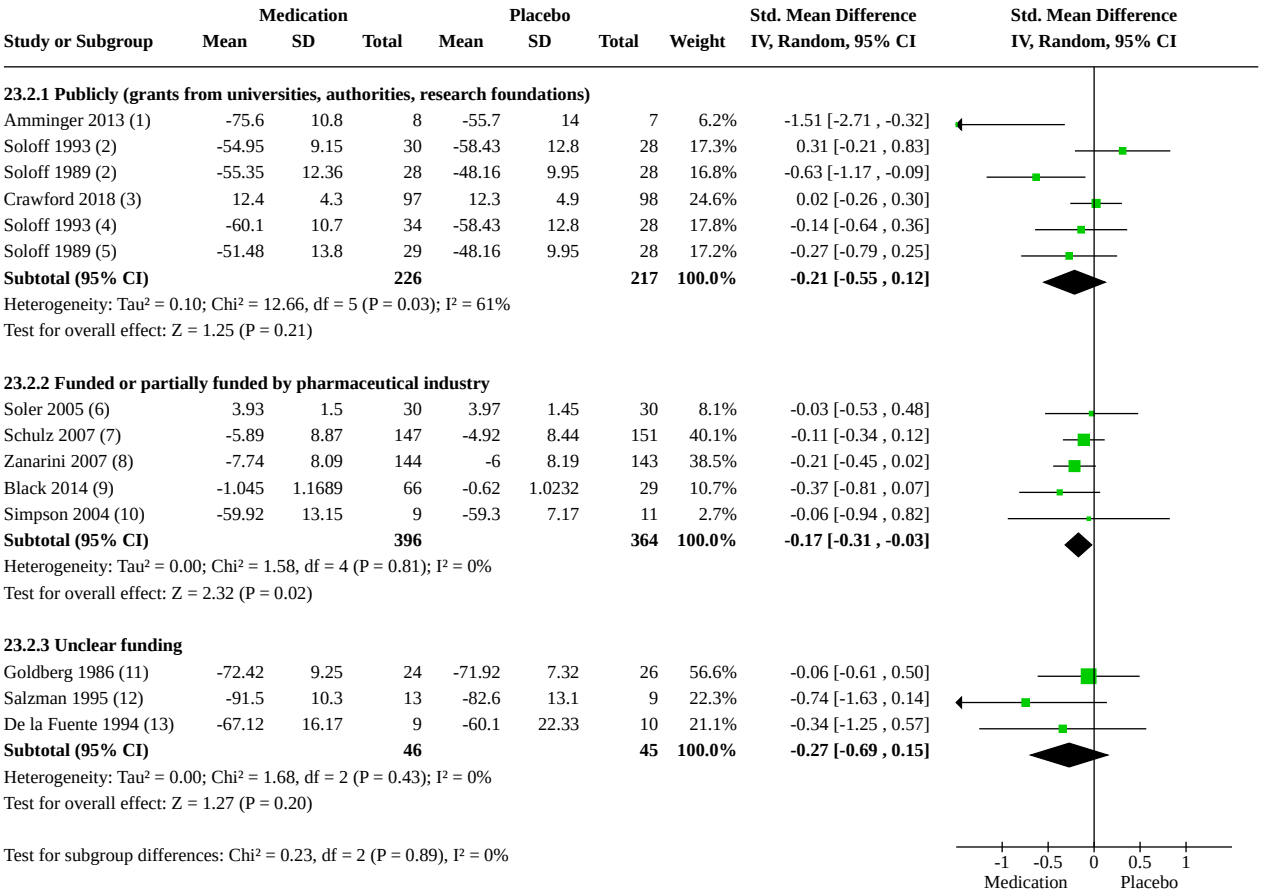
Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
23.1.1 Publicly (grants from universities, authorities, research foundations)								
Crawford 2018 (1)	11.3	6.6	97	11.5	7.7	98	56.4%	-0.03 [-0.31 , 0.25]
Kulkarni 2018 (2)	9.2	5.6	17	7.2	5	16	9.4%	0.37 [-0.32 , 1.06]
Soloff 1993 (3)	24.03	13.24	30	20.08	12.44	28	16.5%	0.30 [-0.22 , 0.82]
Soloff 1993 (4)	18.3	11.24	34	20.08	12.44	28	17.7%	-0.15 [-0.65 , 0.35]
Subtotal (95% CI)			**178**			**170**	**100.0%**	**0.04 [-0.17 , 0.25]**
Heterogeneity: Tau² = 0.00; Chi² = 2.62, df = 3 (P = 0.45); I² = 0%								
Test for overall effect: Z = 0.39 (P = 0.69)								
23.1.2 Funded or partially funded by pharmaceutical industry								
Black 2014 (5)	7.9	4.8151	66	8.6	4.8	29	15.4%	-0.14 [-0.58 , 0.29]
Grant 2022 (6)	3.1	3.9	35	8.4	5.5	34	13.4%	-1.10 [-1.61 , -0.59]
Moen 2012 (7)	28.7	7.1	10	30	11.4	5	4.9%	-0.14 [-1.22 , 0.93]
Pascual 2008 (8)	3.88	0.6	30	4.3	1.1	30	13.3%	-0.47 [-0.98 , 0.05]
Reich 2009 (9)	-8.8	5	15	-6.6	4.8	12	8.1%	-0.43 [-1.20 , 0.34]
Schulz 2007 (10)	-6.37	6.73	150	-6.19	6.89	155	22.6%	-0.03 [-0.25 , 0.20]
Zanarini 2007 (10)	-8.52	6.15	144	-6.69	6.58	147	22.4%	-0.29 [-0.52 , -0.06]
Subtotal (95% CI)			**450**			**412**	**100.0%**	**-0.34 [-0.61 , -0.08]**
Heterogeneity: Tau² = 0.07; Chi² = 15.87, df = 6 (P = 0.01); I² = 62%								
Test for overall effect: Z = 2.58 (P = 0.010)								
23.1.3 Unclear funding								
Cowdry 1988 (11)	4.3	1.77	10	4.08	1.04	13	31.3%	0.15 [-0.67 , 0.98]
Goldberg 1986 (12)	15.2859	4.4436	24	14.0812	4.1812	26	68.7%	0.28 [-0.28 , 0.83]
Subtotal (95% CI)			**34**			**39**	**100.0%**	**0.24 [-0.23 , 0.70]**
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%								
Test for overall effect: Z = 1.00 (P = 0.32)								
Test for subgroup differences: Chi² = 7.00, df = 2 (P = 0.03), I² = 71.4%								



Footnotes

(1) Lamotrigine plus TAU versus placebo plus TAU
(2) Memantine hydrochloride plus TAU versus placebo plus TAU
(3) Haloperidol versus placebo
(4) Phenelzine sulfate versus placebo
(5) Quetiapine versus placebo (both active groups pooled into one), final scores (Tab. 4 + text p. 1179), baseline SDs (Tab. 4)
(6) Brexpiprazole versus placebo
(7) Divalproex versus placebo
(8) Ziprasidone versus placebo
(9) Lamotrigine versus placebo
(10) Olanzapine versus placebo
(11) Trifluoperazine hydrochloride versus placebo - cross-over data
(12) Thiothixine versus placebo

Analysis 23.2. Comparison 23: Subgroup analysis: funding, Outcome 2: Primary: Psychosocial functioning at end of treatment



Study or Subgroup	Medication Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
23.2.1 Publicly (grants from universities, authorities, research foundations)								
Amminger 2013 (1)	-75.6	10.8	8	-55.7	14	7	6.2%	-1.51 [-2.71 , -0.32]
Soloff 1993 (2)	-54.95	9.15	30	-58.43	12.8	28	17.3%	0.31 [-0.21 , 0.83]
Soloff 1989 (2)	-55.35	12.36	28	-48.16	9.95	28	16.8%	-0.63 [-1.17 , -0.09]
Crawford 2018 (3)	12.4	4.3	97	12.3	4.9	98	24.6%	0.02 [-0.26 , 0.30]
Soloff 1993 (4)	-60.1	10.7	34	-58.43	12.8	28	17.8%	-0.14 [-0.64 , 0.36]
Soloff 1989 (5)	-51.48	13.8	29	-48.16	9.95	28	17.2%	-0.27 [-0.79 , 0.25]
Subtotal (95% CI)			**226**			**217**	**100.0%**	**-0.21 [-0.55 , 0.12]**
Heterogeneity: Tau² = 0.10; Chi² = 12.66, df = 5 (P = 0.03); I² = 61%								
Test for overall effect: Z = 1.25 (P = 0.21)								
23.2.2 Funded or partially funded by pharmaceutical industry								
Soler 2005 (6)	3.93	1.5	30	3.97	1.45	30	8.1%	-0.03 [-0.53 , 0.48]
Schulz 2007 (7)	-5.89	8.87	147	-4.92	8.44	151	40.1%	-0.11 [-0.34 , 0.12]
Zanarini 2007 (8)	-7.74	8.09	144	-6	8.19	143	38.5%	-0.21 [-0.45 , 0.02]
Black 2014 (9)	-1.045	1.1689	66	-0.62	1.0232	29	10.7%	-0.37 [-0.81 , 0.07]
Simpson 2004 (10)	-59.92	13.15	9	-59.3	7.17	11	2.7%	-0.06 [-0.94 , 0.82]
Subtotal (95% CI)			**396**			**364**	**100.0%**	**-0.17 [-0.31 , -0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 1.58, df = 4 (P = 0.81); I² = 0%								
Test for overall effect: Z = 2.32 (P = 0.02)								
23.2.3 Unclear funding								
Goldberg 1986 (11)	-72.42	9.25	24	-71.92	7.32	26	56.6%	-0.06 [-0.61 , 0.50]
Salzman 1995 (12)	-91.5	10.3	13	-82.6	13.1	9	22.3%	-0.74 [-1.63 , 0.14]
De la Fuente 1994 (13)	-67.12	16.17	9	-60.1	22.33	10	21.1%	-0.34 [-1.25 , 0.57]
Subtotal (95% CI)			**46**			**45**	**100.0%**	**-0.27 [-0.69 , 0.15]**
Heterogeneity: Tau² = 0.00; Chi² = 1.68, df = 2 (P = 0.43); I² = 0%								
Test for overall effect: Z = 1.27 (P = 0.20)								
Test for subgroup differences: Chi² = 0.23, df = 2 (P = 0.89), I² = 0%								

Footnotes

(1) Long-chain omega-3 polyunsaturated fatty acids versus placebo GAF
(2) Haloperidol versus placebo - GAS
(3) Lamotrigine plus TAU versus placebo plus TAU - SFQ
(4) Amitriptyline versus placebo GAS
(5) Amitriptyline versus placebo - GAS
(6) Olanzapine versus placebo - CGI-S
(7) Olanzapine versus placebo - SDS, mean change from baseline to endpoint
(8) Olanzapine 5-10 mg/d - SDS, mean change from baseline to endpoint
(9) Quetiapine vs. placebo (GAF). Active groups pooled. SDs calculated from SEs. Multiplied by (-1), neg. ES indicating beneficial effects
(10) Fluoxetine versus placebo - GAF
(11) Thiothixene versus placebo - GAS
(12) Fluoxetine versus placebo (GAS)
(13) Carbamazepine versus placebo - GAS

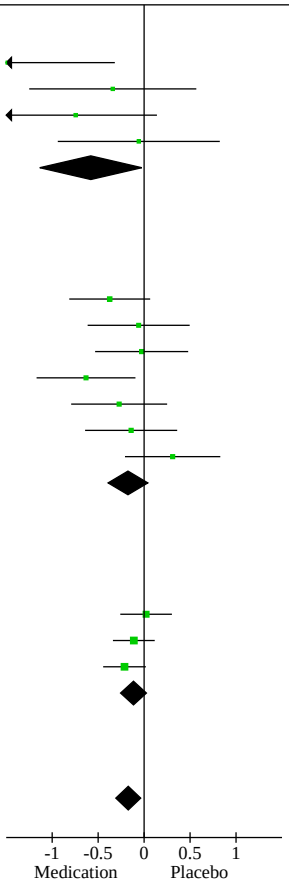
Comparison 24. Subgroup analysis: trial size

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.1 Primary: Psychosocial functioning at end of treatment	12	1294	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.31, -0.04]
24.1.1 ≤ 50	4	76	Std. Mean Difference (IV, Random, 95% CI)	-0.58 [-1.14, -0.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.1.2 ≤ 100	5	438	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.39, 0.04]
24.1.3 ≥ 100	3	780	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.26, 0.02]
24.2 Secondary: Anger at end of treatment	22		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
24.2.1 ≤ 50	13	377	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.00, -0.34]
24.2.2 ≤ 100	7	546	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.14, -0.20]
24.2.3 ≥ 100	2	596	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.41, -0.09]

Analysis 24.1. Comparison 24: Subgroup analysis: trial size, Outcome 1: Primary: Psychosocial functioning at end of treatment

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
24.1.1 ≤ 50								
Amminger 2013 (1)	-75.6	10.8	8	-55.7	14	7	1.2%	-1.51 [-2.71 , -0.32]
De la Fuente 1994 (2)	-67.12	16.17	9	-60.1	22.33	10	2.1%	-0.34 [-1.25 , 0.57]
Salzman 1995 (3)	-91.5	10.3	13	-82.6	13.1	9	2.2%	-0.74 [-1.63 , 0.14]
Simpson 2004 (4)	-59.92	13.15	9	-59.3	7.17	11	2.2%	-0.06 [-0.94 , 0.82]
Subtotal (95% CI)			**39**			**37**	**7.8%**	**-0.58 [-1.14 , -0.02]**
Heterogeneity: Tau² = 0.09; Chi² = 4.08, df = 3 (P = 0.25); I² = 27%								
Test for overall effect: Z = 2.05 (P = 0.04)								
24.1.2 ≤ 100								
Black 2014 (5)	-1.045	1.1689	66	-0.62	1.0232	29	7.6%	-0.37 [-0.81 , 0.07]
Goldberg 1986 (6)	-72.42	9.25	24	-71.92	7.32	26	5.1%	-0.06 [-0.61 , 0.50]
Soler 2005 (7)	3.93	1.5	30	3.97	1.45	30	6.0%	-0.03 [-0.53 , 0.48]
Soloff 1989 (8)	-55.35	12.36	28	-48.16	9.95	28	5.4%	-0.63 [-1.17 , -0.09]
Soloff 1989 (9)	-51.48	13.8	29	-48.16	9.95	28	5.7%	-0.27 [-0.79 , 0.25]
Soloff 1993 (10)	-60.1	10.7	34	-58.43	12.8	28	6.1%	-0.14 [-0.64 , 0.36]
Soloff 1993 (8)	-54.95	9.15	30	-58.43	12.8	28	5.8%	0.31 [-0.21 , 0.83]
Subtotal (95% CI)			**241**			**197**	**41.7%**	**-0.18 [-0.39 , 0.04]**
Heterogeneity: Tau² = 0.02; Chi² = 7.57, df = 6 (P = 0.27); I² = 21%								
Test for overall effect: Z = 1.59 (P = 0.11)								
24.1.3 ≥ 100								
Crawford 2018 (11)	12.4	4.3	97	12.3	4.9	98	14.4%	0.02 [-0.26 , 0.30]
Schulz 2007 (12)	-5.89	8.87	147	-4.92	8.44	151	18.3%	-0.11 [-0.34 , 0.12]
Zanarini 2007 (13)	-7.74	8.09	144	-6	8.19	143	17.9%	-0.21 [-0.45 , 0.02]
Subtotal (95% CI)			**388**			**392**	**50.5%**	**-0.12 [-0.26 , 0.02]**
Heterogeneity: Tau² = 0.00; Chi² = 1.60, df = 2 (P = 0.45); I² = 0%								
Test for overall effect: Z = 1.61 (P = 0.11)								
Total (95% CI)			**668**			**626**	**100.0%**	**-0.17 [-0.31 , -0.04]**
Heterogeneity: Tau² = 0.01; Chi² = 16.40, df = 13 (P = 0.23); I² = 21%								
Test for overall effect: Z = 2.50 (P = 0.01)								
Test for subgroup differences: Chi² = 2.59, df = 2 (P = 0.27), I² = 22.7%								

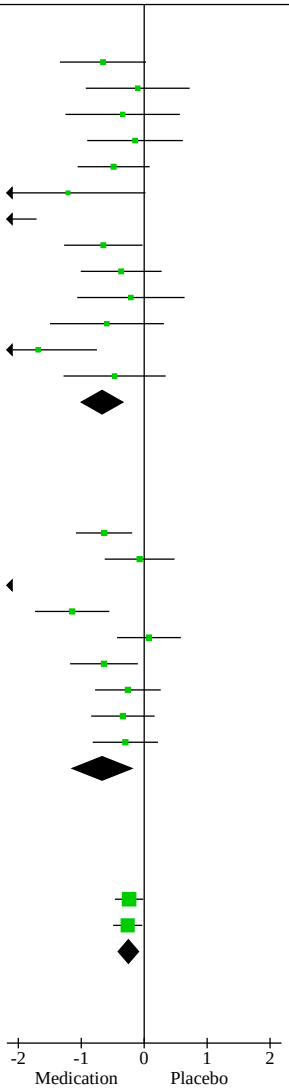


Footnotes

(1) Long-chain omega-3 polyunsaturated fatty acids versus placebo GAF
(2) Carbamazepine versus placebo - GAS
(3) Fluoxetine versus placebo (GAS)
(4) Fluoxetine versus placebo - GAF
(5) Quetiapine vs. placebo (GAF). Active groups pooled. SDs calculated from SEs. Multiplied by (-1), neg. ES indicating beneficial effects
(6) Thiothixene versus placebo - GAS
(7) Olanzapine versus placebo - CGI-S
(8) Haloperidol versus placebo - GAS
(9) Amitriptyline versus placebo - GAS
(10) Amitriptyline versus placebo GAS
(11) Lamotrigine plus TAU versus placebo plus TAU - SFQ
(12) Olanzapine versus placebo - SDS, mean change from baseline to endpoint
(13) Olanzapine 5-10 mg/d - SDS, mean change from baseline to endpoint

Analysis 24.2. Comparison 24: Subgroup analysis: trial size, Outcome 2: Secondary: Anger at end of treatment

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
24.2.1 ≤ 50								
Bogenschutz 2004 (1)	-2.1875	1.68201	16	-1.1053	1.55973	19	9.0%	-0.65 [-1.34 , 0.03]
Cowdry 1988 (2)	4	1.83	10	4.15	0.98	13	7.6%	-0.10 [-0.93 , 0.72]
De la Fuente 1994 (3)	5.57	8.46	9	8.33	6.98	10	6.9%	-0.34 [-1.25 , 0.57]
Frankenburg 2002 (4)	1.5	0.7	20	1.6	0.6	10	8.2%	-0.15 [-0.91 , 0.61]
Hallahan 2007 (5)	10.3	10.57	22	14.5	6.4	27	10.1%	-0.49 [-1.06 , 0.09]
Hollander 2001 (6)	1.8	2.9	12	6	4.4	4	4.8%	-1.21 [-2.44 , 0.02]
Nickel 2004 (7)	17.6	1.8	19	22.6	1.6	10	5.6%	-2.80 [-3.89 , -1.71]
Nickel 2005 (8)	26	2.6	22	27.6	2.2	20	9.6%	-0.65 [-1.27 , -0.03]
Rinne 2002 (9)	1.59	2	20	2.49	2.8	18	9.4%	-0.37 [-1.01 , 0.28]
Salzman 1995 (10)	0.31	0.48	13	0.44	0.73	9	7.4%	-0.21 [-1.06 , 0.64]
Simpson 2004 (11)	2.56	3.81	9	7.45	10.05	11	6.9%	-0.59 [-1.50 , 0.31]
Tritt 2005 (12)	22.1	3.2	18	27.9	3.6	9	6.7%	-1.69 [-2.62 , -0.75]
Zanarini 2003 (13)	7.2	8.1	18	12.9	17.1	9	7.7%	-0.47 [-1.28 , 0.34]
Subtotal (95% CI)			**208**			**169**	**100.0%**	**-0.67 [-1.00 , -0.34]**
Heterogeneity: Tau² = 0.19; Chi² = 26.46, df = 12 (P = 0.009); I² = 55%								
Test for overall effect: Z = 3.98 (P < 0.0001)								
24.2.2 ≤ 100								
Black 2014 (14)	-1.87	2.3469	66	-0.37	2.3156	29	11.7%	-0.64 [-1.08 , -0.19]
Goldberg 1986 (15)	0.6167	0.695	24	0.6769	0.9236	26	11.1%	-0.07 [-0.63 , 0.48]
Loew 2006 (16)	66.5	2.7	28	75.8	3.2	28	9.6%	-3.10 [-3.89 , -2.30]
Nickel 2006 (17)	64.6	6.8	26	73.1	7.8	26	10.9%	-1.14 [-1.73 , -0.55]
Pascual 2008 (18)	3.66	1.4	30	3.56	1.2	30	11.4%	0.08 [-0.43 , 0.58]
Soloff 1989 (19)	0.78	0.82	28	1.39	1.05	28	11.2%	-0.64 [-1.18 , -0.10]
Soloff 1989 (20)	1.12	1.01	29	1.39	1.05	28	11.3%	-0.26 [-0.78 , 0.26]
Soloff 1993 (21)	0.73	0.85	34	1.04	0.97	28	11.4%	-0.34 [-0.84 , 0.17]
Soloff 1993 (19)	0.79	0.66	30	1.04	0.97	28	11.3%	-0.30 [-0.82 , 0.22]
Subtotal (95% CI)			**295**			**251**	**100.0%**	**-0.67 [-1.14 , -0.20]**
Heterogeneity: Tau² = 0.44; Chi² = 55.30, df = 8 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 2.77 (P = 0.006)								
24.2.3 ≥ 100								
Schulz 2007 (1)	-0.91	1.21	150	-0.61	1.28	155	51.2%	-0.24 [-0.47 , -0.01]
Zanarini 2007 (22)	-1.1	1.06	144	-0.81	1.14	147	48.8%	-0.26 [-0.49 , -0.03]
Subtotal (95% CI)			**294**			**302**	**100.0%**	**-0.25 [-0.41 , -0.09]**
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%								
Test for overall effect: Z = 3.05 (P = 0.002)								
Test for subgroup differences: Chi² = 6.78, df = 2 (P = 0.03), I² = 70.5%								



Footnotes

(1) Olanzapine versus placebo
(2) Trifluoperazine hydrochloride versus placebo - cross-over data
(3) Carbamazepine versus placebo
(4) Valproate semisodium versus placebo. Frankenburg 2002 and Hollander 2001 were not pooled, as heterogeneity seemed considerable (I 2 78%), and could not definitely b
(5) Omega-3 fatty acids vs. placebo
(6) Valproate semisodium versus placebo
(7) Topiramate versus placebo
(8) Topiramate (males) versus placebo. cf. to (3)
(9) Fluvoxamine versus placebo
(10) Fluoxetine versus placebo - PDRS-anger
(11) Fluoxetine versus placebo
(12) Lamotrigine versus placebo
(13) Omega-3 fatty acids versus placebo
(14) Quetiapine versus placebo - OAS-M. Active groups pooled. SDs calculated from SEs
(15) Thiothixene versus placebo
(16) Topiramate (females) versus placebo. For Topiramate, data were analysed for male and female samples separately (I 2 of all three estimates 93%).
(17) Aripiprazole versus placebo
(18) Ziprasidone versus placebo

Analysis 24.2. (Continued)

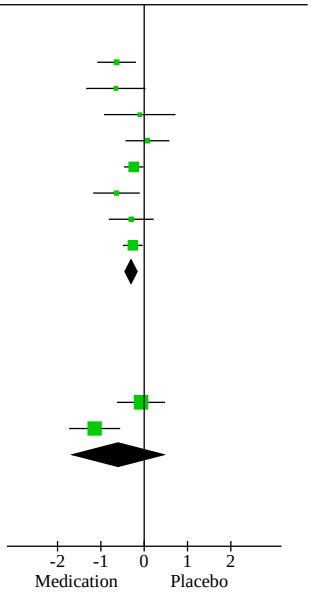
(17) Aripiprazole versus placebo
(18) Ziprasidone versus placebo
(19) Haloperidol versus placebo
(20) Amitriptyline versus placebo
(21) Phenelzine sulfate versus placebo
(22) Olanazapine versus placebo

Comparison 25. Subgroup analysis: recruitment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25.1 Antipsychotics - anger at end of treatment	10		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
25.1.1 Referral	8	923	Std. Mean Difference (IV, Random, 95% CI)	-0.30 [-0.44, -0.16]
25.1.2 Advertisement	2	102	Std. Mean Difference (IV, Random, 95% CI)	-0.60 [-1.65, 0.45]

Analysis 25.1. Comparison 25: Subgroup analysis: recruitment, Outcome 1: Antipsychotics - anger at end of treatment

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
25.1.1 Referral								
Black 2014 (1)	-1.87	2.3469	66	-0.37	2.3156	29	9.3%	-0.64 [-1.08 , -0.19]
Bogenschutz 2004 (2)	-2.1875	1.68201	16	-1.1053	1.55973	19	4.1%	-0.65 [-1.34 , 0.03]
Cowdry 1988 (3)	4	1.83	10	4.15	0.98	13	2.8%	-0.10 [-0.93 , 0.72]
Pascual 2008 (4)	3.66	1.4	30	3.56	1.2	30	7.3%	0.08 [-0.43 , 0.58]
Schulz 2007 (2)	-0.91	1.21	150	-0.61	1.28	155	32.1%	-0.24 [-0.47 , -0.01]
Soloff 1989 (5)	0.78	0.82	28	1.39	1.05	28	6.5%	-0.64 [-1.18 , -0.10]
Soloff 1993 (5)	0.79	0.66	30	1.04	0.97	28	7.0%	-0.30 [-0.82 , 0.22]
Zanarini 2007	-1.1	1.06	144	-0.81	1.14	147	30.8%	-0.26 [-0.49 , -0.03]
Subtotal (95% CI)			**474**			**449**	**100.0%**	**-0.30 [-0.44 , -0.16]**
Heterogeneity: Tau² = 0.00; Chi² = 7.44, df = 7 (P = 0.38); I² = 6%								
Test for overall effect: Z = 4.27 (P < 0.0001)								
25.1.2 Advertisement								
Goldberg 1986 (6)	0.6167	0.695	24	0.6769	0.9236	26	50.5%	-0.07 [-0.63 , 0.48]
Nickel 2006 (7)	64.6	6.8	26	73.1	7.8	26	49.5%	-1.14 [-1.73 , -0.55]
Subtotal (95% CI)			**50**			**52**	**100.0%**	**-0.60 [-1.65 , 0.45]**
Heterogeneity: Tau² = 0.49; Chi² = 6.73, df = 1 (P = 0.009); I² = 85%								
Test for overall effect: Z = 1.13 (P = 0.26)								
Test for subgroup differences: Chi² = 0.31, df = 1 (P = 0.58), I² = 0%								



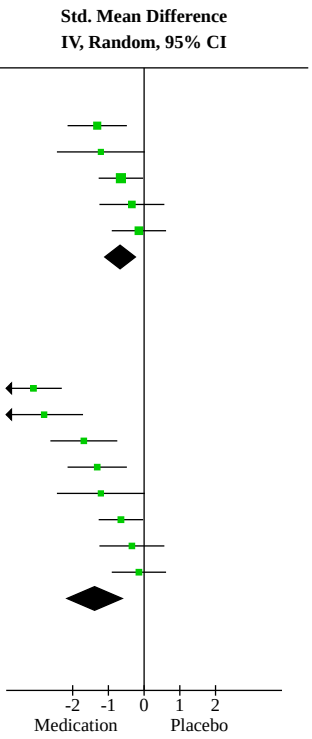
Footnotes
(1) Quetiapine versus placebo - OAS-M. Active groups pooled. SDs calculated from SEs
(2) Olanzapine versus placebo
(3) Trifluoperazine hydrochloride versus placebo - cross-over data
(4) Ziprasidone versus placebo
(5) Haloperidol versus placebo
(6) Thiothixene versus placebo
(7) Aripiprazole versus placebo

Comparison 26. Sensitivity analysis: mood stabiliser trials outliers SMD > 1.5 included

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.1 Secondary: Anger at end of treatment	8		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
26.1.1 Mood stabilisers, outliers (SMD > 1.5) excluded	5	135	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.10, -0.24]
26.1.2 Mood stabilisers, outlier (SMD >1.5) included	8	247	Std. Mean Difference (IV, Random, 95% CI)	-1.39 [-2.16, -0.61]

Analysis 26.1. Comparison 26: Sensitivity analysis: mood stabiliser trials outliers SMD > 1.5 included, Outcome 1: Secondary: Anger at end of treatment

Study or Subgroup	Medication Mean	Medication SD	Medication Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
26.1.1 Mood stabilisers, outliers (SMD > 1.5) excluded								
Cowdry 1988 (1)	2.93	0.83	15	4.15	0.98	13	19.9%	-1.31 [-2.14 , -0.48]
Hollander 2001 (2)	1.8	2.9	12	6	4.4	4	10.5%	-1.21 [-2.44 , 0.02]
Nickel 2005 (3)	26	2.6	22	27.6	2.2	20	29.5%	-0.65 [-1.27 , -0.03]
De la Fuente 1994 (4)	5.57	8.46	9	8.33	6.98	10	17.4%	-0.34 [-1.25 , 0.57]
Frankenburg 2002 (5)	1.5	0.7	20	1.6	0.6	10	22.6%	-0.15 [-0.91 , 0.61]
Subtotal (95% CI)			**78**			**57**	**100.0%**	**-0.67 [-1.10 , -0.24]**
Heterogeneity: Tau² = 0.06; Chi² = 5.38, df = 4 (P = 0.25); I² = 26%								
Test for overall effect: Z = 3.07 (P = 0.002)								
26.1.2 Mood stabilisers, outlier (SMD >1.5) included								
Loew 2006 (6)	66.5	2.7	28	75.8	3.2	28	13.0%	-3.10 [-3.89 , -2.30]
Nickel 2004 (6)	17.6	1.8	19	22.6	1.6	10	11.6%	-2.80 [-3.89 , -1.71]
Tritt 2005 (7)	22.1	3.2	18	27.9	3.6	9	12.3%	-1.69 [-2.62 , -0.75]
Cowdry 1988 (8)	2.93	0.83	15	4.15	0.98	13	12.8%	-1.31 [-2.14 , -0.48]
Hollander 2001 (2)	1.8	2.9	12	6	4.4	4	10.9%	-1.21 [-2.44 , 0.02]
Nickel 2005 (9)	26	2.6	22	27.6	2.2	20	13.7%	-0.65 [-1.27 , -0.03]
De la Fuente 1994 (4)	5.57	8.46	9	8.33	6.98	10	12.5%	-0.34 [-1.25 , 0.57]
Frankenburg 2002 (10)	1.5	0.7	20	1.6	0.6	10	13.1%	-0.15 [-0.91 , 0.61]
Subtotal (95% CI)			**143**			**104**	**100.0%**	**-1.39 [-2.16 , -0.61]**
Heterogeneity: Tau² = 1.03; Chi² = 45.00, df = 7 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 3.52 (P = 0.0004)								



Footnotes

(1) Carbamazepine vs. placebo (crossover data)
(2) Valproate semisodium versus placebo
(3) Topiramate (males) versus placebo. cf. to (5)
(4) Carbamazepine versus placebo
(5) Valproate semisodium versus placebo.
(6) Topiramate versus placebo
(7) Lamotrigine versus placebo
(8) Carbamazepine vs. Placebo (crossover data)
(9) Topiramate versus placebo. cf. to (3)
(10) Valproate semisodium versus placebo. Frankenburg 2002 and Hollander 2001 were not pooled, as heterogeneity seemed considerable (I 2 78%), and could not definitely

ADDITIONAL TABLES

Table 1. Key demographic characteristics of the included studies

Category	Study frequency	Study ID
Sample size		
Sample size above 100 participants	4	Jariani 2010; Schulz 2007; Soloff 1993; Zanarini 2001
Setting		
Trials with inpatient setting	9	De la Fuente 1994; Markovitz 1995a; Moen 2012; Schmahl 2012a; Shafti 2010; Shafti 2014; Simpson 2004; NCT00533117; Ziegenhorn 2009
Trials with outpatient setting	32	Amminger 2013; Bellino 2014; Black 2014; Bogenschutz 2004; Bozzatello 2017; Cowdry 1988; ; Frankenburg 2002; Goldberg 1986; Grant 2022; Hallahan 2007; Hollander 2001; Jariani 2010; Kulkarni 2018; Leone 1982; Linehan 2008; Loew 2006; Montgomery 1982a; Montgomery 1982b; Nickel 2004; Nickel 2005; Nickel 2006; Pascual 2008; Reich 2009; Rinne 2002; Salzman 1995; Schulz 2007; Soler 2005; Tritt 2005; Zanarini 2001; Zanarini 2003; Zanarini 2004; Zanarini 2007
Trials with both inpatient and outpatient settings	4	Crawford 2018; Schmahl 2012b; Soloff 1989; Soloff 1993
Not stated	1	AstraZeneca 2007
Screening methods		
Referral	20	Amminger 2013; Bellino 2014; Bogenschutz 2004; Bozzatello 2017; Cowdry 1988; Crawford 2018; Hallahan 2007; Hollander 2001; Montgomery 1982a; Montgomery 1982b; Pascual 2008; Schmahl 2012a; Schmahl 2012b; Shafti 2010; Shafti 2014; Simpson 2004; Soler 2005; Soloff 1989; Soloff 1993; Ziegenhorn 2009
Advertisement	11	Frankenburg 2002; Goldberg 1986; Loew 2006; Moen 2012; Nickel 2006; Reich 2009; Salzman 1995; Tritt 2005; Zanarini 2001; Zanarini 2003; Zanarini 2004
Both referral and advertisement	6	Black 2014; Grant 2022; Kulkarni 2018; NCT00533117; Nickel 2005; Rinne 2002
Not stated	9	AstraZeneca 2007; De la Fuente 1994; Jariani 2010; Leone 1982; Linehan 2008; Markovitz 1995a; Nickel 2004; Schulz 2007; Zanarini 2007
Participant mean age		
below 18 years	1	Amminger 2013
18-26 years	6	Bellino 2014; Bozzatello 2017; Loew 2006; Nickel 2006; Soloff 1989; Zanarini 2004
26-30 years	15	Black 2014; Frankenburg 2002; Jariani 2010; Nickel 2004; Nickel 2005; Pascual 2008; Rinne 2002; Schmahl 2012a; Schmahl 2012b; Shafti 2010; Shafti 2014; Soloff 1993; Tritt 2005; Zanarini 2001; Zanarini 2003
above 30 years	22	Bogenschutz 2004; Cowdry 1988; Crawford 2018; De la Fuente 1994; Goldberg 1986; Grant 2022; Hallahan 2007; Hollander 2001; Kulkarni 2018; Leone 1982; Linehan 2008; Moen 2012, Montgomery 1982a; Montgomery 1982b;

Table 1. Key demographic characteristics of the included studies *(Continued)*

		NCT00533117; Reich 2009; Salzman 1995; Schulz 2007; Simpson 2004; Soler 2005; Zanarini 2007; Ziegenhorn 2009
mean age not reported	2	AstraZeneca 2007; Markovitz 1995a
Psychiatric comorbidity		
Comorbidity	22	Amminger 2013; Black 2014; Bogenschutz 2004; Cowdry 1988; Frankenburg 2002; Goldberg 1986; Grant 2022; Jariani 2010; Kulkarni 2018; Markovitz 1995a; Moen 2012; Nickel 2005; Nickel 2006; Reich 2009; Rinne 2002; Schmahl 2012b; Simpson 2004; Soloff 1989; Soloff 1993; Zanarini 2004; Zanarini 2007; Ziegenhorn 2009
No comorbidity	6	Bellino 2014; Salzman 1995; Schulz 2007; Shafti 2010; Shafti 2014; Soler 2005
Not stated	18	AstraZeneca 2007; Bozzatello 2017; Crawford 2018; De la Fuente 1994; Hallahan 2007; Hollander 2001; Leone 1982; Linehan 2008; Loew 2006; Montgomery 1982a; Montgomery 1982b; NCT00533117; Nickel 2004; Pascual 2008; Schmahl 2012a;Tritt 2005; Zanarini 2001; Zanarini 2003
Sex		
Only females included	15	Cowdry 1988; Frankenburg 2002; Linehan 2008; Loew 2006; Nickel 2004; Rinne 2002; Schmahl 2012a; Schmahl 2012b; Shafti 2010; Shafti 2014; Simpson 2004; Tritt 2005; Zanarini 2001; Zanarini 2003; Zanarini 2004
Only males included	1	Nickel 2005
Not stated	1	Markovitz 1995a
Severity of impairment at baseline		
Mild symptoms, slight impairment	3	GAF/GAS scores 60 or higher Black 2014; Goldberg 1986; Salzman 1995
Moderate impairment	10	GAF/GAS scores 51 to 60 Amminger 2013; De la Fuente 1994;Frankenburg 2002; Hollander 2001; Reich 2009; Schulz 2007; Zanarini 2003; Zanarini 2004; Zanarini 2007 CGi score 4 Bogenschutz 2004
Serious impairment, markedly ill	6	GAF/GAS scores 41 to 50 Linehan 2008; Simpson 2004; Soloff 1989; Soloff 1993 CGI score 5 Soler 2005 SFQ score 15 Crawford 2018
Diagnostic classification		

Table 1. Key demographic characteristics of the included studies *(Continued)*

DSM	2	Black 2014; Loew 2006
DSM-III diagnosis	7	Cowdry 1988; De la Fuente 1994; Goldberg 1986; Leone 1982; Montgomery 1982a; Montgomery 1982b; Soloff 1989
DSM-III-R diagnosis	3	Markovitz 1995a; Salzman 1995; Soloff 1993
DSM-IV diagnosis	28	Amminger 2013; AstraZeneca 2007; Bogenschutz 2004; Bozzatello 2017; Crawford 2018; Frankenburg 2002; Hallahan 2007; Hollander 2001; Kulkarni 2018; Linehan 2008; Moen 2012 Nickel 2004; Nickel 2005; Nickel 2006; Pascual 2008; Reich 2009; Rinne 2002; Schmahl 2012a; Schmahl 2012b; Schulz 2007; Shafti 2010; Simpson 2004; Soler 2005; Tritt 2005; Zanarini 2001; Zanarini 2003; Zanarini 2004; Ziegenhorn 2009
DSM-IV-TR diagnosis	4	Bellino 2014; Jariani 2010; Shafti 2014; Zanarini 2007
DSM-5	1	Grant 2022
Not stated	1	NCT00533117
Diagnostic assessment		
DIB	4	Cowdry 1988; De la Fuente 1994; Soloff 1989; Soloff 1993
DIB-R	4	Reich 2009; Zanarini 2001; Zanarini 2003; Zanarini 2004
Clinical consensus	1	Amminger 2013
DIPD-IV	1	Frankenburg 2002
DIPD-IV and ZAN-BPD	2	Schulz 2007; Zanarini 2007
IPDE	2	Schmahl 2012a; Schmahl 2012b
IPDE and SCID-I	1	Crawford 2018;
Not stated	4	Leone 1982; NCT00533117 Shafti 2010; Shafti 2014;
MINI and SCID-II	1	Ziegenhorn 2009
SCID (unspecified)	1	Black 2014
SCID-I and SCID-II	3	Bellino 2014; Bozzatello 2017; Moen 2012
SCID-II	11	AstraZeneca 2007; Bogenschutz 2004; Hallahan 2007; Hollander 2001; Linehan 2008; Loew 2006; Nickel 2004; Nickel 2005; Nickel 2006; Simpson 2004; Tritt 2005
SCID-II, ADP-IV and BPDSI	1	Rinne 2002
SCID-II and DIB20	1	Markovitz 1995a
SCID-II and DIB-R	3	Pascual 2008; Salzman 1995; Soler 2005
SIB	1	Goldberg 1986

Table 1. Key demographic characteristics of the included studies *(Continued)*

Unspecified clinical interview	3	Jariani 2010; Montgomery 1982a; Montgomery 1982b
ZAN-BPD	2	Grant 2022; Kulkarni 2018
Most common exclusion criteria in included studies		
Participants with alcohol or substance abuse or dependence excluded	31	Amminger 2013; AstraZeneca 2007; Bellino 2014; Black 2014; Bogenschutz 2004; Bozzatello 2017; De la Fuente 1994; Frankenburg 2002; Goldberg 1986; Grant 2022; Hallahan 2007; Hollander 2001; Kulkarni 2018; Linehan 2008; Loew 2006; Moen 2012; NCT00533117; Nickel 2004; Nickel 2005; Pascual 2008; Salzman 1995; Schmahl 2012a; Schmahl 2012b; Schulz 2007; Shafti 2014; Simpson 2004; Soloff 1993, Tritt 2005; Zanarini 2001; Zanarini 2007; Ziegenhorn 2009
Participants with acute suicidal or aggressive behaviour excluded	15	Amminger 2013; Black 2014; Bogenschutz 2004; Frankenburg 2002; Grant 2022; Linehan 2008; Loew 2006; Nickel 2004; Nickel 2005; Nickel 2006; Reich 2009; Salzman 1995; Tritt 2005; Zanarini 2001; Zanarini 2007
Participants with current major depression, bipolar affective disorders or psychotic disorders excluded	38	Amminger 2013; AstraZeneca 2007; Bellino 2014; Black 2014; Bogenschutz 2004; Bozzatello 2017; Crawford 2018; De la Fuente 1994; Frankenburg 2002; Goldberg 1986; Hallahan 2007; Hollander 2001; Kulkarni 2018; Linehan 2008; Loew 2006; Moen 2012; Montgomery 1982a; Montgomery 1982b; NCT00533117; Nickel 2004; Nickel 2005; Nickel 2006; Pascual 2008; Reich 2009; Salzman 1995; Schmahl 2012a; Schmahl 2012b; Schulz 2007; Shafti 2010; Shafti 2014; Simpson 2004; Soloff 1989; Tritt 2005; Zanarini 2001; Zanarini 2003; Zanarini 2004; Zanarini 2007; Ziegenhorn 2009
Participants with organic illness, mental retardation, cognitive disorder or impairment excluded	18	Bellino 2014; Black 2014; Bogenschutz 2004; Bozzatello 2017; Crawford 2018; Goldberg 1986; Grant 2022: Kulkarni 2018; Leone 1982; Linehan 2008; Montgomery 1982a; Montgomery 1982b; NCT00533117; Pascual 2008; Reich 2009; Shafti 2014; Soloff 1989; Soloff 1993;
Participants with severe somatic illness or chronic medical conditions excluded	19	Crawford 2018; Frankenburg 2002; Goldberg 1986; Grant 2022: Hollander 2001; Jariani 2010; Kulkarni 2018; Leone 1982; Loew 2006; NCT00533117; Nickel 2004; Nickel 2005; Nickel 2006; Reich 2009; Schmahl 2012a; Schmahl 2012b; Tritt 2005; Zanarini 2001; Ziegenhorn 2009
Pregnant or breastfeeding participants excluded	20	Bogenschutz 2004; Black 2014; Frankenburg 2002; Grant 2022; Hallahan 2007; Hollander 2001; Kulkarni 2018; Linehan 2008; Moen 2012; NCT00533117; Nickel 2004; Nickel 2006; Reich 2009; Schmahl 2012a; Schmahl 2012b; Simpson 2004; Tritt 2005; Zanarini 2001; Zanarini 2007; Ziegenhorn 2009
Not stated	2	Cowdry 1988; Markovitz 1995a

*Trials may be mentioned more than once in this table section due to several exclusion criteria in each trial. This section lists the most common exclusion criteria in the included trials and is not exhaustive.

Duration of intervention		
Between three and 12 months	11	Cowdry 1988; Crawford 2018; Frankenburg 2002; Grant 2022; Linehan 2008; Markovitz 1995a; Moen 2012; Montgomery 1982a; Montgomery 1982b; NCT00533117; Zanarini 2001
Less than three months	35	Amminger 2013; AstraZeneca 2007; Bellino 2014; Black 2014; Bozzatello 2017; Bogenschutz 2004; De la Fuente 1994; Goldberg 1986; Hallahan 2007; Hollander 2001; Jariani 2010; Kulkarni 2018; Leone 1982; Loew 2006; Nickel 2004; Nickel 2005; Nickel 2006; Pascual 2008; Reich 2009; Rinne 2002; Salzman

Table 1. Key demographic characteristics of the included studies *(Continued)*

		1995, Schmahl 2012a; Schmahl 2012b; Schulz 2007; Shafti 2010; Shafti 2014; Simpson 2004; Soler 2005; Soloff 1989; Soloff 1993; Tritt 2005; Zanarini 2003; Zanarini 2004; Zanarini 2007; Ziegenhorn 2009
Concomitant treatment		
Dialectic Behaviour therapy (DBT) and supportive psychotherapy	1	NCT00533117
Dialectic Behavioural therapy (DBT)	4	Linehan 2008; Moen 2012; Simpson 2004; Soler 2005
Non-specific need-based psychological and psychosocial interventions	1	Amminger 2013
Supportive atheoretical psychotherapy	1	De la Fuente 1994
Nonspecific supportive psychotherapy	6	Kulkarni 2018; Montgomery 1982a; Montgomery 1982b; Pascual 2008; Schmahl 2012a; Schmahl 2012b
Psychotherapy allowed if initiated prior to randomisation	1	Bogenschutz 2004
Psychotherapy not allowed	12	Black 2014; Bozzatello 2017 Frankenburg 2002; Hallahan 2007; Loew 2006; Nickel 2004; Nickel 2005; Nickel 2006; Reich 2009; Rinne 2002; Shafti 2010; Tritt 2005
Not stated	20	AstraZeneca 2007; Bellino 2014; Cowdry 1988; Crawford 2018; Goldberg 1986; Grant 2022; Hollander 2001; Jariani 2010; Leone 1982; Markovitz 1995a; Salzman 1995; Schulz 2007; Shafti 2014; Soloff 1989; Soloff 1993; Zanarini 2001; Zanarini 2003; Zanarini 2004; Zanarini 2007; Ziegenhorn 2009
Concomitant medication		
Concomitant medication not allowed	8	Bellino 2014; Bozzatello 2017; Moen 2012; Nickel 2004; Nickel 2006; Salzman 1995; Shafti 2014; Soloff 1993
Benzodiazepines or SSRIs (or both) allowed	13	Amminger 2013; AstraZeneca 2007; Black 2014; Kulkarni 2018; Leone 1982; NCT00533117; Pascual 2008; Reich 2009; Schulz 2007; Simpson 2004, Soler 2005; Soloff 1989; Ziegenhorn 2009
Medication for stable, chronic medical conditions allowed	1	Bogenschutz 2004
Antidepressants, mood stabilisers and stimulants allowed	1	Grant 2022
Psychothropics allowed	2	Hallahan 2007; Jariani 2010
Psychothropics not allowed	7	Frankenburg 2002; Loew 2006; Nickel 2005; Rinne 2002; Shafti 2010; Tritt 2005; Zanarini 2001

Table 1. Key demographic characteristics of the included studies *(Continued)*

Not stated	14	Cowdry 1988; Crawford 2018; De la Fuente 1994; Goldberg 1986; Hollander 2001; Linehan 2008; Markovitz 1995a Montgomery 1982a; Montgomery 1982b; Schmahl 2012a; Schmahl 2012b; Zanarini 2003; Zanarini 2004; Zanarini 2007
Pharmacotherapy type		
Antidepressants		
fluoxetine	3	Markovitz 1995a; NCT00533117; Salzman 1995; Simpson 2004;
fluvoxamine	1	Rinne 2002
mianserin	1	Montgomery 1982b
amitriptyline	1	Soloff 1989
phenelzine sulphate	1	Soloff 1993
tranylcypromine sulfate	1	Cowdry 1988
First-generation antipsychotics		
haloperidol	2	Soloff 1989; Soloff 1993
thiothixene	1	Goldberg 1986
loxapine	1	Leone 1982
flupenthixol	1	Montgomery 1982a
trifluoperazine hydrochloride	1	Cowdry 1988
Second-generation antipsychotics		
olanzapine	7	Bogenschutz 2004; Bozzatello 2017; Linehan 2008; Schulz 2007; Soler 2005; Zanarini 2001, Zanarini 2007
aripiprazole	1	Nickel 2006
asenapine	1	Bozzatello 2017
brexpiprazole	1	Grant 2022
ziprasidone	1	Pascual 2008
quetiapine	1	Black 2014
Anticonvulsants		
lamotrigine	3	Crawford 2018; Reich 2009; Tritt 2005
topiramate	3	Loew 2006; Nickel 2004; Nickel 2005
valporate	3	Frankenburg 2002; Hollander 2001; Moen 2012

Table 1. Key demographic characteristics of the included studies *(Continued)*

carbamazepine	2	Cowdry 1988; De la Fuente 1994
Miscellaneous		
Miscellaneous omega-3 fatty acids	3	Amminger 2013; Hallahan 2007; Zanarini 2003
Antidementia drug: memantine hydrochloride	1	Kulkarni 2018
Opioid antagonist: naltrexone	2	Schmahl 2012a; Schmahl 2012b
Antihypertensive: clonidine	1	Ziegenhorn 2009
Benzodiazepine: alprazolam	1	Cowdry 1988
Funding		
Funded by grants from universities, authorities or research foundations	10	Amminger 2013; Crawford 2018; Hallahan 2007; Kulkarni 2018; NCT00533117; Rinne 2002; Shafti 2014; Soloff 1989; Soloff 1993; Zanarini 2003
Funded or partially funded by pharmaceutical industry	17	AstraZeneca 2007; Black 2014; Bogenschutz 2004; Frankenburg 2002; Grant 2022; Hollander 2001; Leone 1982; Linehan 2008; Moen 2012; Pascual 2008; Reich 2009; Schulz 2007; Simpson 2004; Soler 2005; Zanarini 2001; Zanarini 2004; Zanarini 2007
No funding received	8	Bellino 2014; Bozzatello 2017; Loew 2006; Nickel 2005; Nickel 2006; Shafti 2010; Tritt 2005; Ziegenhorn 2009
Unclear funding	11	Cowdry 1988; De la Fuente 1994; Goldberg 1986; Jariani 2010; Markovitz 1995a; Montgomery 1982a; Montgomery 1982b; Nickel 2004; Salzman 1995; Schmahl 2012a; Schmahl 2012b

ADP-IV: Assessment of DSM-IV Personality Disorders questionnaire;**BPDSI-IV:** Borderline Personality Disorder Severity Index; **BSI:** Borderline Syndrome Index; **CI-BPD:** Childhood Interview for DSM-IV Borderline Personality Disorder; **DBT:** Dialectal Behaviour Therapy; **DIB:** Diagnostic Interview for Borderline Patients; **DIB-R:** Diagnostic Interview for Borderline Patients - revised version; **DIPD-IV:** Diagnostic Interview for DSM-IV Personality Disorders; **DSM-III:** Diagnostic and Statistical Manual of Mental Disorders, Third Edition; **DSM-III-R:** Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised; **DSM-IV:** Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; **DSM-IV-TR:** Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; **ICD-10:** International Classification of Diseases, Tenth Revision; **ID:** Identifier;**IPDE:** International Personality Disorder Examination; **MINI:** The *Mini*-International Neuropsychiatric Interview;**IPDE:** Personality Disorders Examination; **SCID-II**: Structured Clinical Interview for DSM-IV Axis II Personality Disorders; **SIB:** self-injurious behaviour; **SIDP-IV:** Structured Interview for DSM-IV Personality; **SSRI:** selective serotonin reuptake inhibitors; **ZAN-BPD:** Zanarini Rating Scale for Borderline Personality Disorder.

Table 2. Adverse events of pharmacotherapies versus placebo

Outcome or subgroup title	Pharmacotherapy	No. of studies	No. of participants	Statistical method	Effect estimate	Study ID
Central nervous system						

Table 2. Adverse events of pharmacotherapies versus placebo *(Continued)*

Headache	Antipsychotics	4	754	Risk Ratio (M-H, Random, 95% CI)	1.01 (0.63 to 1.62)	Black 2014; Grant 2022; Schulz 2007; Zanarini 2007
	Mood stabilisers	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.00 (0.15 to 6.61)	Loew 2006
	Memantine hydrochloride	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.29 (0.71 to 2.36)	Kulkarni 2018
Dizziness	Antipsychotics	2	68	Risk Ratio (M-H, Random, 95% CI)	3.07 (0.40 to 23.45)	Black 2014; Pascual 2008
	Mood stabilisers	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.50 (0.27 to 8.30)	Loew 2006
	Memantine hydrochloride	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.69 (0.72 to 3.98)	Kulkarni 2018
Fatigue	Antipsychotics	3	692	Risk Ratio (M-H, Random, 95% CI)	1.50 (0.58 to 3.89)	Grant 2022; Schulz 2007; Zanarini 2007
	Mood stabilisers	1	56	Risk Ratio (M-H Fixed, 95% CI)	2.00 (0.40 to 10.05)	Loew 2006
	Memantine hydrochloride	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.32 (0.52 to 3.31)	Kulkarni 2018
Somnolence	Antipsychotics	2	615	Risk Ratio (M-H, Random, 95% CI)	2.97 (1.75 to 5.03)	Schulz 2007; Zanarini 2007
	Memantine hydrochloride	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.65 (0.59to 4.57)	Kulkarni 2018
Sedation	Antipsychotics	4	445	Risk Ratio (M-H, Random, 95% CI)	2.66 (0.99 to 7.12)	Black 2014; Pascual 2008; Schulz 2007; Zanarini 2001
Anxiety	Antipsychotics	1	314	Risk Ratio (M-H, Fixed, 95% CI)	0.90 (0.33 to 2.42)	Schulz 2007
Insomnia	Antipsychotics	2	615	Risk Ratio (M-H, Random, 95% CI)	0.68 (0.33 to 1.37)	Schulz 2007; Zanarini 2007
Hyperinsomnia	Antipsychotics	1	62	Risk Ratio (M-H, Fixed, 95% CI)	2.34 (0.69 to 8.01)	Black 2014

Table 2. Adverse events of pharmacotherapies versus placebo *(Continued)*

Increased appetite	Antipsychotics	3	692	Risk Ratio (M-H, Random, 95% CI)	2.68 (1.71 to 4.19)	Grant 2022; Schulz 2007; Zanarini 2007
Change in appetite	Antipsychotics	1	17	Risk Ratio (M-H, Fixed, 95% CI)	0.65 (0.10 to 4.06)	Black 2014
Forgetfulness or confusion	Antipsychotics	1	17	Risk Ratio (M-H, Fixed, 95% CI)	1.46 (0.38 to 5.60)	Black 2014
Disturbances in attention	Antipsychotics	1	301	Risk Ratio (M-H, Fixed, 95% CI)	11.37 (0.63 to 203.81)	Zanarini 2007
Restlessness	Antipsychotics	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.93 (0.20 to 4.30)	Grant 2022
Hallucinations	Antipsychotics	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.19 (0.01 to 3.74)	Grant 2022
Sleep problems	Antipsychotics	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.19 (0.01 to 3.74)	Grant 2022
Tremor	Antipsychotics	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.31 (0.01 to 7.36)	Grant 2022
Memory problems	Mood stabilisers	1	56	Risk Ratio (M-H, Fixed, 95% CI)	2.00 (0.55 to 7.22)	Loew 2006
Paraesthesia	Mood stabilisers	1	56	Risk Ratio (M-H, Fixed, 95% CI)	3.00 (0.33 to 27.12)	Loew 2006
Gait/balance disturbances	Memantine hydrochloride	1	33	Risk Ratio (M-H, Fixed, 95% CI)	2.35 (0.53 to 10.45)	Kulkarni 2018
Nervous system disorders	Mood stabilisers	1	276	Risk Ratio (M-H, Fixed, 95% CI)	1.05 (0.68 to 1.62)	Crawford 2018
Psychiatric disorders	Mood stabilisers	1	276	Risk Ratio (M-H, Fixed, 95% CI)	0.94 (0.64 to 1.37)	Crawford 2018
Cardiovascular and respiratory system						
Cold/flu symptoms	Antipsychotics	1	62	Risk Ratio (M-H, Fixed, 95% CI)	1.54 (0.50 to 4.73)	Black 2014
Nasopharyngitis	Antipsychotics	1	301	Risk Ratio (M-H, Fixed, 95% CI)	0.62 (0.23 to 1.66)	Schulz 2007
Sweating	Antipsychotics	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.31 (0.01 to 7.36)	Grant 2022
Blood and lymphatic system disorders	Mood stabilisers	1	276	Risk Ratio (M-H, Fixed, 95% CI)	0.68 (0.11 to 3.99)	Crawford 2018

Table 2. Adverse events of pharmacotherapies versus placebo *(Continued)*

Cardiac disorders	Mood stabilisers	1	276	Risk Ratio (M-H, Fixed, 95% CI)	0.34 (0.01 to 8.23)	Crawford 2018
Endocrine disorders	Mood stabilisers	1	276	Risk Ratio (M-H, Fixed, 95% CI)	0.34 (0.01 to 8.23)	Crawford 2018
Respiratory, thoracic and mediastinal disorders	Mood stabilisers	1	276	Risk Ratio (M-H, Fixed, 95% CI)	1.80 (0.83 to 3.94)	Crawford 2018
Diastolic blood pressure in standing position (mean change from baseline to endpoint)	Antipsychotics	1	290	Mean Difference (IV, Fixed, 95% CI)	-0.28 (-2.29 to 1.73)	Zanarini 2007
Diastolic blood pressure in supine position (mean change from baseline to endpoint)	Antipsychotics	1	290	Mean Difference (IV, Fixed, 95% CI)	-0.11 (-2.28 to 2.06)	Zanarini 2007
Systolic blood pressure in standing position (mean change from baseline to endpoint)	Antipsychotics	1	290	Mean Difference (IV, Fixed, 95% CI)	0.35 (-2.39 to 3.09)	Zanarini 2007
Systolic blood pressure in supine position (mean change from baseline to endpoint)	Antipsychotics	1	290	Mean Difference (IV, Fixed, 95% CI)	-1.31 (-4.00 to 1.38)	Zanarini 2007
Pulse in standing position (mean change from baseline to endpoint)	Antipsychotics	1	290	Mean Difference (IV, Fixed, 95% CI)	0.85 (-1.65 to 3.35)	Zanarini 2007
Pulse in supine position (mean change from baseline to endpoint)	Antipsychotics	1	290	Mean Difference (IV, Fixed, 95% CI)	-0.11 (-2.28 to 2.06)	Zanarini 2007
Gastrointestinal system						
Nausea	Antipsychotics	4	754	Risk Ratio (M-H, Random, 95% CI)	0.80 (0.49 to 1.29)	Black 2014; Grant 2022; Schulz 2007; Zanarini 2007
	Memantine hydrochloride	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.00 (0.45 to 2.23)	Kulkarni 2018
Uneasy feeling	Antipsychotics	1	60	Risk Ratio (M-H, Fixed, 95% CI)	7.00 (0.38 to 129.93)	Pascual 2008
Constipation	Antipsychotics	1	28	Risk Ratio (M-H, Fixed, 95% CI)	6.50 (0.41 to 104.20)	Zanarini 2001

Table 2. Adverse events of pharmacotherapies versus placebo *(Continued)*

	Memantine hydrochloride	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.65 (0.59 to 4.57)	Kulkarni 2018
Dry mouth	Antipsychotics	4	754	Risk Ratio (M-H, Random, 95% CI)	2.60 (1.46 to 4.64)	Black 2014; Grant 2022; Schulz 2007; Zanarini 2007
Gastrointestinal disorders	Mood stabilisers	1	276	Risk Ratio (M-H, Random, 95% CI)	0.70 (0.50 to 0.98)	Crawford 2018
General disorders and administration site conditions	Mood stabilisers	1	276	Risk Ratio (M-H, Random, 95% CI)	1.01 (0.50 to 2.05)	Crawford 2018
Hepatobiliary disorders	Mood stabilisers	1	276	Risk Ratio (M-H, Random, 95% CI)	3.04 (0.13 to 74.07)	Crawford 2018
Metabolism and nutrition disorders	Mood stabilisers	1	276	Risk Ratio (M-H, Random, 95% CI)	2.03 (0.19 to 22.12)	Crawford 2018
Liver function: ALT/SGPT baseline to endpoint mean change (U/L)	Antipsychotics	2	530	Std. Mean Difference (IV, Random, 95% CI)	0.46 (0.29 to 0.63)	Schulz 2007; Zanarini 2007
Liver function: AST/SGOT baseline to endpoint mean change (U/L)	Antipsychotics	2	526	Std. Mean Difference (IV, Random, 95% CI)	0.35 (0.18 to 0.52)	Schulz 2007; Zanarini 2007
Liver function: total bilirubin baseline to endpoint mean change (µmol/L)	Antipsychotics	1	264	Mean Difference (IV, Fixed, 95% CI)	-0.98 (-1.80 to -0.16)	Schulz 2007
Liver function: direct bilirubin baseline to endpoint mean change (µmol/L)	Antipsychotics	1	258	Mean Difference (IV, Fixed, 95% CI)	-0.30 (-0.51 to -0.09)	Schulz 2007
Liver function: Gamma-Glutamyl Transferase (GGT) baseline to endpoint mean change	Antipsychotics	1	268	Mean Difference (IV, Fixed, 95% CI)	2.96 (0.22 to 5.70)	Zanarini 2007
Lipids: total cholesterol baseline to endpoint change (mmol/L)	Antipsychotics	2	327	Std. Mean Difference (IV, Random, 95% CI)	0.42 (0.20 to 0.64)	Schulz 2007; Soler 2005
Lipids: Low-density lipoprotein (LDL) cholesterol baseline to endpoint mean change (mmol/L)	Antipsychotics	1	259	Mean Difference (IV, Fixed, 95% CI)	0.21 (0.06 to 0.36)	Schulz 2007
Lipids: High-density lipoprotein (HDL) cho-	Antipsychotics	1	269	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.11 to -0.01)	Zanarini 2007

Table 2. Adverse events of pharmacotherapies versus placebo *(Continued)*

lesterol (dextran precip.) baseline to endpoint mean change (mmol/L)						
Lipids: triglycerides, fasting, baseline to endpoint mean change (mmol/L)	Antipsychotics	1	203	Mean Difference (IV, Fixed, 95% CI)	0.27 (0.07 to 0.47)	Zanarini 2007
Prolactin: baseline to endpoint mean change (µg/L)	Antipsychotics	1	259	Mean Difference (IV, Fixed, 95% CI)	7.10 (1.64 to 12.56)	Schulz 2007
Platelet count baseline to endpoint mean change (GI/L)	Antipsychotics	2	517	Std. Mean Difference (IV, Random, 95% CI)	0.03 (-0.53 to 0.59)	Schulz 2007; Zanarini 2007
Erythrocyte count baseline to endpoint mean change (TI/L)	Antipsychotics	1	262	Mean Difference (IV, Fixed, 95% CI)	-0.05 (-0.12 to 0.02)	Zanarini 2007
Leukocyte count baseline to endpoint mean change (GI/L)	Antipsychotics	1	262	Mean Difference (IV, Fixed, 95% CI)	-0.70, (-1.12 to -0.28)	Zanarini 2007
Neutrophils, segmented, baseline to endpoint mean change (GI/L)	Antipsychotics	1	262	Mean Difference (IV, Fixed, 95% CI)	-0.60 (-0.97 to -0.23)	Zanarini 2007
Basophils baseline to endpoint mean change (GI/L)	Antipsychotics	1	262	Mean Difference (IV, Fixed, 95% CI)	-0.01 (-0.02 to -0.00)	Zanarini 2007
Monocytes baseline to endpoint mean change (GI/L)	Antipsychotics	1	262	Mean Difference (IV, Fixed, 95% CI)	-0.04, (-0.07 to -0.01)	Zanarini 2007
Haemoglobin baseline to endpoint mean change (mml/L-F)	Antipsychotics	1	262	Mean Difference (IV, Fixed, 95% CI)	-0.11 (-0.24 to 0.02)	Zanarini 2007
Mean cell haemoglobin concentration (MCHC) baseline to endpoint mean change (mml/L-F)	Antipsychotics	1	260	Mean Difference (IV, Fixed, 95% CI)	0.02 (-0.17 to 0.21)	Zanarini 2007
Calcium baseline to endpoint mean change (mmol/L)	Antipsychotics	1	268	Mean Difference (IV, Fixed, 95% CI)	-0.03 (-0.05 to -0.01)	Schulz 2007
Albumin baseline to endpoint mean change (g/L)	Antipsychotics	1	269	Mean Difference (IV, Fixed, 95% CI)	-0.67 (-1.42 to 0.08)	Zanarini 2007
Creatine phosphokinase baseline to endpoint mean change (U/L)	Antipsychotics	1	268	Mean Difference (IV, Fixed, 95% CI)	-44.81 (-95.39 to 5.77)	Zanarini 2007

Table 2. Adverse events of pharmacotherapies versus placebo *(Continued)*

Urea nitrogen baseline to endpoint mean change (mmol/L)	Antipsychotics	1	269	Mean Difference (IV, Fixed, 95% CI)	-0.17 (-0.46 to 0.12)	Zanarini 2007
Musculoskeletal system						
Bodily pain	Antipsychotics	1	62	Risk Ratio (M-H, Fixed, 95% CI)	0.88 (0.47 to 1.64)	Black 2014
Musculoskeletal and connective tissue disorders	Mood stabilisers	1	276	Risk Ratio (M-H, Fixed, 95% CI)	1.16 (0.43 to 3.11)	Crawford 2018
Body weight change	Antipsychotics	7	810	Std. Mean Difference (IV, Random, 95% CI)	0.78 (0.44 to 1.12)	Bogenschutz 2004; Linehan 2008; Schulz 2007; Soler 2005; Soloff 1993; Zanarini 2001; Zanarini 2007
	Antidepressants	1	62	Mean Difference (IV, Fixed, 95% CI)	0.09 (-0.31 to 0.49)	Soloff 1993
	Mood stabilisers	5	184	Std. Mean Difference (IV, Random, 95% CI)	-0.26 (-0.72 to 0.20)	Frankenburg 2002; Loew 2006; Nickel 2004; Nickel 2005; Tritt 2005
Sensory system						
Eye disorders	Mood stabilisers	1	276	Risk Ratio (M-H, Fixed, 95% CI)	0.17 (0.02 to 1.39)	Crawford 2018
Reproductive system						
Pregnancy, puerperium and perinatal conditions	Mood stabilisers	1	276	Risk Ratio (M-H, Fixed, 95% CI)	1.52 (0.26 to 8.97)	Crawford 2018
Reproductive system and breast disorders	Mood stabilisers	1	276	Risk Ratio (M-H, Fixed, 95% CI)	3.04 (0.32 to 28.90)	Crawford 2018
Menstrual pain	Mood stabilisers	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.67 (0.44 to 6.31)	Loew 2006
Other						
Injury, poisoning or procedural complications	Mood stabilisers	1	276	Risk Ratio (M-H, Fixed, 95% CI)	0.44 (0.26 to 0.74)	Crawford 2018
Skin and subcutaneous tissue disorders	Mood stabilisers	1	276	Risk Ratio (M-H, Fixed, 95% CI)	1.15 (0.75 to 1.75)	Crawford 2018

Table 2. Adverse events of pharmacotherapies versus placebo *(Continued)*

Social circumstances	Mood stabilisers	1	276	Risk Ratio (M-H, Fixed, 95% CI)	1.01 (0.06 to 16.06)	Crawford 2018
Surgical and medical procedures	Mood stabilisers	1	276	Risk Ratio (M-H, Fixed, 95% CI)	4.06 (0.46 to 35.85)	Crawford 2018

ALT: alanine aminotransferase.
AST: aspartate transaminase.
CI: confidence interval.
ID: identifier.
IV: inverse variance.
M-H: Mantel-Haenszel.
No.: number.
SGOT: Serum glutamic-oxaloacetic transaminase
SGPT: Serum glutamic-pyruvic transaminase

APPENDICES

Appendix 1. DSM diagnostic criteria for BPD (301.83)

DSM Third Edition (DSM-III; APA 1980) **301.83 BPD**	**DSM Fourth Edition Text Revision (DSM-IV-TR; APA 2000)** **301.83 BPD**	**DSM Fifth Edition (DSM-5; APA 2013)** **301.83 BPD**
Diagnostic criterion A 5 of the following are required: 1. Impulsivity or unpredictability in at least 2 areas that are potentially self-damaging (e.g. spending, sex, substance use, shoplifting, overeating, physically self-damaging acts) 2. A pattern of unstable and intense interpersonal relationships (e.g. marked shifts of attitude, idealisation, devaluation, manipulation (consistently using others for one's own ends)) 3. Inappropriate, intense anger or lack of control of anger (e.g. frequent displays of temper, constant anger) 4. Identity disturbance manifested by uncertainty about several issues relating to identity, such as self-image, gender identity, long-term goals or career choice, friendship patterns, values, and loyalties (e.g. 'Who am I', 'I feel like I am my sister when I am good') 5. Affective instability: marked shifts from normal mood to depression, irritability, or anxiety, usually lasting a few hours and	**Diagnostic criterion A** A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity beginning by early adulthood and present in a variety of contexts, as indicated by 5 (or more) of the following: 1. Frantic efforts to avoid real or imagined abandonment (note: do not include suicidal or self-mutilating behaviour covered in criterion 5) 2. A pattern of unstable and intense interpersonal relationships characterised by alternating between extremes of idealisation and devaluation 3. Identity disturbance: markedly and persistently unstable self-image or sense of self 4. Impulsivity in at least 2 areas that are potentially self-damaging (e.g. spending, sex, substance abuse, reckless driving, binge eating) (note: do not include suicidal or self-mutilating behaviour covered in criterion 5)	**Diagnostic criterion A** A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity, beginning by early adulthood and present in a variety of contexts, as indicated by 5 (or more) of the following: 1. Frantic efforts to avoid real or imagined abandonment (note: do not include suicidal or self-mutilating behaviour covered in criterion 5) 2. A pattern of unstable and intense interpersonal relationships characterised by alternating between extremes of idealisation and devaluation 3. Identity disturbance: markedly and persistently unstable self-image or sense of self 4. Impulsivity in at least 2 areas that are potentially self-damaging (e.g. spending, sex, substance abuse, reckless driving, binge eating) (note: do not include suicidal or self-mutilating behaviour covered in criterion 5)

(Continued)

only rarely more than a few days, with a return to normal mood	5. Recurrent suicidal behaviour, gestures, or threats, or self-mutilating behaviour	5. Recurrent suicidal behaviour, gestures or threats, or self-mutilating behaviour
6. Intolerance of being alone (e.g. frantic efforts to avoid being alone, depressed when alone)	6. Affective instability due to a marked reactivity of mood (e.g. intense episodic dysphoria, instability, or anxiety usually lasting a few hours and only rarely more than a few days)	6. Affective instability due to a marked reactivity of mood (e.g. intense episodic dysphoria, irritability, or anxiety of mood) usually lasting a few hours and only rarely more than a few days
7. Physically self-damaging acts (e.g. suicidal gestures, self-mutilation, recurrent accidents or physical fights)	7. Chronic feelings of emptiness	7. Chronic feelings of emptiness
8. Chronic feelings of emptiness or boredom	8. Inappropriate, intense anger or difficulty controlling anger (e.g. frequent displays of temper, constant anger, recurrent physical fights)	8. Inappropriate, intense anger or difficulty controlling anger (e.g. frequent displays of temper, constant anger, recurrent physical fights)
	9. Transient, stress-related paranoid ideation or severe dissociative symptoms	9. Transient, stress-related paranoid ideation or severe dissociative symptoms
Diagnostic criterion B		
If under 18, does not meet the criteria for Identity Disorder		

BPD: Borderline personality disorder; DSM: Diagnostic and Statistical Manual of Mental Disorders

Appendix 2. ICD-10 research criteria for emotionally unstable personality disorder (F60.3)

F 60.30: ICD-10 Emotionally unstable personality disorder, impulsive type	F 60.31: ICD-10 Emotionally unstable personality disorder, borderline type	ICD-11: 6D11.5 Borderline pattern
Diagnostic criterion A	**Diagnostic criterion A**	General criteria for personality disorders +
The general criteria of personality disorder (F60) must be met	The general criteria of personality disorder (F60) must be met	borderline pattern: pervasive pattern of instability of: - interpersonal relationships, - self-image, and - affects, and - marked impulsivity, as indicated by many of the following 9 criteria:
Diagnostic criterion B	**Diagnostic criterion B**	**Borderline pattern:**
At least 3 of the following must be present, 1 of which is 2: 1. Marked tendency to act unexpectedly and without consideration of the consequences 2. Marked tendency to quarrelsome behaviour and to conflicts with others, es-	At least 3 of the symptoms mentioned in criterion B (F60.30) must be present, and in addition at least 2 of the following: 6. Disturbances in and uncertainty about self-image, aims and internal preferences (including sexual)	• frantic efforts to avoid real or imagined abandonment • pattern of unstable and intense interpersonal relationships • identity disturbance, manifested in markedly and persistently unstable self-image or sense of self

(Continued)

pecially when impulsive acts are thwarted or criticised 3. Liability of outbursts of anger or violence, with inability to control the resulting behavioural explosions 4. Difficulty in maintaining any course of action that offers no immediate reward 5. Unstable and capricious mood	7. Liability to become involved in intense and unstable relationships, often leading to emotional crises 8. Excessive efforts to avoid abandonment 9. Recurrent threats or acts of self-harm 10. Chronic feelings of emptiness	• tendency to act rashly in states of high negative affect, leading to potentially self-damaging behaviours • recurrent episodes of self-harm • emotional instability due to marked reactivity of mood • chronic feelings of emptiness • inappropriate intense anger or difficulty controlling anger • transient dissociative symptoms or psychotic-like features in situations of high affective arousal

ICD-10: International Classification of Diseases - Tenth Edition

Appendix 3. Neuroscience-based nomenclature

Substance/ current nomenclature	Current nomenclature	ATC classification	Neuroscience-based nomenclature I: pharmacology domain	Neuroscience-based nomenclature II: mode of action	Side effects[1]
Antidepressants					
Amitriptyline	antidepressant	psychoanaleptic - antidepressant - monoamine reuptake inhibitor, non-selective	serotonin, norepinephrine	reuptake inhibitor, antagonist at serotonergic receptors	e.g. dry mouth, blurry vision, urinary hesitancy, constipation, orthostatic hypotension, sedation; toxic (potentially lethal) in overdosage
Fluoxetine	antidepressant	psychoanaleptic - antidepressant - selective serotonin reuptake inhibitor	serotonin	reuptake inhibitor	e.g. GI symptoms, anxiety, changes in sleep early in treatment, sexual dysfunction. No need for down titration upon discontinuation as has very long half-life[1] CAVE: Increased risk of drug-drug interactions by inhibition of CYP2D6 enzymes
Fluvoxamine	antidepressant	psychoanaleptic - antidepressant - selective serotonin reuptake inhibitor	serotonin	reuptake inhibitor	e.g. GI symptoms, anxiety and/or changes in sleep early in treatment, sexual dysfunction. Must be gradually decreased on discontinuation[1] CAVE: Increased risk of drug-drug interactions by inhibition of CYP2D6 enzymes.
Mianserin	antidepressant	psychoanaleptic - antidepressant - other	serotonin, norepinephrine	multimodal, alpha2-receptor antagonist	e.g. sedation, dizziness, dry mouth, rarely granulocytopenia or agranulocytosis[1]

(Continued)

Phenelzine sulfate	antidepressant	psychoanaleptic - antidepressant - monoamine oxidase inhibitors, non-selective	serotonin, norepinephrine, dopamine	enzyme (MAOI) inhibitor	e.g. high probability of producing orthostatic hypotension; foods containing tyramine must be avoided; must not be used with medications inhibiting 5-HT reuptake[1]
Sertraline	antidepressant	psychoanaleptic - antidepressant - selective serotonin reuptake inhibitor, non-selective	serotonin	reuptake inhibitor	e.g. GI symptoms, anxiety, changes in sleep early in treatment, sexual dysfunction. Must be gradually decreased on discontinuation[1]
Tranylcypromine sulfate	antidepressant	psychoanaleptic - antidepressant - monoamine oxidase reuptake inhibitor, non-selective	serotonin, norepinephrine, dopamine	multimodal	e.g. high probability of producing orthostatic hypotension; foods containing tyramine must be avoided; must not be used with medications inhibiting 5-HT reuptake
Antipsychotics					
Flupenthixol	antipsychotic, first-generation	psycholeptic - antipsychotic - thioxanthene derivative	dopamine, serotonin	antagonist	e.g. EPS, galactorrhoea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS[1]
Haloperidol	antipsychotic, first-generation	psycholeptic - antipsychotic - butyrophenone derivative	dopamine	antagonist	e.g. EPS, galactorrhoea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS[1]
Loxapine	antipsychotic, first-generation	psycholeptic - antipsychotic - diazepines, oxazepines, thiazepines and oxepines	dopamine, serotonin	antagonist	EPS, galactorrhoea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS[1]
Thiothixene[2]	antipsychotic, first-generation	psycholeptic - antipsychotic - thioxanthene derivates	dopamine, serotonin	antagonist	e.g. potentially severe cardiac side effects
Trifluoperazine	antipsychotic, first-generation	psycholeptic - antipsychotic - phenothiazines with piperazine structure	dopamine, serotonin	antagonist	e.g. EPS (low), galactorrhoea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS
Aripiprazole	antipsychotic, second-generation	psycholeptic - antipsychotic - other	dopamine, serotonin	partial agonist and antagonist	e.g. agitation, anxiety, insomnia, akathisia. Weight gain and risk of diabetes low but monitoring recommended as a class warning. Class warning for increased mortality in elderly dementia patients[1]
Asenapine	antipsychotic, second-generation	psycholeptic - antipsychotic - diazepines, oxazepines, thi-	dopamine, serotonin, norepinephrine	antagonist	e.g. sedation, dizziness, weight gain, EPS, galactorrhoea. Risk of tardive dyskinesia, NMS. Risk of diabetes low but monitoring recommended as a class warning. Class warning for in-

(Continued)

		azepines and oxepines			creased mortality in elderly dementia patients[1]
Brexpiprazole	antipsychotic, second-generation	psycholeptic - antipsychotic - other	dopamine, serotonin	partial agonist and antagonist	e.g. akathisia (less than aripiprazole) weight gain and risk of diabetes low but monitoring recommended as a class warning. Class warning for increased mortality in elderly dementia patients[1]
Olanzapine	antipsychotic, second-generation	psycholeptic - antipsychotic - diazepines, oxazepines, thiazepines and oxepines	dopamine, serotonin	antagonist	e.g. weight gain, metabolic syndrome, EPS, sedation, galactorrhoea (low), dizziness, risk of tardive dyskinesia, NMS (low). Risk of diabetes; monitoring recommended as a class warning. Class warning for increased mortality in elderly dementia patients[1]
Quetiapine	antipsychotic, second-generation	psycholeptic - antipsychotic - diazepines, oxazepines, thiazepines and oxepines	dopamine, serotonin, norepinephrine	multimodal	e.g. sedation, dizziness, weight gain; galactorrhoea (low), EPS (low); Risk of tardive dyskinesia, NMS (low). Clearance reduced in elderly; Risk of diabetes; monitoring recommended as a class warning. Class warning for increased mortality in elderly dementia patients[1]
Ziprasidone	antipsychotic, second-generation	psycholeptic - antipsychotic - indole derivative	dopamine, serotonin	antagonist	e.g. EPS, galactorrhoea, sedation, dizziness, weight gain (low), QTc issues. Risk of tardive dyskinesia, NMS. Risk of diabetes low but monitoring recommended as a class warning. Class warning for increased mortality in elderly dementia patients[1]
Mood stabilisers					
Carbamazepine	mood stabiliser/anticonvulsant	antiepileptic - carboxamide derivative	glutamate	channel blocker	e.g. dizziness, somnolence, leukopenia[1] CAVE: must not be used during pregnancy
Valproate	mood stabiliser/anticonvulsant	antiepileptic - fatty acids derivative	glutamate	unclear	e.g. weight gain, sedation, elevated liver enzymes, hair loss[1] CAVE: Must not be used by women of childbearing age without effective contraception
Lamotrigine	mood stabiliser/anticonvulsant	antiepileptic - other	glutamate	channel blocker	e.g. dizziness, rash[1]

(Continued)

Topiramate	mood stabiliser/anticonvulsant	antiepileptic - other	GABA, glutamate	unclear	e.g. dizziness, weight loss, paraesthesiae, somnolence, nausea, diarrhoea, fatigue, depression. Rarely acute myopia and secondary angle closure glaucoma. Pregnancy category D (positive evidence of human foetal risk)[1]
Miscellaneous					
Clonidine	antihypertensive	antihypertensive - antiadrenergic agent, analgesic - antimigraine preparation	norepinephrine	agonist	e.g. hypotension, somnolence, fatigue[1]
Memantine hydrochloride	antidementia drug	psychoanaleptics - antidementia drugs - other	glutamate	antagonist (NMDA)	e.g. sleepiness, dizziness and balance problems, restlessness, nausea, other GI symptoms[1]
Naltrexone	opioid antagonist	analgesics - opioids - natural opium alkaloid; other nervous system drugs - drugs used in addictive disorders - drugs used in alcohol dependence	opioid	antagonist	e.g. nonspecific GI symptoms, can cause liver damage in high doses[1]
Omega-3 fatty aids	miscellaneous omega-3 fatty acids	cardiovascular system, lipid modifying agents - other	n/a	n/a	e.g. fishy taste, eructation, dyspepsia, diarrhoea, gas, nausea, and arthralgia[3]
Alprazolam	benzodiazepine	psycholeptic - anxiolytic - benzodiazepine derivative	GABA	Benzodiazepine receptor agonist (non selective GABA-A receptor positive allosteric modulator-PAM)	e.g. sedation, somnolence, ataxia, muscle relaxation, memory deficit

[1]reference: nbn2r.com/ (accessed 21 November 2021)

[2]this drug has been withdrawn from the market by its manufacturer due to severe cardiac side effects.

[3]reference: Novotny K, Fritz K, Parmar M. Omega-3 Fatty Acids. [Updated 2021 Oct 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. Available from: www.ncbi.nlm.nih.gov/books/NBK564314/

Abbreviations: ATC: Anatomical Therapeutic Chemical; EPS: extrapyramidal syndrome; GABA-A: gamma-aminobutyric acid-A; GI: gastrointestinal; MAOI: monoaminoxidase inhibitors; NMS: neuroleptic malignant syndrome; PAM: positive allosteric modulator; QTc: corrected QT interval

Appendix 4. Search strategies

Cochrane Central Register of Controlled Trials, in the Cochrane Library

#1 MeSH descriptor: [Borderline Personality Disorder] explode all trees

#2 borderline next state*
#3 borderline next personalit*
#4 "axis II" or "cluster B"
#5 idealization next devaluation
#6 (vulnerable or hyperbolic) next temper*
#7 (((unstab* or instab* or poor or disturb* or fail* or weak* or dysregulat*) next (self* or impuls* or interperson* or identit* or relation* or emotion* or affect*)) and (person* or character or PD))
#8 impulsiv* near personalit*
#9 (self next (injur* or damag* or destruct* or harm* or hurt* or mutilat*))
#10 suicidal next behavio?r
#11 (feel* next (empt* or bored*))
#12 (anger next control*)
#13 (risk-taking next (behavior or behaviour))
#14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

MEDLINE Ovid

1 Borderline Personality Disorder/
2 ((borderline or border-line) adj3 (state* or personalit*)).kf,tw.
3 ("Axis II" or "Cluster B" or flamboyant or "F60.3" or "F60.30" or "F60.31").kf,tw.
4 (idealization adj5 devaluation).kf,tw.
5 ((vulnerable or hyperbolic) adj3 temperament).kf,tw.
6 (((unstab* or instab* or poor or disturb* or fail* or weak or dysregulat*) adj3 (self* or impuls* or interperson* or identit* or relationship* or emotion* or affect*)) and (personality or character or PD)).kf,tw.
7 (impulsiv* adj5 (behavio?r or character or personalit*)).kf,tw.
8 (self adj3 (injur* or damag* or destruct* or harm* or hurt* or mutilat*)).kf,tw.
9 (suicidal adj3 behavio?r).kf,tw.
10 (feel* adj3 (empt* or bored*)).kf,tw.
11 (anger adj5 control*).kf,tw.
12 (risk-taking adj3 behavio?r).kf,tw.
13 or/1-12
14 randomised controlled trial.pt.
15 controlled clinical trial.pt.
16 randomi#ed.ab.
17 placebo.ab.
18 randomly.ab.
19 trial.ab.
20 groups.ab.
21 drug therapy.fs.
22 or/14-21
23 exp Animals/ not Humans/
24 22 not 23
25 13 and 24

Embase Ovid

1 borderline state/
2 ((borderline or border-line) adj3 (personalit* or state*)).kw,tw.
3 ("Axis II" or "Cluster B" or flamboyant or "F60.3" or "F60.30" or "F60.31").kw,tw.)
4 (idealization adj5 devaluation).kw,tw.
5 ((vulnerable or hyberbolic) adj3 temperament).kw,tw.
6 (((unstab* or instab* or poor or disturb* or fail* or weak or dysregulat*) adj3 (self* or impuls* or interperson* or identit* or relationship* or emotion* or affect*)) and (personality or character or PD)).kw,tw.
7 (impulsiv* adj5 (behavio?r or character or personalit*)).kw,tw.
8 (self adj3 (injur* or damag* or destruct* or harm* or hurt* or mutilat*)).kw,tw.
9 (suicidal adj3 (behavior or behaviour)).kw,tw.
10 (feel* adj3 (empt* or bored*)).kw,tw.
11 "anger adj5 control*".kw,tw.
12 (risk-taking adj3 (behavior or behaviour)).kw,tw.
13 or/1-12
14 randomised controlled trial/
15 double blind procedure/
16 crossover procedure/

17 single blind procedure/
18 (random* or factorial* or crossover* or cross-over* or placebo* or double-blind* or doubleblind* or single-blind* or singleblind* or assign* or allocat* or volunteer*).ab,pt,sh,de,ti.
19 or/14-18
20 13 and 19

CINAHL EBSCOhost (Cumulative Index to Nursing and Allied Health Literature)

S1 (MH "Borderline Personality Disorder")
S2 TX borderline N3 (state* or personalit*)
S3 TX "Axis II" OR "Cluster B"
S4 TX idealization N3 devaluation
S5 TX ((vulnerable OR hyperbolic) N3 temperament)
S6 TX (((unstab* or instab* or poor or disturb* or fail* or weak or dysregulat*) N3 (self or impuls* or interperson* or identit* or relationship* or emotion* or affect*)) AND (person* or character or PD))
S7 TX (impulsiv* N3 (behavio?r OR character or personalit*))
S8 TX (feel* N3 (empt* OR bored*))
S9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S10 (MH "randomised Controlled Trials") OR (MH "Random Assignment") OR (MH "Random Sample+")
S11 TX random* N4 (trial* OR study OR studies)
S12 TX random* N4 (allocat* OR allot* OR assign* OR basis OR divid* OR order)
S13 AB placebo*
S14 AB trial
S15 (MH "Drug Therapy+")
S16 S10 OR S11 OR S12 OR S13 OR S14 OR S15
S17 S9 AND S16

PsycINFO Ovid

1 exp Borderline Personality Disorder/
2 borderline adj3 (personalit* or state*).id,ti,ab.
3 ("Axis II" or "Cluster B").id,ti,ab.
4 (idealization adj5 devaluation).ab,id,ti.
5 ((vulnerable or hyperbolic) adj3 temperament).id,ab,ti.
6 (((unstab* or instab* or poor or disturb* or fail* or weak or dysregulat*) adj3 (self* or impuls* or interperson* or identit* or relationship* or emotion* or affect*)) and (personality or character or PD)).id,ab,ti.
7 (impulsiv* adj5 (behavio?r or character or personalit*)).id,ab,ti.
8 (self adj3 (injur* or damag* or destruct* or harm* or hurt* or mutilat*)).id,ab,ti.
9 (suicidal adj3 behavio?r).id,ab,ti.
10 (feel* adj3 (empt* or bored*)).ab,id,ti.
11 "anger adj5 control*".ab,id,ti.
12 (risk-taking adj3 behavio?r).id,ab,ti.
13 or/1-12
14 exp Clinical Trials/ (
15 (random* adj allocat*).ab.
16 randomi?ed.ab.
17 placebo.ab.
18 randomly.ab.
19 trial.ab.
20 groups.ab.
21 drug therapy.sh.
22 exp Animals/ not Humans/
23 or/14-21
24 23 not 22
25 13 and 24

ERIC EBSCOhost (Education Resources Information Center)

S23 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22
S22 TX risk-taking N5 behaviour
S21 TX anger N5 control*
S20 TX feel* N3 (empt* or bored*)
S19 TX suicidal N3 behavior

S18 TX ((unstab* or instab* or poor or disturb* or fail* or weak or dysregulat*) N3 TX (self or impuls* or interperson* or identit* or relationship* or emotion* or affect*)) AND TX (personality OR character OR PD)
S17 AB (self AND (injur* or damag* or destruct* or harm or hurt* or mutilat*))
S16 AB impulsivity
S15 TI impulsivity
S14 TX impulsiv* N3 person*
S13 TX "Axis II" OR "Cluster B"
S12 TX borderline N3 state
S11 TX borderline personality
S10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9
S9 AB drug
S8 AB trial
S7 AB randomly
S6 AB placebo
S5 AB randomi?ed
S4 AB controlled clinical trial*
S3 SU controlled clinical trial
S2 TX controlled clinical trial
S1 DE "randomised Controlled Trials"

BIOSIS Previews Web of Science Clarivate Analytics

#1 TOPIC: (borderline personality disorder)
#2 TOPIC: ((borderline NEAR/3 (state))
#3 TOPIC: ((borderline NEAR/3 personalit*))
#4 TOPIC: (("Axis II" OR "Cluster B"))
#5 TOPIC: (idealization NEAR/5 devaluation)
#6 TOPIC: ((vulnerable OR hyperbolic) NEAR/3 temperament*)
#7 TOPIC: (impulsiv* NEAR/5 personalit*)
#8 TOPIC: ((self NEAR/3 (injur* OR damag* OR destruct* OR harm* OR hurt* OR mutilat*)))
#9 TOPIC: ((((unstab* OR instab* OR poor OR disturb* OR fail* OR weak OR dysregulat*) NEAR/3 (self* OR impuls* OR interperson* OR identit* OR relationship* OR emotion* OR affect*)) AND (personality OR character OR PD)))
#10 TOPIC: (suicidal NEAR/3 behavio?r)
#11 TOPIC: (((feel* NEAR/3 (empt* OR bored*))))
#12 TOPIC: ((anger NEAR/5 control*))
#13 TOPIC: (risk-taking NEAR/3 behavio?r)
#14 #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#15 TOPIC: (controlled clinical trial)
#16 TOPIC: (randomised controlled trial)
#17 #16 OR #15
#18 #17 AND #14

Science Citation Index and Social Science Citation Index Web of Science Clarivate Analytics

#18 #17 AND #14
#17 #16 OR #15
#16 TOPIC: (controlled clinical trial)
#15 TOPIC: (randomised controlled trial)
#14 #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#13 TITLE: ((risk-taking NEAR/3 behavio?r))
#12 TOPIC: ((risk-taking NEAR/3 behavio?r))
#11 TITLE: ((anger NEAR/5 control*))
#10 TOPIC: ((feel* NEAR/3 (empt* OR bored*)))
#9 TITLE: ((feel* NEAR/3 (empt* OR bored*)))
#8 TITLE: (suicidal NEAR/3 behavio?r)
#7 TITLE: (impulsivity)
#6 TOPIC: ((((unstab* OR instab* OR poor OR disturb* OR fail* OR weak OR dysregulat*) NEAR/3 (self* OR impuls* OR interperson* OR identit* OR relationship* OR emotion* OR affect*)) AND (personality OR character OR PD)))
#5 TOPIC: ((vulnerable or hyperbolic) NEAR/3 temperament)
#4 TOPIC: ((idealization NEAR/5 devaluation))
#3 TOPIC: ("axis II" OR "Cluster B")
#2 TOPIC: (borderline NEAR/3 state)
#1 TOPIC: (borderline personality disorder)

Sociological Abstracts ProQuest

(((randomised controlled trial) OR (controlled clinical trial) OR SU.exact("CLINICAL TRIALS")) OR AB(randomi?ed) OR AB(randomly) OR AB(placebo) OR AB(trial)) AND ((borderline personality) OR "axis II" OR "Cluster B" OR (idealization AND devaluation) OR ((vulnerable OR hyperbolic) AND temperament) OR (((unstab* OR instab* or poor or disturb* or fail* or weak or dysregulat*) AND (self* or impuls* or interperson* or identit* or relationship* or emotion* or affect*)) AND (personality OR character OR PD)) OR (self AND (injur* OR damag* OR destruct* OR harm OR hurt* OR mutilat*)) OR "suicidal behavio?r" OR "self destructive behavio?r" OR (feel* AND (empt* OR bored*)))

LILACS (Latin American and Caribbean Health Science Information Database)

“Borderline personality disorder”, limits: Controlled clinical study

Library Hub Discover (previously COPAC)

“Borderline personality disorder”

ProQuest Dissertations A&I

(SU(borderline personality disorder) OR AB("Axis II") OR AB("Cluster B")) AND (("randomised controlled study" OR "controlled clinical study") OR AB(randomi?ed) OR AB(placebo) OR AB(randomly))

OpenGrey

“Borderline personality disorder”

DART Europe E-theses portal

“Borderline personality disorder”

Networked Digital Library of Theses and Dissertations (NDLTD)

“Borderline personality disorder”

Australian New Zealand Clinical Trials Registry (ANZCTR)

“Borderline personality disorder”

ClinicalTrials.gov

“Borderline personality disorder”

EU Clinical Trials Register

“Borderline personality disorder”

ISRCTN Registry

“Borderline personality disorder”

UK Clinical Trials Gateway

“Borderline personality disorder”

WHO International Clinical Trials Registry Platform

“Borderline personality disorder”

US Food and Drugs Administration FDA

“Borderline personality disorder”

European Medicines Agency EMA

“Borderline personality disorder”

Appendix 5. Outcomes

Primary outcomes

1. BPD severity

Name of scale/means of assessment	Abbreviation	Clinician-rated (CR)/self-rated (SR)	Study
Adapted Clinical Global Impression - Improvement scale	-	Unclear	Cowdry 1988
Borderline Evaluation of Severity over Time	BEST	SR	Grant 2022; Moen 2012
Borderline Personality Disorder Severity Index	BPDSI-IV	CR	Bellino 2014; Bozzatello 2017
Borderline Syndrome Index	BSI	SR	Soloff 1993
Borderline Symptom List	BSL	Unclear	Ziegenhorn 2009
Borderline Symptom List 95	BSL-95	Unclear	Schmahl 2012b
Clinical Global Impression scale for Borderline Personality Disorder patients	CGI-BPD-Global	Unclear	Pascual 2008
Schedule of Interviewing Schizotypal Personalities - Borderline score	SIB-Borderline score	CR	Goldberg 1986
Zanarini Rating Scale for Borderline Personality Disorder	ZAN-BPD	CR	Black 2014; Crawford 2018; Grant 2022; Kulkarni 2018; Reich 2009; Schulz 2007; Zanarini 2007

2. Self-harm

Name of scale/means of assessment	Abbreviation	Clinician-rated (CR)/self-rated (SR)	Study
Borderline Personality Disorder Symptom Index	BPDSI-IV-Parasuicidal behaviour	CR	Bozzatello 2017
Deliberate Self-harm Inventory	DSHI	CR	Crawford 2018
Overt Aggression Scale Modified - Auto aggression	OAS-M-Auto aggression	Unclear	Simpson 2004
Retrospective reporting	-	-	Schmahl 2012b
Self-Harm Inventory	SHI	SR	Bellino 2014
Spontaneous reporting	-	-	Grant 2022: Hallahan 2007; Linehan 2008; Nickel 2006

3. Suicide-related outcomes

Name of scale/means of assessment	Abbreviation	Clinician-rated (CR)/self-rated (SR)	Study
Adapted Clinical Global Impression - Improvement scale	-	Unclear	Cowdry 1988
Behavioural reports of numbers of episodes of self-injuring behaviour/suicide attempts	-	-	Soler 2005
Borderline Personality Disorder Severity Index	BPDSI-Parasuicidal behaviours	CR	Bellino 2014
Clinical Global Impression scale for Borderline Personality Disorder patients	CGI-BPD	CR	Pascual 2008
Clinical Global Impression scale for Borderline Personality Disorder patients	CGI-BPD-Recurrent suicidal ideation	CR	Bogenschutz 2004; Pascual 2008
Columbia Suicide Severity Rating Scale	C-SSRS	CR	Grant 2022
Overt Aggression Scale Modified - Suicidal ideation	OAS-M-Suicidal ideation	CR	Schulz 2007; Zanarini 2007
Overt Aggression Scale Modified - Suicidality	OAS-M-Suicidality	CR	Hallahan 2007; Hollander 2001; Linehan 2008; Simpson 2004
Spontaneous reporting	-	-	Montgomery 1982a; Montgomery 1982b
Zanarini Rating Scale for Borderline Personality Disorder	ZAN-BPD-Suicidal or self-mutilating behaviour	CR	Schulz 2007; Zanarini 2007

4. Psychosocial functioning

Name of scale/means of assessment	Abbreviation	Clinician-rated (CR)/self-rated (SR)	Study
Adapted Clinical Global Impression - Improvement scale	-	Unclear	Cowdry 1988
Clinical Global Impression Scale - Severity[1]	CGI-S	CR	Bellino 2014; Bogenschutz 2004; Bozzatello 2017; Shafti 2010; Shafti 2014; Soler 2005
Clinical Global Impression Scale - Improvement[1]	CGI-I	CR	Hollander 2001
Global Assessment of Functioning Scale[2]	GAF	CR	Amminger 2013; Black 2014; Schulz 2007; Simpson 2004; Zanarini 2001; Zanarini 2007

(Continued)

Global Assessment Scale[2]	GAS	CR	De la Fuente 1994; Goldberg 1986; Markovitz 1995a; Salzman 1995; Soloff 1989; Soloff 1993
Sheehan Disability Scale[1]	SDS	SR	Grant 2022; Schulz 2007; Zanarini 2007
Social Functioning Questionnaire[1]	SFQ	SR	Crawford 2018
Systematic Nurses' Observation of Psychopathology[1]	SNOOP	CR	Leone 1982

[1]For the following scales, higher scores indicate a worse situation: CGI-I, CGI-S, SDS, SFQ, SNOOP

[2] For the following scales, lower scores indicate a worse situation: GAF, GAS. To fit effect sizes of the remaining pathology outcomes, where negative effect sizes indicate an amelioration, the scores of these scales were multiplied by (-1), meaning that negative effect estimates indicate beneficial effects.

Secondary outcomes

1. Anger

Name of scale/means of assessment	Abbreviation	Clinician-rated (CR)/self-rated (SR)	Study
Adapted Clinical Global Impression - Improvement scale	-	Unclear	Cowdry 1988
Anger, Irritability, and Assault Questionnaire	AIAQ	Unclear	Bogenschutz 2004
Borderline Personality Disorder Severity Index - Anger	BPDSI-Anger	CR	Bellino 2014; Bozzatello 2017; Rinne 2002
Buss-Durkee Hostility Inventory	BDHI	Unclear	Pascual 2008; Soloff 1989; Soloff 1993; Shafti 2014; Shafti 2010
Clinical Global Impression scale for Borderline Personality Disorder patients - Inappropriate anger	CGI-BPD-Inappropriate anger	CR	Bogenschutz 2004; Pascual 2008
Modified Overt Aggression Scale	OAS-M	CR	Bellino 2014; Black 2014; Zanarini 2003
Modified Bunney-Hamburg rating scale	-	Unclear	Cowdry 1988
Overt Aggression Scale Modified - Total	OAS-M-Total	SR	Hallahan 2007
Overt Aggression Scale Modified - Aggression	OAS-M-Aggression	SR	Hollander 2001; Simpson 2004
Overt Aggression Scale Modified - Anger against objects	OAS-M-Anger against objects	SR	Salzman 1995
Overt Aggression Scale Modified - Irritability	OAS-M-Irritability	SR	Schulz 2007; Zanarini 2007

(Continued)

Personality Disorder Rating Scale - Anger	PDRS-Anger	CR	Salzman 1995
Spielberger State-Trait Anger Expression Inventory - Anger	STAXI-trait-Anger	SR	Nickel 2004; Nickel 2005; Nickel 2006; Tritt 2005
Symptom Check List-90 - Hostility	SCL-90-HOS	SR	De la Fuente 1994; Frankenburg 2002; Goldberg 1986; Jariani 2010; Loew 2006; Nickel 2006; Soloff 1993; Soloff 1989, Zanarini 2001
Zanarini Rating Scale for Borderline Personality Disorder - Intense anger	ZAN-BPD-Intense anger	CR	Schulz 2007; Zanarini 2007

2. Affective instability

Name of scale/means of assessment	Abbreviation	Clinician-rated (CR)/self-rated (SR)	Study
Affective Lability Scale	ALS	SR	Reich 2009
Borderline Personality Disorder Severity Index - Rapid mood shifts	BPDSI-Rapid mood shifts	CR	Rinne 2002
Borderline Personality Disorder Severity Index - Affective Instability	BPDSI-Affective instability	CR	Bellino 2014; Bozzatello 2017
Clinical Global Impression scale for Borderline Personality Disorder patients - Affective instability	CGI-BPD-Affective instability	CR	Bogenschutz 2004; Pascual 2008
Profile of Mood States Scale	POMS	SR	Leone 1982
Zanarini Rating Scale for Borderline Personality Disorder - Affective disturbance	ZAN-BPD-Affective disturbance	CR	Crawford 2018
Zanarini Rating Scale for Borderline Personality Disorder - Affective instability Score	ZAN-BPD-Affective instability score	CR	Reich 2009; Schulz 2007; Zanarini 2007

3. Chronic feeling of emptiness

Name of scale/means of assessment	Abbreviation	Clinician-rated (CR)/self-rated (SR)	Study
Borderline Personality Disorder Severity index - Affective Instability	BPDSI-IV-Chronic feelings of emptiness	CR	Bellino 2014; Bozzatello 2017
Clinical Global Impression scale for Borderline Personality Disorder patients - Chronic feelings of emptiness	CGI-BPD-Chronic feelings of emptiness	CR	Bogenschutz 2004; Pascual 2008

(Continued)

Zanarini Rating Scale for Borderline Personality Disorder - Chronic feeling of emptiness	ZAN-BPD-Chronic feelings of emptiness	CR	Schulz 2007; Zanarini 2007

4. Impulsivity

Name of scale/means of assessment	Abbreviation	Clinician-rated (CR)/self-rated (SR)	Study
Adapted Clinical Global Impression - Improvement scale	-	Unclear	Cowdry 1988
Acting-Out Scale	AOS	CR	De la Fuente 1994
Barrett Impulsiveness Scale	BIS	CR, SR	Bellino 2014; Black 2014; Grant 2022; Pascual 2008; Soloff 1989; Soloff 1993
Behavioural biweekly reports of episodes of impulsivity/aggressive behaviour	-	CR	Soler 2005
Borderline Personality Disorder Severity Index - Impulsivity	BPDSI-Impulsivity	CR	Bellino 2014; Bozzatello 2017; Rinne 2002
Clinical Global Impression scale for Borderline Personality Disorder patients - Impulsivity	CGI-BPD-Impulsivity	CR	Bogenschutz 2004; Pascual 2008
Positive and Negative Syndrome Scale - Poor Impulse Control	PANSS-Poor impulse control	CR	Amminger 2013
Zanarini Rating Scale for Borderline Personality Disorder - Impulsivity	ZAN-BPD-Impulsivity	CR	Crawford 2018; Reich 2009; Schulz 2007; Zanarini 2007

5. Interpersonal problems

Name of scale/means of assessment	Abbreviation	Clinician-rated (CR)/self-rated (SR)	Study
Atypical Depression Diagnostic Scale - Rejection sensitivity	ADDS-Rejection sensitivity	SR	Soloff 1993
Borderline Personality Disorder Severity Index - Interpersonal problems	BPDSI-IV-Interpersonal problems	CR	Bellino 2014; Bozzatello 2017
Clinical Global Impression scale for Borderline Personality Disorder patient - Unstable interpersonal relationships	CGI-BPD-Unstable interpersonal relationships	CR	Bogenschutz 2004; Pascual 2008
Hopkins Symptoms check List - Interpersonal sensitivity	HSCL-INT	SR	Goldberg 1986

(Continued)

Symptom Check List-90 - Interpersonal sensitivity	SCL-90-INT	SR	De la Fuente 1994; Frankenburg 2002; Soloff 1989; Zanarini 2001; Zanarini 2007
Symptom Check List-90 - Revised - Interpersonal sensitivity	SCL-90-R-INT	SR	Loew 2006; Nickel 2006
Zanarini Rating Scale for Borderline Personality Disorder - Unstable interpersonal relationships	ZAN-BPD-Unstable interpersonal relationships	CR	Schulz 2007; Zanarini 2007
Zanarini Rating Scale for Borderline Personality Disorder - Disturbed relationships	ZAN-BPD-Disturbed relationships	CR	Bellino 2014; Crawford 2018

6. Abandonment

Name of scale/means of assessment	Abbreviation	Clinician-rated (CR)/self-rated (SR)	Study
Borderline Personality Disorder Severity Index - Abandonment	BPDSI-Abandonment	CR	Bellino 2014; Bozzatello 2017
Clinical Global Impression scale for Borderline Personality Disorder patient - Abandonment	CGI-BPD-Abandonment	CR	Bogenschutz 2004; Pascual 2008
Zanarini Rating Scale for Borderline Personality Disorder - Frantic efforts to avoid abandonment	ZAN-BPD-Frantic efforts to avoid abandonment	CR	Schulz 2007; Zanarini 2007

7. Identity disturbance

Name of scale/means of assessment	Abbreviation	Clinician-rated (CR)/self-rated (SR)	Study
Borderline Personality Disorder Severity Index - Identity	BPDSI-Identity	CR	Bellino 2014; Bozzatello 2017
Clinical Global Impression scale for Borderline Personality Disorder patient - Identity disturbance	CGI-BPD-Identity disturbance	CR	Bogenschutz 2004; Pascual 2008
Zanarini Rating Scale for Borderline Personality Disorder - Identity disturbance	ZAN-BPD-Identity disturbance	CR	Schulz 2007; Zanarini 2007

8. Dissociation and psychotic-like symptoms

Name of scale/means of assessment	Abbreviation	Clinician-rated (CR)/self-rated (SR)	Study
Borderline Personality Disorder Severity Index - Dissociation/paranoid ideation	BPDSI-Dissociation/paranoid ideation	CR	Bellino 2014; Bozzatello 2017
Brief Psychiatric Rating Scale	BPRS	Unclear	AstraZeneca 2007; Leone 1982; Pascual 2008; Shafti 2010; Shafti 2014
Clinical Global Impression scale for Borderline Personality Disorder patient - Paranoid ideation	CGI-BPD-Paranoid ideation	CR	Pascual 2008
Clinical Global Impression scale for Borderline Personality Disorder patient - Transient paranoia or dissociation	CGI-BPD-Transient paranoia or dissociation	CR	Bogenschutz 2004; Pascual 2008
Dissociation State Scales	DSS	SR	Schmahl 2012a; Schmahl 2012b
Dissociation Questionnaire	DIS-Q	SR	AstraZeneca 2007
Dissociative Experiences Scale	DES	SR	Simpson 2004; Zanarini 2001
Positive and Negative Symptoms Scale	PANNS	CR	Amminger 2013; AstraZeneca 2007; Zanarini 2001
Schedule of Interviewing Schizotypal Personalities - Borderline score - Suspicious/paranoid	SIB-Suspicious/paranoid	CR	Goldberg 1986
Symptom Check List-90 - Revised - Paranoid ideation	SCL-90-R-PAR	SR	De la Fuente 1994; Loew 2006; Nickel 2006; Soloff 1989; Soloff 1993; Zanarini 2001; Zanarini 2007
Symptom Check List-90 - Revised - Psychoticism	SCL-90-R-PSY	SR	Loew 2006; Nickel 2006; Soloff 1989; Soloff 1993; Zanarini 2001
Zanarini Rating Scale for Borderline Personality Disorder - Paranoid ideation or dissociation	ZAN-BPD-Paranoid ideation or dissociation	CR	Schulz 2007; Zanarini 2007
Zanarini Rating Scale for Borderline Personality Disorder - Cognitive Disturbance	ZAN-BPD-Cognitive disturbance	CR	Crawford 2018

9. Depression

Name of scale/means of assessment	Abbreviation	Clinician-rated (CR)/self-rated (SR)	Study

(Continued)

Adapted Clinical Global Impression - Improvement scale	-	Unclear	Cowdry 1988
Beck Depression Inventory	BDI	SR	Crawford 2018; Hallahan 2007; Hollander 2001; Schmahl 2012b; Simpson 2004; Soloff 1989; Soloff 1993; Ziegenhorn 2009
Hamiltons 24-item Depression Rating scale	HDRS-24	Unclear	De la Fuente 1994
Hamilton Rating scale for Depression	Ham-D	SR, CR	Bellino 2014; Bozzatello 2017; Grant 2022; Linehan 2008; Markovitz 1995a; Moen 2012; Nickel 2006; Salzman 1995, Schmahl 2012b, Soler 2005; Soloff 1989; Soloff 1993; Zanarini 2001
Hamilton Rating scale for Depression	Ham-D-17	Unclear	Pascual 2008
Hopkins Symptoms check List - Depression	HSCL-DEP	SR	Goldberg 1986
Modified Bunney-Hamburg rating scale	-	Unclear	Cowdry 1988
Montgomery Åsberg Depression Rating Scale	MADRS	CR	Amminger 2013; Black 2014; Moen 2012; Schulz 2007; Zanarini 2003; Zanarini 2004; Zanarini 2007
Personality Disorder Rating Scale - Depression	PDRS-Depression	CR	Salzman 1995
Positive and Negative Syndrome Scale - Depression	PANSS-Depression	Unclear	Amminger 2013
Profile of Mood States - Depression	POMS-Depression	SR	Salzman 1995
Symptom Checklist-90 - Depression	SCL-90-DEP	SR	De la Fuente 1994; Frankenburg 2002; Soloff 1989; Soloff 1993; Zanarini 2001
Symptom Checklist-90 - Revised - Depression	SCL-90-R-DEP	SR	Jariani 2010; Loew 2006; Nickel 2006; Zanarini 2007

10. Attrition

Name of scale/ means of assessment	Abbreviation	Clinician-rated (CR)/self-rated (SR)	Study
Number of patients lost after randomisation	-	-	Amminger 2013; AstraZeneca 2007; Bellino 2014; Black 2014; Bogenschutz 2004; Bozzatello 2017; Cowdry 1988; Crawford 2018; De la Fuente 1994; Frankenburg 2002; Goldberg 1986; Grant 2022; Hallahan 2007; Hollander 2001; Kulkarni 2018; Leone 1982; Linehan 2008; Loew 2006; Markovitz 1995a; Montgomery 1982b; NCT00533117; Nickel 2004; Nickel 2005; Pascual 2008; Reich 2009; Rinne 2002; Schmahl 2012a; Schmahl

(Continued)

	2012b; Schulz 2007; Shafti 2014, Shafti 2010; Simpson 2004; Soler 2005; Soloff 1989; Soloff 1993; Tritt 2005; Zanarini 2001; Zanarini 2003; Zanarini 2004; Zanarini 2007; Ziegenhorn 2009

11. Adverse effects

Name of scale/means of assessment	Abbreviation	Clinician-rated (CR)/self-rated (SR)	Study
Abnormal Involuntary Movement Scale	AIMS	Unclear,	Black 2014; Schulz 2007; Zanarini 2001, Zanarini 2004; Zanarini 2007
Adverse effects questionnaire	-	SR	Kulkarni 2018
Anthropometric values	-	-	Bogenschutz 2004; Frankenburg 2002; Linehan 2008; Nickel 2005; Schulz 2007; Soler 2005; Soloff 1993; Tritt 2005; Zanarini 2001; Zanarini 2004; Zanarini 2007
Barnes Akathisia Scale	-	Unclear	Black 2014, Zanarini 2001; Zanarini 2007
Dosage Record and Treatment Emergent Symptom Scale	DOTES	CR	Bellino 2014; Bozzatello 2017
Laboratory values	-	-	Pascual 2008; Schulz 2007; Shafti 2010; Soler 2005; Zanarini 2007
Non-structured questionnaire	-	SR	Loew 2006; Nickel 2004; Tritt 2005
Pro forma document	-	SR	Crawford 2018
Scales assessing extrapyramidal side effects	-	Unclear	Soler 2005
Simpson-Angus Scale	SAS	Unclear	Black 2014; Schulz 2007; Zanarini 2001; Zanarini 2004; Zanarini 2007
Spontaneous reporting	-	-	De la Fuente 1994; Frankenburg 2002; Goldberg 1986; Grant 2022; Leone 1982; NCT00533117; Nickel 2006; Pascual 2008; Reich 2009; Rinne 2002; Schmahl 2012a; Schmahl 2012b; Shafti 2010; Shafti 2014; Soler 2005; Soloff 1989; Soloff 1993; Tritt 2005; Zanarini 2004; Zanarini 2007; Ziegenhorn 2009
Standard reporting form	-	Unclear	Montgomery 1982a
Structured questionnaire	-	SR	Zanarini 2001; Zanarini 2003; Zanarini 2004
Udvaget for Kliniske Undersoegelser - Side Effect Rating Scale for extrapyramidal side effects	UKU	CR, SR	Amminger 2013; Pascual 2008

Appendix 6. Trial Sequential Analysis (TSA) and funnel plot figures

Primary outcomes

BPD symptom severity

We performed a TSA on the primary outcome of borderline symptom severity at end of treatment for the antipsychotics. The analysis shows that the z-curve ended in the futility area. See Figure 4 below.

Secondary outcomes

Anger

We drew a funnel plot for the comparison between antipsychotics and placebo for the secondary outcome of anger. The funnel plot shows a small asymmetry. See Figure 5 below.

Impulsivity

We drew a funnel plot for the comparison between antipsychotics and placebo for the secondary outcome of impulsivity. The funnel plot shows a small asymmetry. See Figure 6 below.

Interpersonal problems

We performed a TSA on the secondary outcome of interpersonal problems at end of treatment for the antipsychotics. The analysis shows that the required information size was reached. See Figure 7 below.

Attrition

We performed a TSA on the secondary outcome attrition at end of treatment for the antispychotics. The analysis shows that the z-curve ended in the futility area. See Figure 8 below.

We drew a funnel plot for the comparison between antipsychotics and placebo for the secondary outcome of attrition. The funnel plot shows a small asymmetry. See Figure 9 below.

Non-serious adverse events

We performed a TSA on the secondary outcome of non-serious adverse events at end of treatment for the antipsychotics. The analysis shows that the z-curve ended in the futility area. See Figure 10 below.

Attrition

We performed a TSA on the secondary outcome attrition at end of treatment for the antidepressants. The analysis shows that the required information size was not reached. See Figure 11 below.

We performed a TSA on the secondary outcome attrition at end of treatment for the mood stabilisers. The analysis shows that the required information size was not reached.See Figure 12 below.

Appendix 7. Methods for future versions of this review

Issue	Methods
Interventions	Consider classifying medications according to neuroscience-based nomenclature (NbN is not well-established among potential consumers of this review as yet; see Appendix 3 for guidance how to translate conventional terms into the NbN nomenclature).
Outcomes	Consider analysing psychotic symptoms separately from DSM-IV/5 critierion 9 ("transient, stress-related paranoid ideation or severe dissociative symptoms"; analyses were conducted in accordance with the review protocol in this version; Stoffers-Winterling 2018)

Footnotes
DSM-IV/5: Diagnostic and Statistical Manual of Mental Disorders-Fourth/-Fifth Edition.

Appendix 8. Unused methods

Section	Protocol (Stoffers-Winterling 2018)	Review
Search methods for identification of studies	**Electronic searches** We intended to search the UK Clinical Trials Gateway database for relevant trials.	We did not search the UK Clinical Trials Gateway (now included in Be Part of Research) because records are fed in there from both ISRCTN and CT.gov, both of which were searched separately.
Unit of analysis issues	**Cluster-randomised trials** Had trials used cluster randomisation, we would have anticipated that investigators would have presented their results after appropriately controlling for clustering effects (robust standard errors or hierarchical linear models). If it had been unclear whether a cluster-randomised trial had used appropriate controls for clustering, we would have contacted the investigators for further information. We would have requested and re-analysed individual patient data using multilevel models that controlled for clustering, if appropriate controls had not been used. Following this, we would have analysed effect sizes and standard errors in RevMan 5 (RevMan Web 2020), using the generic inverse method (Higgins 2019). If there had been insufficient information to control for clustering, we would have entered outcome data using individuals as the units of analysis, and then conducted a sensitivity analysis to assess the potential biasing effects of inadequately controlled cluster-randomised trials (Donner 2002). If individual participant data had not been available, we would have looked for information on intra-class correlation coefficients to adjust for the potential clustering effects.	We did not include any cluster-randomised trial.
Dealing with missing data	Had dichotomous data not been presented on the basis of ITT data, we would have added the number of participants lost in each group to the participants with unfavourable results, acting on the assumption that most people with BPD do not get lost at random.	We were unable to perform this analysis due to insufficient information.
Subgroup analysis and investigation of heterogeneity	We intended to conduct subgroup analyses to make hypotheses about the subgroups mentioned below. 1. Age (15 to under 18 years of age, 18 to 50 years of age, above 50 years of age). 2. Sex (men versus women). 3. Different setting (outpatient compared to inpatient). 4. Difference in doses.	We did not conduct these preplanned analyses because of a lack of data.
Sensitivity analysis	We intended to assess the impact of heterogeneity on the overall pooled effect estimate by removing trials ('outliers') that contributed to heterogeneity. We intended to remove outliers one by one and assess the impact on the overall outcome. 1. Impact of bias (trials with low and high risk of bias). 2. Type of data collection (for example, different ways to measure adverse events). 3. Imputed data (comparing the analyses with available outcome data with those using the intention-to-treat (ITT) approach).	We were not able to perform these analyses due to a lack of sufficient data.

(Continued)

TSA	We intended to calculate post hoc, low bias, risk diversity-adjusted required information size TSA analyses for the primary outcomes.	We were not able to perform these analyses with low risk of bias trials as no trials were assessed as being at low risk of bias overall.

HISTORY

Protocol first published: Issue 2, 2018

CONTRIBUTIONS OF AUTHORS

Jutta M Stoffers-Winterling: protocol development; study selection; conception and design of the review; data extraction; data entry; interpretation of data; assessment of risk of bias and GRADE; data analysis; and writing of final report

Ole Jakob Storebø: protocol development; study selection; conception, design and coordination of the review; data extraction; data entry; interpretation of data; assessment of risk of bias and GRADE; data analysis; and writing of final report

Birgit A Völlm: protocol development; study selection; data extraction; and writing of final report

Mickey T Kongerslev: protocol development; study selection; data extraction; assessment of risk of bias; and writing of final report

Jessica T Mattivi: protocol development; study selection; data extraction; and writing of final report

Mie Sedoc Jørgensen: study selection; data extraction; assessment of risk of bias; and writing of final report

Johanne Marie Pereira Ribero: study selection; data extraction; data entry; interpretation of data; assessment of risk of bias; data analysis and writing of final report

Erlend Faltinsen: study selection; data extraction; data entry; assessment of risk of bias; data analysis; and writing of final report

Adnan Todorovac: study selection; data extraction; data entry; assessment of risk of bias; data analysis; and writing of final report

Christian Paul Sales: study selection; data extraction; and writing of final report

Julie Perrine Schaug: study selection; data extraction; assessment of risk of bias; and writing of final report

Henriette E Callesen: study selection, data extraction; assessment of risk of bias and GRADE; data analysis; and writing of final report

Klaus Lieb: protocol development; and writing of final report

Erik Simonsen: protocol development; and writing of final report

All authors contributed to writing the review.

Jutta Stoffers-Winterling is the guarantor for the review.

DECLARATIONS OF INTEREST

Jutta M Stoffers-Winterling (JSW) is a board-certified clinical psychologist ('Psychologische Psychotherapeutin', cognitive behaviour therapy). She does not prescribe or administer medication in a clinical context.

Ole Jakob Storebø (OJS) is a clinical psychologist with the Psychiatric Research Unit, Region Zealand Psychiatry, Denmark, and does not prescribe or administer medication in a clinical context. He also reports being the trial coordinator for an ongoing study at Region Zealand investigating a new drug treatment for people with borderline personality disorder (NCT04566601), which is included in this review; the study is funded and designed by Boehringer Ingelheim. OJS did not assess the eligibility of this trial which was assessed by two independent reviewers (JPR and JSW). In addition, OJS is an editor for Cochrane Developmental, Psychosocial and Learning Problems (DPLP); however, he was not involved in the editorial process for this review. OJS is also Editor-in-Chief for the Scandinavian Journal of Child and Adolescent Psychiatry and Psychology.

Jessica T Mattivi (JTM) is currently working with Psychiatric Services in Meran, Italy. JTM has declared a grant from the German Federal Ministry of Education and Research, paid to University Medical Center Mainz, Germany. The grant was for a systematic review on

psychosocial interventions for self-harm in adolescents; the funder did not have any role in design, methods, data analysis and reporting of the study.

Mickey T Kongerlev is a clinical psychologist and does not prescribe or administer medication in a clinical context. He is employed as manager of a District Psychiatric Service in Region Zealand Mental Health Services, Roskilde, Denmark, and is President of the Institute of Personality Theory and Psychopathology.

Birgit A Völlm is a medical practitioner with the University of Rostock, with the authority to prescribe medication in a clinical context. She is affiliated to the Royal College of Psychiatrists and the DGPPN (Deutsche Gesellschaft für Psychiatrie, Psychotherapie, Psychosomatik und Nervenheilkunde; the German Association for Psychiatry, Psychotherapy and Psychosomatics, which is the largest scientific medical association focusing on mental health in Germany), who have declared an opinion or position on the topic.

Henriette E Callesen is a neuroscientist and does not prescribe or administer medication in a clinical context. She has declared that she has no conflicts of interest.

Adnan Todorovac is a clinical psychologist and does not prescribe or administer medication in a clinical context. He has declared that he has no conflicts of interest.

Christian P Sales is a clinical psychologist with Nottinghamshire Healthcare NHS Foundation Trust, UK, and does not prescribe or administer medication in a clinical context. He has declared that he has no conflicts of interest.

Erlend Faltinsen is a clinical psychologist and does not prescribe or administer medication in a clinical context.

Mie S Jørgensen is a clinical psychologist with Region Zealand Mental Health Services, Denmark, and does not prescribe or administer medication in a clinical context. She has declared that she has no conflicts of interest.

Johanne P Ribeiro is a registered nurse with the authority to administer prescribed medications; however, she is employed as a research assistant at Region Zealand and therefore does not administer medication in a clinical context. She has declared that she has no conflicts of interest.

Julie P Schaug is a psychologist and does not prescribe or administer medication in a clinical context. She has declared that she has no conflicts of interest.

Erik Simonsen (ES) is a psychiatrist with the authority to prescribe medication in a clinical context but does not exercise this authority as he is currently employed as a research director. ES reports that he is the Princpal Investigator of one site (Slagelse, Denmark) of an ongoing, international, multi-site study investigating a new drug treatment for people with borderline personality disorder (NCT04566601), which is included in this review; the study is funded and designed by Boehringer Ingelheim. ES did not assess the eligibility of this trial, which was assessed by two independent reviewers (JPR and JSW). ES also reports travel and associated expenses (congress fees and accommodation) from Boehringer Ingelheim.

Klaus Lieb (KL) is a board-certified cognitive behaviour therapist with a special interest in schema therapy. He is also a psychiatrist with the authority to prescribe medication (i.e. recommend treatments for personality disorders); however, he is employed as Director of the Department of Psychiatry and Psychotherapy, University Medical Centre Mainz, Germany and therefore does not prescribe or administer medication in a clinical context. KL is also an editor for DPLP but was not involved in the editorial process for this review.

SOURCES OF SUPPORT

Internal sources

- Psychiatric Research Unit, Region Zealand Psychiatry, Roskilde, Denmark

  Ole Jakob Storebø, Johanne Pereira Ribeiro and Erik Simonsen worked on this review during office hours.
- University Medical Center Mainz, Germany, Denmark

  Jutta Stoffers-Winterling, Klaus Lieb and Jessica Mattivi worked on this review during office hours.

External sources

- The Psychiatric Management Research Fund, Psychiatry Region Zealand, Denmark

  This is a small fund where the management of psychiatry in Region Zealand in Denmark distributes small amounts to research projects within psychiatry.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Methods

Data collection and analysis

Selection of studies

The protocol specified that six review authors (JMSW, OJS, BAV, MLK, JTM, SSN) would work in pairs and independently screen titles and abstracts of all records retrieved by the searches. However, the following additional review authors also selected trials: AT, EF, MSJ, JPR, JPS, and HEC.

The following authors, who worked on the protocol for the review, selected some trials but left the author group early in the development of the review as they no longer wished to be authors: SSN and MTK.

The protocol, moreover, specified that KL and ES would act as arbiters. However, in the review, OJS and JMSW also functioned as arbiters.

Unit of analysis issues

Repeated observations

We planned to conduct separate analyses for different follow-up time points, but we did not have data for this, so we only used end-of-treatment data.

Cross-over trials

We included data from four randomised cross-over trials (Cowdry 1988; Schmahl 2012a; Schmahl 2012b; Ziegenhorn 2009). We were not able to obtain first-period data from these cross-over trials and therefore used end-of-period data (Curtin 2002; Elbourne 2002) (we wrote to the study authors and asked for the first-period data, but they did not have these data). This approach might introduce the risk of a unit-of-analysis error. In addition, the confidence intervals are likely to be too wide and the trial will receive too little weight in the analysis. There is also the possibility that we could overlook important heterogeneity too. The Cochrane Handbook, however, states that this approach is conservative, as the studies are under-weighted instead of over-weighted (Higgins 2022), and some might argue that the unit-of-analysis error introduced by doing this is less serious than some other types of unit-of-analysis errors. The cross-over trial by Cowdry is the only one pooled with parallel-group trials (Cowdry 1988). Cowdry and colleagues reported a washout period of one week before cross-over (Cowdry 1988). When excluding the Cowdry study from the analysis with the parallel-group trials, we found no differences in the results. The other cross-over trials were reported separately in the analyses (Schmahl 2012a; Schmahl 2012b; Ziegenhorn 2009).

Subgroup analysis

We added a post hoc subgroup analysis on funding, as we believe it is important to conduct an empirical test of the influence of funding on the effect estimates. Andreas Lundh and colleagues have shown that there are many subtle mechanisms through which sponsorship and conflict of interest may influence intervention effects on outcomes (Lundh 2018). The AMSTAR (A MeaSurement Tool to Assess systematic Reviews) tool for the assessment of the methodological quality of systematic reviews also includes funding and conflicts of interest as a domain (Shea 2017). In addition, we added subgroup analyses on differences in psychosocial functioning at baseline, trial size and type of recruitment, as we believe it is important to conduct an empirical test of the influence of these factors on the effect estimates. Trial sizes varied considerably from 13 in the smallest trial (Schmahl 2012a) to 451 in the largest (Zanarini 2007). Since trial size is connected to the precision of effect estimates, we believe the impact of trial sizes on the findings of this review should be investigated.

Heterogeneity-adjusted required information size and Trial Sequential Analysis

When performing the TSAs, we did not use a standard deviation (SD) for the primary outcome of 1.0, and we did not always use an anticipated intervention effect of Hedge's g of 0.5 (½ SD), as described in the protocol (Stoffers-Winterling 2018). Instead, we used the SD from the trial as a basis for the transformation of SMD values to MD values. Also, we preferred to use the MIREDIF reported in articles; only if we could not find it did we use the ½ SD on the specific scale, as this can be used as a MIREDIF (Norman 2004). The MIREDIF reported in articles is the best, as these often have data from epidemiological studies, but the MIREDIFs on different rating scales are seldom reported.

Sensitivity analysis

We added one analysis post hoc: imprecision, assessed by GRADE, by conducting TSAs on the primary outcomes and the three secondary outcomes not closely connected to the BPD core symptoms (interpersonal functioning, attrition and adverse effects) for the main comparison. We conducted these sensitivity analyses only on outcomes where we were uncertain about the GRADE assessment of imprecision. These analyses tested whether the effect estimates were imprecise due to too low number of participants in the meta-analyses and therefore not enough information size to detect or reject the intervention effect, or whether the required information size was large enough to detect or reject the intervention effect. We tested our GRADE assessment of imprecision by using TSA on one primary outcome and three secondary outcomes.

We also conducted a sensitivity analysis for the secondary outcome of anger, for the comparison of mood stabliisers versus placebo, as a high amount of heterogeneity was found (I^2 = 84%), and the range of effect estimates included extraordinarily high scores (SMD -3.10 to -0.15). Therefore, we removed outliers exceeding effect estimates of SMD 1.5.

We added one sensitivity analysis testing whether including end-of-period data in cross-over trials in some of the analyses changed the statistical significance. We did as we were not able to obtain first-period data from these cross-over trials.

In addition, we conducted a sensitivity analysis testing the impact of our choice of data sources. For one trial, Black 2014, data were available for the outcome of BPD severity from both the trial registry entry (NCT00880919) as well as from the full journal publication. We conducted a sensitivity analysis to test the impact of choosing the peer-reviewed journal publication as our primary data source.

NOTES

This review supersedes a previously published review on this topic: Stoffers J, Völlm BA, Rücker G, Timmer A, Huband N, Lieb K. Pharmacological interventions for borderline personality disorder. Cochrane Database of Systematic Reviews 2010, Issue 6. Art. No.: CD005653. DOI: 10.1002/14651858.CD005653.pub2. The protocol of this current review was published in 2018 (Stoffers-Winterling 2018).

INDEX TERMS

Medical Subject Headings (MeSH)

Antidepressive Agents [therapeutic use]; *Antipsychotic Agents [therapeutic use]; *Borderline Personality Disorder [drug therapy]; *Depressive Disorder, Major [drug therapy]; Reproducibility of Results

MeSH check words

Adolescent; Adult; Female; Humans; Male; Young Adult