Appendix 1 to Liang S, Sun C, Fan H. Therapeutic effects of antidepressants for global improvement and subdomain symptoms of autism spectrum disorders: a systematic review and meta-analysis. J Psychiatry Neurosci 2022. doi: 10.1503/jpn.210191.

eTable 1. Applied keywords and the search results from each database

Database	Keywords	Filter	Date (yyyy/mm/dd)	Result
PubMed	("Autistic Disorder"[Mesh] OR "Autism Spectrum Disorder"[Mesh]) AND ("Antidepressive Agents"[Mesh] OR "Antidepressive Agents" [Pharmacological Action] OR "Antidepressive Agents, Second-Generation"[Mesh] OR "Antidepressive Agents, Tricyclic"[Mesh] OR "Antidepressive Agents, Second-Generation" [Pharmacological Action] OR "Antidepressive Agents, Tricyclic" [Pharmacological Action] OR "Adrenergic Uptake Inhibitors"[Mesh] OR "Fluvoxamine"[Mesh] OR "Bupropion"[Mesh] OR "Citalopram"[Mesh] OR "Monoamine Oxidase Inhibitors"[Mesh] OR "Serotonin and Noradrenaline Reuptake Inhibitors"[Mesh])	RCT	2022/02/28	40
Embase	(antidepressant agent'/exp OR 'antidepressant agent) AND (autism'/exp OR 'autism)	RCT	2022/02/28	192
ClinicalKey	(Antidepressants) AND (autism)	RCT	2022/02/28	36
Cochrane CENTRAL	(antidepressants or SSRI or SNRI or TCA or MAOI or NASSA or Bupropion) AND (autism or ASD or autism spectrum disorder or pervasive developmental disorder or Asperger syndrome)	Trials	2022/02/28	47
ScienceDirect	(Antidepressants) AND (autism) Areas: Pharmacology, Toxicology and Pharmaceutical Science	Research article	2022/02/28	243
Web of Science	(antidepressants or SSRI or SNRI or TCA or MAOI or NASSA or Bupropion) AND (autism or ASD or autism spectrum disorder or pervasive developmental disorder or Asperger syndrome)	Article	2022/02/28	372
ClinicalTrials.gov	(Autism) AND (antidepressants)	NA	2022/02/28	39

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Abbreviations: NA, not applied; RCT, randomized controlled trials

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eTable 2. Reasons for study exclusion

Reason	Number of trials	References
No antidepressant treatment	17	1-17
Not RCT	7	18-24
Lack of adequate data for analysis	5	25-29
Included diagnoses other than ASD	8	30-37
Duplicated sample source	3	38-40

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eTable 3. Regression coefficients of improvement in restricted and repetitive behaviors (RRBs), and global symptoms in included studies using the mixed-effects model

	Coefficient (95% CI)			
Variables	RRBs (Number of trials)	*p*	Global	*p*
Percentage of women	0.01 (-0.01 to 0.04) (n=12)	0.30	-0.04 (-0.13 to 0.06) (n=10)	0.44
Age	0.02 (-0.004 to 0.04) (n=11)	0.11	0.08 (0.01 to 0.16) (n=9)	0.02
Duration	0.00 (-0.03 to 0.03) (n=13)	1.00	-0.02 (-0.12 to 0.07) (n=11)	0.62
IQ	0.004 (-0.02 to 0.02) (n=5)	0.68	0.04 (-0.04 to 0.11) (n=5)	0.33
CGI-S	-0.95 (-1.76 to -0.14) (n=5)	0.02	*	

Abbreviations: CGI-S, global impression scale-severity; IQ, Intelligent quotient; *no analysis for avoiding collinearity

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eTable 4. Summary of side effect profiles in different studies

Source	Medications	DDD	Age (yrs)	Serious AE	Frequent side effects
Reddihough et al,[41] 2019	Fluoxetine 4–30 mg/d	NA	7.5–18	None	Irritability (12%), insomnia (17.3%), nausea (13.3%)
Herscu et al,[30] 2020	Fluoxetine 2–18 mg/d	0.59	5–17	Urticaria (n=1) Suicidal ideation (n=1)	Agitation (13%), insomnia (10%), activation (11%),
Carminati et al,[40] 2016	Venlafaxine 18.75 mg/d	0.185	18–45	None	Excessive stiffness and rigidity
Hollander et al,[39] 2012	Fluoxetine 20–80 mg/d	3.24	18–60	None	Insomnia (13.6%), headache (13.6%), agitation (4.5%). fatigue (4.5%)
King et al,[38] 2009	Citalopram 10–20 mg/d	0.825	5–17	Prolonged seizure (n=1)	Insomnia (38.4%), irritability (24.7), fatigue (13.7%)
Sugie et al,[37] 2005	Fluvoxamine 1–3 mg/kg/d	NA	3–8.5	None	Transient nausea or hyperactivity
Hollander et al,[36] 2005	Fluoxetine 4.8–20 mg/d	0.495	5–17	None	Fatigue (17.9%), agitation (46.2%), insomnia (35.9%)
Remington et al,[35] 2001	Clomipramine 100–250 mg/d	1.31	10–36	None	Fatigue (12.5%), tremor (6.2%), tachycardia (3.1%),
McDougle et al,[34] 1996	Fluvoxamine 50–300 mg/d	2.77	18–53	None	Nausea (9.7%), sedation (6.5%)
Gordon et al,[33] 1993	Clomipramine 25–250 mg/d	1.52	6–23	Severe tachycardia (n=1) Grand mal seizure (n=1)	Sedation (23%), twitching (21%), constipation (25%), insomnia (29%)
Gordon et al,[31] 1992	Clomipramine 25–250 mg/d Desipramine 25–250 mg/d	1.29 1.11	6–18	None	Sleep disturbance, dry mouth, constipation
Chugani et al,[32] 2015	Buspirone 5 mg/d Buspirone 10 mg/d	NA	2–6	None	Sleep disturbance (16.3%), fatigue (2.2%), irritability (12.0%)

Potter et al,[29] 2019	Sertraline 2.5–5 mg/d	NA	2–6	Viral infection (n=1)	Irritability (5.42%), sleep disturbance (8.43%), lethargy (1.81%)
Sanchez et al,[42] 1995	NA	NA	NA	NA	NA
Sikich et al,[44] 2014*	Fluoxetine 2–20 mg/d	NA	< 6	None	Irritability (40%), insomnia (50%), rash (50%)
McDougle et al,[43] 2018*	Mirtazapine 7.5–45 mg/d	NA	5–17	None	Sedation (60%), appetite increase (50%), irritability (35%)

Abbreviations: *Studies identified from ClinicalTrials.gov; AE, adverse events; d, day; DDD, defined daily dose; NA, not available or not applicable;

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eTable 5. Specific data points for each of the measures extracted from original studies

Author[Ref] (year)	Comparison	N	Outcome	Duration (weeks)	Study group		Control group	
					Pre-Tx mean (sd) Mean change (sd)	Post-Tx mean (sd)	Pre-Tx mean (sd) Mean change (sd)	Post-Tx mean (sd)
SSRI vs. placebo								
Herscu et al.[30] (2020)	Fluoxetine 2-18 mg/d	78	1. RRB: CYBOCS-PDD	14	15.6 (2.1)	13.5 (3.3)	15 (2.2)	12.4 (3.6)
	Placebo	80						
Reddihough et al.[41] (2019)	Fluoxetine 4-30 mg/d	75	1. RRB: CYBOCS-PDD	16	12.8 (3.41)	9.02 (4.84)	13.13 (3.36)	10.89 (4.92)
			2. Global: CGI-I		3.22 (1.12)		3.38 (1.1)	
			3. Irritability: ABC irritability		18.57 (10)	12.28 (9.19)	17.87 (11.8)	13.34 (11.29)
			4. Hyperactivity: ABC hyperactivity		21.71 (11.11)	16.21 (10.48)	21.28 (11.51)	17.6 (12.52)
	Placebo	71	5. Social withdrawal: ABC social withdrawal		12.57 (8.03)	9.49 (6.77)	16.8 (10.6)	13.85 (9.32)
			6. Inappropriate speech: ABC inappropriate speech		4.48 (3.65)	3.6 (3.18)	4.8 (3.37)	4.04 (3.44)
			7. Anxiety: Spence children anxiety		31.24 (21.72)	20.58 (18.17)	32.17 (20.15)	24.7 (17.11)
Hollander et al.[36] (2012)	Fluoxetine 20-80 mg/d	22	1. RRB: Y-BOCS	12	12.48 (2.71)	10.48 (3.92)	11.92 (2.02)	11.15 (3.05)
	Placebo	15	2. Global: CGI-I		3.05 (0.93)		3.68 (0.45)	
Hollander et al.[39] (2005)	Fluoxetine 4.8–20 mg/day	19	1. RRB: CY-BOCS	8	12.84 (2.6)	11.63 (3.8)	13.45 (2.9)	12.95 (3.2)
	Placebo	20	2. Global: CGI-I		3.42 (1.2)		3.06 (1.1)	

Sikich et al.[44] (2014)*	Fluoxetine 2-20 mg/d	8	1. Irritability: ABC irritability	48	−8.5 (change from baseline; sd: 10.6)		−0.7 (change from baseline; sd:: 2.9)	
	Placebo	10						
Sugie et al.[37] (2005)	fluvoxamine 1-3 mg/kg/day	18	1. Irritability: BAS emotional instability	12	0.5208 (mean difference between drug and placebo); p>0.05			
			2. Hyperactivity: BAS hyperactivity		0.4575 (mean difference between drug and placebo); p>0.05			
	Placebo	18	3. Social withdrawal: BAS social withdrawal		0.6819 (mean difference between drug and placebo); p>0.05			
			4. Inappropriate speech: BAS inappropriate speech		0.0400 (mean difference between drug and placebo); p<0.05			
McDougle et al.[34] (1996)	Fluvoxamine 50-300 mg/d	15	1. RRB: Y-BOCS	12	21.4 (7.3)	13.7 (9.1)	21.5 (6.8)	21.9 (6.7)
			2. Global: CGI-I		2.6 (0.3)		4.33 (0.18)	
	Placebo	15	3. Irritability: Brown Aggression Scale		F=6.40; p<0.02	(Between groups)		
Potter et al.[29] (2019)	Sertraline 2.5-5 mg/d	32	1. RRB: VAS A/OCB	24	4.87 (2.58)	6.48 (2.61)	4.98 (2.3)	6.86 (2.37)
			2. Global: CGI-I		1.23 (1.11)		1.14 (0.96)	
			3. Inappropriate speech: VAS L/C		2.03 (1.7)	4.7 (2.73)	2.84 (2.04)	5.53 (2.95)
	Placebo	26	4. Social withdrawal: SRS		99.63 (27.45)	94.42 (29.71)	101.63 (28.41)	94.19 (30.12)
			5. Anxiety: PARS-R		14.75 (11.58)	14.77 (14.45)	15.38 (12.51)	11.43 (10.04)
King et al.[38] (2009)	Citalopram 10-20 mg/d	73	1. RRB: CYBOCS-PDD	12	15.1 (1.8)	13.1 (3.7)	15 (2.1)	13.1(3.2)
			2. Irritability: ABC irritability		13.2 (8.8)	10.1 (9.3)	11.2 (8.5)	10.2 (8.9)
			3. Hyperactivity: ABC hyperactivity		20.2 (11.7)	18.5 (12.9)	20.2 (11.2)	17.4 (11.5)
	Placebo	76	4. Social withdrawal: ABC social withdrawal		11.4 (8.2)	8.1 (8.1)	11.1(8)	8.2 (7.5)
			5. Inappropriate speech: ABC inappropriate speech		5.3 (3.7)	4.4 (3.7)	5 (3.7)	4.2 (3.3)

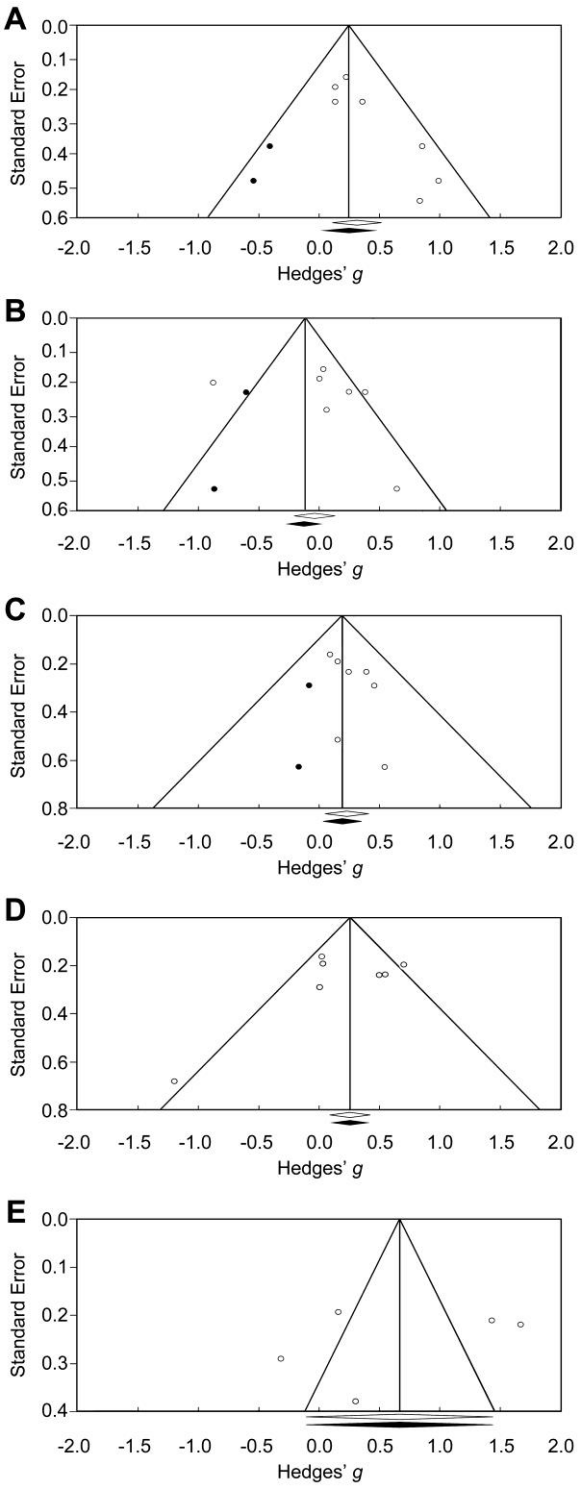
SNRI vs. placebo							
Carminati et al.[40] (2016)	Venlafaxine 18.75 mg/d	6	1. RRB: ABC stereotype	8	+0.5 (Change in Median); *p*=0.75		0 (Change in Median); *p*=0.69	
			2. Global: CGI-I		3 (Median); 2 to 5 (range)		2 (Median); 1 to 6 (range)	
			3. Irritability: ABC irritability		−1 (Change in Median); *p*=0.63		−10 (Change in Median); *p*=0.078	
			4. Hyperactivity: ABC hyperactivity		−1.5 (Change in Median), *p*=0.75		-3 (Change in Median); *p*=0.30	
	Placebo	7	5. Social withdrawal: ABC social withdrawal		+1.5 (Change in Median); *p*=0.81		-6 (Change in Median); *p*=0.031	
			6. Inappropriate speech: ABC inappropriate speech		0 (Change in Median); *p*=0.75		0 (Change in Median) ; *p*=1	
TCA vs. placebo								
Remington et al.[35] (2001)	Clomipramine 100-150 mg/d	36	1. RRB: ABC: repetitive behaviors	7	9.24	5.94; *p*>0.05	9.24	6.77; *p*>0.05
			2. Global: CARS		41.8 (7.1)	37.8 (8.7)	41.8 (7.1)	39.4 (7.0)
			3. Irritability: ABC irritability		19.18	15.99; *p*>0.05	19.18	17.5; *p*>0.05
			4. Hyperactivity: ABC hyperactivity		25.9	23.33; *p*>0.05	25.9	25.03; *p*>0.05
	Placebo	36	5. Social withdrawal: ABC social withdrawal		11.74	10.97; *p*>0.05	11.74	9.24; *p*>0.05
			6. Inappropriate speech: ABC inappropriate speech		3.4	2.78; *p*>0.05	3.4	4.24; *p*>0.05
Gordon et al.[33] (1993)	Clomipramine 25-250 mg/d	12	1. RRB: Modified CPRS OCD subscale	10	12.2 (3.31)	8.58 (4.75)	12.2 (3.31)	12.1 (3.33)
			2. Global: CPRS – autism relevant subscale		47.3 (8.4)	37.6 (7.9)	47.3 (8.4)	46.3 (8.2)
	Placebo	12						
Gordon et al.[31] (1992)	Clomipramine 25-250mg/d	7	1. RRB: NIMH-GOCS	5	19 (11)	7 (11)	19 (11)	20 (12)

(Clomipramine)	Placebo	**4**	2. Global: Children's Psychiatric Rating Scale Score		42 (4)	24 (7)	42 (4)	46 (4)
Gordon et al.[31] (1992)	Desipramine 25-250 mg/d	7	1. RRB: NIMH-GOCS	5	19 (11)	18 (9)	19 (11)	20 (12)
(Desipramine)			2. Global: Children's Psychiatric Rating Scale Score		42 (4)	41 (8)	42 (4)	46 (4)
	Placebo	**3**						
Other antidepressants								
Chugani et al.[32] (2016)	Buspirone (5 mg/d+10mg/d)	109	1. RRB: CY-BOCS	24	11.80 (0.67)	10.90 (0.63)	11.9 (0.6)	11.2 (0.6)
			2. Global: ADOS-CTS		18.35 (0.65)	17.06 (1.1)	19.6 (0.6)	18.6 (0.7)
			3. Social withdrawal: ABC social withdrawal,		13.53 (2.13)	11.34 (1.3)	14.2 (1.2)	11 (1.1)
			4. Inappropriate speech: ABC inappropriate speech		4.0.5 (0.61)	3.80 (0.54)	3.8 (0.5)	3.9 (0.5)
	Placebo	57	5. Anxiety: Anxiety composite score(ABC irritability + Leiter emotion regulation)		0.26 (0.29)	-0.002 (0.16)	0.008 (0.1)	-0.242 (0.1)
McDougle et al.[43] (2018)*	Mirtazapine 7.5-45 mg/d	20	1. Anxiety: PARS	10	-4.9 (Change from baseline); sd: 5.47		-3.2 (Change from baseline); sd: 5.31	
	Placebo	10						
Antidepressants vs. antipsychotics								
Sanchez et al.[42] (1995)	Clomipramine 2.8-4.4 mg/kg/d	8	1. CGI-S	4.5	F=27.74; p=0.01	(diff. btw. groups)		
			2. CPRS: hyperactivity, speech deviance		4	3.75; p>0.05	3.82	3.38; p>0.05
	Haloperidol 0.02-0.05 mg/kg/d	8						

Abbreviations: *Studies identified from ClinicalTrials.gov; ABC, aberrant behavior checklist; ADOS-CTS, autism diagnostic observation schedule – composite total score; A/H/H, aggression/hyperarousal/hyperactivity; A/OCB, anxiety/obsessive compulsive behavior; BAS, behavioral assessment scale; btw. between; CARS, childhood autism rating scale; CGI-I, clinical global impression – improvement; CGI-S, clinical global impression – severity; CPRS, comprehensive psychopathological rating scale; CY-BOCS, children's Yale-Brown obsessive compulsive

scale; CYBOCS-PDD, children's Yale-Brown obsessive compulsive scale – modified for pervasive developmental disorders; diff. difference; L/C language/communication; N, number of participants; NIMH-GOCS, national institute of mental health global obsessive compulsive scale; OCD, obsessive-compulsive disorder; PARS, pediatric anxiety rating scale; PARS-R, pediatric anxiety rating scale - revised; sd, standard deviation; SNRI, Serotonin and norepinephrine reuptake inhibitors; SRS, social responsiveness scale; SSRI, Selective serotonin reuptake inhibitors; TCA, Tricyclic Antidepressants; Tx, treatment; VAS, visual analog scale; Y-BOCS, Yale-Brown obsessive compulsive scales.

Appendix 1 to Liang S-C, Sun C-K, Fan H-Y. Therapeutic effects of antidepressants for global improvement and subdomain symptoms of autism spectrum disorders: a systematic review and meta-analysis. J Psychiatry Neurosci 2022. doi: 10.1503/jpn.210191.



eFigure 1. Random-effects funnel plot detailing publication bias in the studies reporting **(A)** irritability, **(B)** social withdrawal, **(C)** hyperactivity, **(D)** inappropriate speech, and **(E)** anxiety between antidepressant group and its comparators.