Supplementary Appendix:

Search terms.

Antipsychotics
atypical antipsychotics OR second generation antipsychotics OR new generation antipsychotics OR antipsychotic OR aripiprazole OR quetiapine OR olanzapine OR risperidone OR clozapine OR old generation antipsychotics OR typical antipsychotics OR first generation antipsychotics OR second generation antipsychotics OR chlorpromazine OR haloperidol OR paliperidone OR asenapine OR ziprasidone OR lurasidone OR cariprazine.

AND

ASD descriptors:
child developmental disorder* OR pervasive developmental disorder* OR autis* OR PDD* OR ASD* OR Kanner* OR Asperger* OR Asperger* syndrome OR autism spectrum disorder OR Rett Syndrome OR childhood schizophrenia OR Fragile X syndrome OR neurodevelopmental disorder* OR NDD*.

AND

Outcome:
Psychosis OR schizophrenia OR hallucination OR delusion OR mania OR hypomania OR autism core symptoms OR ASD core symptoms OR ASD symptoms OR autism symptoms OR social interaction OR communication problems OR social communication OR agitation OR irritability OR aggression OR behavioural problems OR problem behaviors OR challenging behaviour OR behaviour* that challenge OR behaviour of concern OR maladaptive behaviour OR disruptive behaviour OR disturbed behaviour OR distressed behaviour OR stereotypy OR restricted behaviour OR repetitive patterns of behaviour OR restricted interests OR restrictive activities OR social communication OR repetitive behaviour OR communication* OR inattention OR hyperactivity OR insistence on sameness OR sameness OR sleep problem OR insomnia OR self injurious behaviour OR self-mutilation OR temper tantrum OR tantrum OR aggression to others OR aggression to property OR sexual aggression OR sexual deviance OR mental state OR global improvement OR quality of life OR CGI.

AND

RCT:
clinical trial* OR randomization* OR randomisation OR research design OR randomized controlled trial OR randomi#ed control* trial* OR RCT OR controlled clinical trial OR double-blind procedure OR random* OR trial* OR control* OR blind* OR crossover OR crossover procedure OR crossover trial* OR volunteer* OR placebo* OR randomly OR control* OR ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)) OR comparative stud* OR psychopharmacology AND not (animal OR nonhuman) treatment OR effectiveness evaluation OR treatment outcomes OR follow-up studies OR evaluat* adj3 stud*.

Eligibility criteria

Citation:
Reviewer's initials:
Date of scoring:

Study design: Is the study a randomized controlled trial?	Y	N	U
Intervention: Does the intervention involve antipsychotics?	Y	N	U
Population: Do all participants have ASD (defined using a standardised method)?	Y	N	U
Is the control group matched/unmatched?	Y	N	U
Outcome: Are the outcome measures repeatable?	Y	N	U
If all yes, include it for review.	Y	N	U
If uncertain get the full paper for further check.	Y	N	U
If not all yes and no uncertainty exclude.	Y	N	U

Decision:

Y: yes; N: No; U: uncertain.

Reason for exclusion:

Data extraction proforma (adapted from Cochrane Collaboration template)

Notes on using data extraction form:

- Be consistent in the order and style you use to describe the information for each report.
- Record any missing information as unclear or not described, to make it clear that the information was not found in the study report(s), not that you forgot to extract it.
- Include any instructions and decision rules on the data collection form, or in an accompanying document. It is important to practice using the form and give training to any other authors using the form.

Title of the systematic review:

General Information

Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	
Reference citation (full citation)	
Study author contact details (Email)	
Publication type *(e.g., full report, abstract, letter)*	
Notes:	

Characteristics of the included study

Participants

	Description *Include comparative information for each intervention or comparison group if available*
Population description *(from which study participants are drawn)*	

Setting *(e.g., intensive care unit, service providers, institutions, day care centre etc)*		
Method of recruitment of participants *(e.g., phone, mail, clinic patients)*		
Informed consent obtained	Yes No Unclear	
Intervention group	Age of participants (range, mean & SD)	
	Number (%) of participants by gender	
	Number (%) with ID, ADHD or other NDDs	
	Type of pharmacological regime (name of the antipsychotic) and the dose	
	Co morbidity (psychiatric)	
	Co morbidity (physical)	
	Adverse events (number and %)	
Control group	Age of participants (range, mean & SD)	
	Number (%) of participants by gender	
	Number (%) with ID, ADHD or other NDDs	
	Type of pharmacological regime (placebo or another medication) + name + dose	
	Co morbidity (psychiatric)	
	Co morbidity (physical)	
	Adverse events (number and %)	

Methods

	Descriptions as stated in report/paper	Location in text or source *(page & ¶/fig/table/other)*
Aim of study *(e.g., efficacy, equivalence, pragmatic)*		
Design *(e.g., parallel, crossover)*		
Sampling technique (e.g., random)		

Method of establishing ASD diagnosis (if known) (clinical or ICD or DSM or ADI-R or ADOS etc.)		

Outcomes

Copy and paste table for each outcome.

	Description as stated in report/paper				Location in text or source *(page & ¶/fig/table/other)*
Primary outcome if dichotomous (e.g., %) (name the outcome and the instrument used to measure the outcome)	Number (%) in the intervention arm	Total number of participants in the intervention arm	Number (%) in the control arm	Total number of participants in the control arm	
Primary outcome if continuous	Mean in the intervention arm (95% CI)	SD in the intervention arm (95% CI)	Mean in the control arm (95% CI)	SD in the control arm (95% CI)	
Duration of intervention (weeks/months) (if crossover, add duration of baseline and washout period)					
Duration of follow up (weeks/months)					
Statistical methods used and appropriateness of these *(e.g., proportion, %, risk ratio, odds ratio)*					
Secondary outcomes					
Number of missing data					
Reason for missing data					
Other					

Is outcome/tool validated?	Yes No Unclear	Name of the tool:	
Notes:			

Other information

	Description as stated in report/paper	Location in text or source *(page & ¶/fig/table/other)*
Main findings (statistically significant difference or not; provide P value or other relevant data in support of main findings (primary and secondary outcomes)		
Key conclusions of study authors		
Your critique of the study (any design flaw etc.)		
Your own overall conclusion		
Correspondence required for further study information *(from whom, what and when)*		
Notes:		

Other

Study funding sources *(including role of funders)*		
Possible conflicts of interest *(for study authors)*		
Notes:		

Cochrane Risk of bias checklist

See Chapter 8 of the Cochrane Handbook. Additional domains may be added for non-randomised studies.

Domain	Risk of bias Low High Unclear	Support for judgement *(include direct quotes where available with explanatory comments)*	Location in text or source *(page & ¶/fig/table/other)*

Random sequence generation *(selection bias)*	☐ ☐ ☐		
Allocation concealment *(selection bias)*	☐ ☐ ☐		
Blinding of participants and personnel *(performance bias)*	☐ ☐ ☐	Outcome group: All/	
(if separate judgement by outcome(s) required)	☐ ☐ ☐	Outcome group:	
Blinding of outcome assessment *(detection bias)*	☐ ☐ ☐	Outcome group: All/	
(if separate judgement by outcome(s) required)	☐ ☐ ☐	Outcome group:	
Incomplete outcome data *(attrition bias)*	☐ ☐ ☐	Outcome group: All/	
(if separate judgement by outcome(s) required)	☐ ☐ ☐	Outcome group:	
Selective outcome reporting? *(reporting bias)*	☐ ☐ ☐		
Other bias	☐ ☐ ☐		
Notes:			

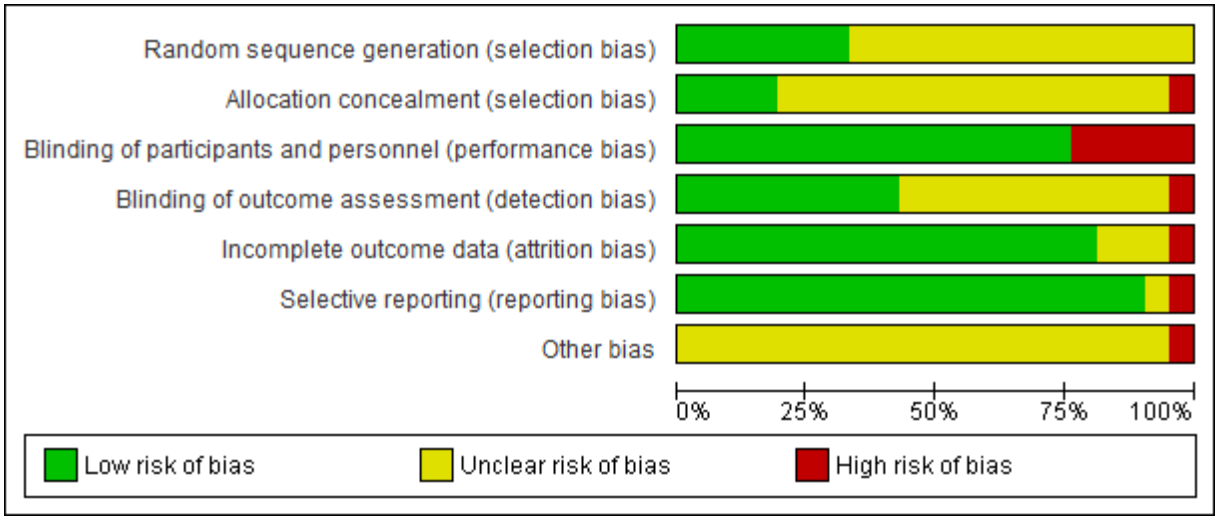
Definitions

Assumed risk estimate	An estimate of the risk of an event or average score without the intervention, used in Cochrane 'Summary of findings tables'. If a study provides useful estimates of the risk or average score of different subgroups of the population, or an estimate based on a representative observational study, you may wish to collect this information.
Bias	A systematic error or deviation in results or inferences from the truth. In studies of the effects of health care, the main types of bias arise from systematic differences in the groups that are compared (selection bias), the care that is provided, exposure to other factors apart from the intervention of interest (performance bias), withdrawals or exclusions of people entered into a study (attrition bias) or how outcomes are assessed (detection bias). Reviews of studies may also be particularly affected by reporting bias, where a biased subset of all the relevant data is available.
Change from baseline	A measure for a continuous outcome calculated as the difference between the baseline score and the post-intervention score.
Clusters	A group of participants who have been allocated to the same intervention arm together, as in a cluster-randomised trial, e.g. a whole family, town, school or patients in a clinic may be allocated to the same intervention rather than separately allocating each individual to different arms.

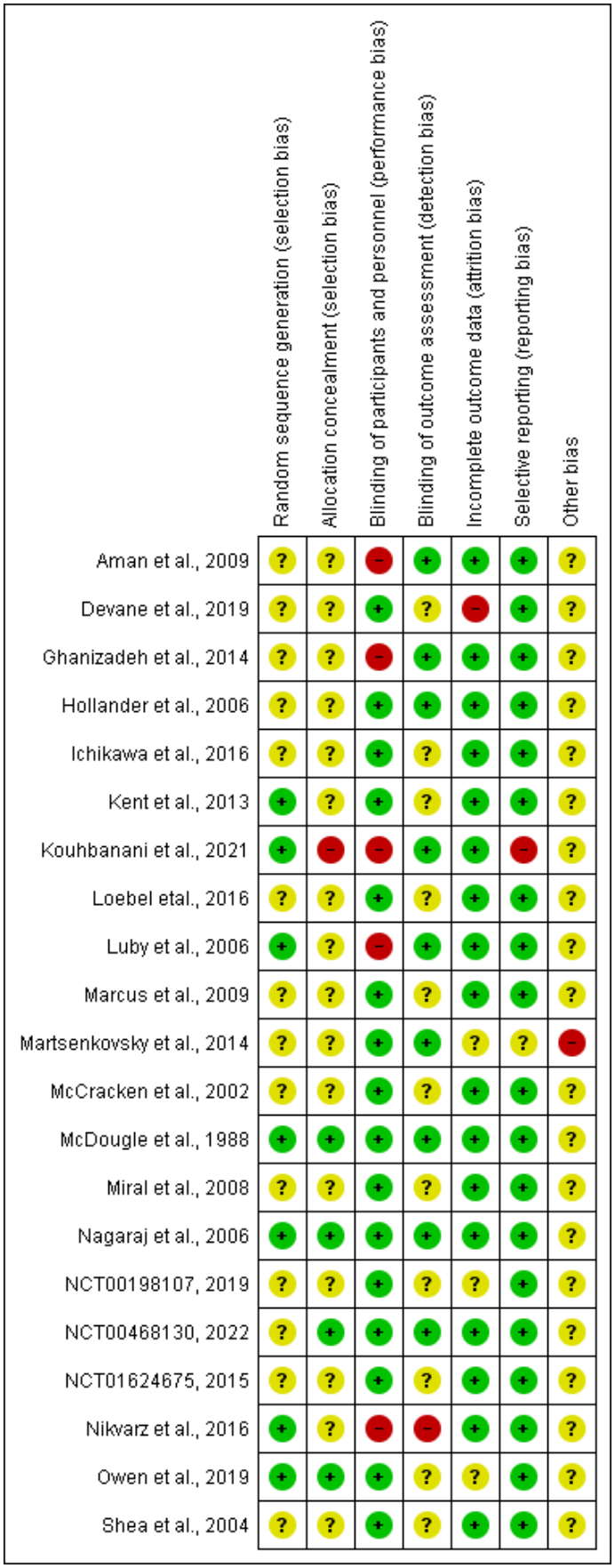
Co-morbidities	The presence of one or more diseases or conditions other than those of primary interest. In a study looking at treatment for one disease or condition, some of the individuals may have other diseases or conditions that could affect their outcomes.
Compliance	Participant behaviour that abides by the recommendations of a doctor, other health care provider or study investigator (also called adherence or concordance).
Contemporaneous data collection	When data are collected at the same point(s) in time or covering the same time period for each intervention arm in a study (that is, historical data are not used as a comparison).
Controlled Before and After Study (CBA)	A non-randomised study design where a control population of similar characteristics and performance as the intervention group is identified. Data are collected before and after the intervention in both the control and intervention groups
Exclusions	Participants who were excluded from the study or the analysis by the investigators.
Imputation	Assuming a value for a measure where the true value is not available (e.g. assuming last observation carried forward for missing participants).
Integrity of delivery	The degree to which the specified procedures or components of an intervention are delivered as originally planned.
Interrupted Time Series (ITS)	A research design that collects observations at multiple time points before and after an intervention (interruption). The design attempts to detect whether the intervention has had an effect significantly greater than the underlying trend.
Post-intervention	The value of an outcome measured at some time point following the beginning of the intervention (may be during or after the intervention period).
Power	In clinical trials, power is the probability that a trial will obtain a statistically significant result when the true intervention effect is a specified size. For a given size of effect, studies with more participants have greater power. Note that power should not be considered in the risk of bias assessment.
Providers	The person or people responsible for delivering an intervention and related care, who may or may not require specific qualifications (e.g. doctors, physiotherapists) or training.
Quasi-randomised controlled trial	A study in which the method of allocating people to intervention arms was not random, but was intended to produce similar groups when used to allocate participants. Quasi-random methods include: allocation by the person's date of birth, by the day of the week or month of the year, by a person's medical record number, or just allocating every alternate person.
Reanalysis	Additional analysis of a study's results by a review author (e.g. to introduce adjustment for correlation that was not done by the study authors).
Report ID	A unique ID code given to a publication or other report of a study by the review author (e.g. first author's name and year of publication). If a study has more than one report (e.g. multiple publications or additional unpublished data) a separate Report ID can be allocated to each to help review authors keep track of the source of extracted data.
Sociodemographics	Social and demographic information about a study or its participants, including economic and cultural information, location, age, gender, ethnicity, etc.
Study ID	A unique ID code given to an included or excluded study by the review author (e.g. first author's name and year of publication from the main report of the study). Although a study may have multiple reports or references, it should have one single Study ID to help review authors keep track of all the different sources of information for a study.

Theoretical basis	The use of a particular theory (such as theories of human behaviour change) to design the components and implementation of an intervention
Unit of allocation	The unit allocated to an intervention arm. In most studies individual participants will be allocated, but in others it may be individual body parts (e.g. different teeth or joints may be allocated separately) or clusters of multiple people.
Unit of analysis	The unit used to calculate N in an analysis, and for which the result is reported. This may be the number of individual people, or the number of body parts or clusters of people in the study.
Unit of measurement	The unit in which an outcome is measured, e.g. height may be measured in cm or inches; depression may be measured using points on a particular scale.
Validation	A process to test and establish that a particular measurement tool or scale is a good measure of that outcome.
Withdrawals	Participants who voluntarily withdrew from participation in a study before the completion of outcome measurement.

Supplementary Appendix: Summary of Cochrane risk of bias scores.



Summary graph of Risk of bias scores for 21 primary RCTs



Risk of bias summary Table for 21 primary RCTs

Supplementary Appendix: AMSTAR 2 scores.

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☐ Population
- ☐ Intervention
- ☐ Comparator group
- ☐ Outcome

Optional (recommended)
- ☐ Timeframe for follow-up

- ☒ Yes
- ☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☐ review question(s)
- ☐ a search strategy
- ☐ inclusion/exclusion criteria
- ☐ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, *and*
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

- ☒ Yes
- ☐ Partial Yes
- ☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☐ *Explanation for* including only RCTs
- ☐ OR *Explanation for* including only NRSI
- ☐ OR *Explanation for* including both RCTs and NRSI

- ☒ Yes
- ☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☐ searched at least 2 databases (relevant to research question)
- ☐ provided key word and/or search strategy
- ☐ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- ☐ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

- ☐ Yes
- ☒ Partial Yes
- ☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- ☒ Yes
- ☐ No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

- ☐ at least two reviewers achieved consensus on which data to extract from included studies
- ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

☒ Yes
☐ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:

- ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:

- ☐ Justified the exclusion from the review of each potentially relevant study

☒ Yes
☐ Partial Yes
☐ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):

- ☐ described populations
- ☐ described interventions
- ☐ described comparators
- ☐ described outcomes
- ☐ described research designs

For Yes, should also have ALL the following:

- ☐ described population in detail
- ☐ described intervention in detail (including doses where relevant)
- ☐ described comparator in detail (including doses where relevant)
- ☐ described study's setting
- ☐ timeframe for follow-up

☒ Yes
☐ Partial Yes
☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from

- ☐ unconcealed allocation, *and*
- ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:

- ☐ allocation sequence that was not truly random, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☒ Yes
☐ Partial Yes
☐ No
☐ Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:

- ☐ from confounding, *and*
- ☐ from selection bias

For Yes, must also have assessed RoB:

- ☐ methods used to ascertain exposures and outcomes, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☐ No
☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes

- ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

☒ Yes
☐ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
  - ☐ AND investigated the causes of any heterogeneity

☒ Yes
☐ No
☐ No meta-analysis conducted

For NRSI

For Yes:

- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  - ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  - ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

☐ Yes
☐ No
☐ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

☒ Yes
☐ No
☐ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

☒ Yes
☐ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

- ☐ There was no significant heterogeneity in the results
- ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

☒ Yes
☐ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

- ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

☒ Yes
☐ No
☐ No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

- ☐ The authors reported no competing interests OR
- ☐ The authors described their funding sources and how they managed potential conflicts of interest

☒ Yes
☐ No

Supplementary Appendix: PRISMA-P 2015 Checklist.

Section/topic	#	Checklist item	Information reported		Page Numbers
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title Effectiveness of antidepressant and anti-anxiety medications in people with autism spectrum disorder: a systematic review and meta-analysis.					
Identification	1a	Identify the report as a protocol of a systematic review	x		2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		x	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	x		2
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	x		1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	x		9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		x	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	x		9
Sponsor	5b	Provide name for the review funder and/or sponsor	x		NA
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	x		NA
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	x		3 + ST 1

Section/topic	#	Checklist item	Information reported		Page Numbers
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	x		3
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	x		SA 1
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	x		3
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	x		SA 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	x		3 + SA 1
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	x		3 + SA 1
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	x		SA 1
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	x		SA 1
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	x		SA 1
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or	x		3 + SA 1 + SA 2

Section/topic	#	Checklist item	Information reported		Page Numbers
			Yes	No	
		study level, or both; state how this information will be used in data synthesis			
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	x		3-4
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	x		3-4 + PROSPERO protocol
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	x		3-4
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	x		3-4
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	x		4
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	x		5 (GRADE + AMSTAR 2)