Appendix:
Pharmacological and dietary supplement treatments for autism spectrum disorder: a systematic review and network meta-analysis

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eAppendix-1 PRISMA NMA checklist

1.1 PRISMA NMA checklist

PISMA NMA checklist according to Hutton et al 2015 [1].

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	5
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	6, eAppendix-2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the*	6-7, eAppendix-2

		treatment network, and note whether any have been clustered or merged into the same node (with justification).	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-7, eAppendix-3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	eAppendix-3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7, eAppendix-2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7, eAppendix-2, eAppendix-4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-8, eAppendix-2
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	n.i.
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7, 9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	8
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	6, 8-9
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	9

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9, eAppendix-9
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	9
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	eAppendix-4
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Figure-S1
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10-1, eAppendix-5, eAppendix-4.3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	eAppendix-5.2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	Figure-S3
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If	11-18, Figure-1, Figure-S2, Figure-2/3/4, Table-S1

		additional summary measures were explored (such as treatment rankings), these should also be presented.	
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	11, 13, 16, eAppendix-6.5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	11-13, eAppendix-6.8/9
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	eAppendix-6.6, Figure-S4
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	19-23
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	24-25
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	26
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	36

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.
n.i.: not indicated

1.2 References

1. Hutton B, Catala-Lopez F, Moher D. The PRISMA statement extension for systematic reviews incorporating network meta-analysis: PRISMA-NMA. Med Clin (Barc). 2016;147(6):262-6.

eAppendix-2 Protocol and methods

2.1. PROSPERO protocol

This manuscript refers to the second objective of the PROSPERO protocol below, i.e. network meta-analysis to investigate the comparative efficacy and tolerability of pharmacological and dietary supplement interventions for ASD. The analysis of the first objective, i.e. placebo response, is reported elsewhere [1].

2.1.1 Second version of the protocol (submitted to PROSPERO on 31.03.2020, online on 29.10.2020)

Pharmacological and dietary supplement interventions for autism spectrum disorders (ASD): a systematic review, network meta-analysis, and meta-regression-analysis of placebo response
Spyridon Siafis, Oğulcan Çıray, Irene Bighelli, Johannes Schneider-Thoma, Stefan Leucht

Citation
Spyridon Siafis, Oğulcan Çıray, Irene Bighelli, Johannes Schneider-Thoma, Stefan Leucht. Pharmacological and dietary supplement interventions for autism spectrum disorders (ASD): a systematic review, network meta-analysis, and meta-regression-analysis of placebo response. PROSPERO CRD42019125317 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019125317

Changes from previous version
1) Review questions are clearly presented. 2) A network meta-analysis will be conducted, if possible, to investigate the efficacy and tolerability of pharmacological and dietary supplement interventions. For this reason, head-to-head trials will also be eligible. 3) The outcome 'important side effects' is specified.

Review question
1) The first objective is to investigate predictors of placebo response and efficacy (drug-placebo differences) in placebo-controlled pharmacological and dietary supplement trials in ASD. Single-group and pairwise meta-analysis as well as meta-regression-analysis are planned.
2) The second objective is to investigate the comparative efficacy and tolerability of pharmacological and dietary supplement interventions for ASD. Pairwise and network meta-analysis are planned.

Searches
1) Electronic databases: Comprehensive searches will be conducted in ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE, PsycINFO, PubMed, World Health Organization International Clinical Trials Registry Platform (WHO ICTRP). There will be no date/time, language, document type, and publication status limitations.
2) Reference searching: Reference lists of included records will be hand-searched for potentially relevant studies.
3) Previous reviews: Relevant reviews on pharmacological and dietary supplement treatments for ASD will be hand-searched for potentially relevant studies.
4) Personal contact: In addition, we will contact the first and/or corresponding author of each included study published in the last 30 years for missing information.
At least two reviewers will independently inspect the titles and abstracts of non-duplicated references identified through the search and will exclude those not pertinent. Discrepancies between the two reviewers will be resolved by discussion reaching consensus. If doubts still remain, the full-text will be obtained. In a second step, full-texts will be independently assessed by two reviewers for eligibility. Again, disagreements will be resolved by discussion and, if needed,

a third senior author will be involved. When required, further information will be requested from study authors.

Search strategy
https://www.crd.york.ac.uk/PROSPEROFILES/125317_STRATEGY_20190213.pdf

Types of study to be included
Randomized controlled trials (RCT) in which participants with ASD received pharmacological treatments or dietary supplements compared to each other or placebo will be eligible.
Inclusion:
- Both open and blinded RCTs will be eligible.
- Randomization will be implied if not explicitly reported, when the study is stated as double-blind.
- In case of cross-over studies only data from the first phase before the crossover will be eligible, in order to avoid carry-over effects.
- No restriction in terms of language or country of origin.

Exclusion:
- Quasi-randomized trials and studies with high risk of bias in randomization as described in the Cochrane Handbook [2].
- Cluster randomized trials.
- Long-term studies with maintenance design, studies with placebo-controlled discontinuation or withdrawal design.
- Studies published before 1980 (see participants/population).
- Studies with less than 10 participants.

Condition or domain being studied
Autism spectrum disorders (ASD), including autistic disorder, Asperger's syndrome and pervasive developmental disorder-not otherwise specified, as they were previously classified as independent categorical entities in DSM-IV.

Participants/population
Inclusion:
- ASD as diagnosed by standardized diagnostic criteria (such as DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR, DSM-5, ICD-10) and/or validated diagnostic tools.
- Studies including participants with ASD and associated conditions (e.g. ADHD symptoms, irritability) will be accepted.
- Studies with all or some of the participants having a genetic syndrome (such as Fragile X syndrome) will be accepted, when all participants had also ASD (defined by inclusion criteria).
- Trials in which less than 20% of participants had a developmental or psychiatric disorder other than ASD will be eligible.
- There will be no restriction in terms of age, sex, ethnicity, setting, initial severity of ASD symptoms.

Exclusion:
- Participants characterized as 'autistic' or with 'autistic behavior' and 'autistic traits' without using standardized diagnostic criteria or validated diagnostic tools for ASD. Studies published before 1980 will also be excluded, because ASD was clearly separated from childhood schizophrenia after the introduction of DSM-III (published in 1980). In addition, DSM-II and ICD-9 did not have standardized criteria.
- Studies requiring all participants to have a genetic syndrome, but not all of the participants had ASD defined by inclusion criteria.

- Studies focused on stable patients (controlled-discontinuation or withdrawal studies).

Intervention(s), exposure(s)
Any pharmacological treatment and dietary supplement will be eligible.
Inclusion:
- Any application form or route of administration (e.g. oral, intramuscular, intravenous, intranasal)
- Both fixed- and flexible-dose designs.
- The minimum duration of treatment will be seven days.

Exclusion:
- Other interventions, such as psychological/behavioral, traditional medicine, homeopathic, dietary interventions, such as elimination diets (gluten/casein-free, ketogenic diets) or milk formulations.
- Augmentation treatments.
- Studies using single doses.

Comparator(s)/control
Placebo or any eligible intervention can be a comparator in a network meta-analysis. Placebo will be used as reference for presentation.

Context

Main outcome(s)
The co-primary outcomes will be:
1) Overall ASD core symptoms.
2) Social communication/interaction deficits.
3) Repetitive behaviors/restricted interests.

* Measures of effect
Outcomes should be measured by published and validated scales. Scales could be filled by different raters, and in the primary analyses, we will prefer clinicians' to parents/caregivers' to teachers' ratings. Subgroup analysis of the co-primary outcomes will be conducted by pooling separately rating scales filled by parent/caregivers, teachers and clinicians. Outcomes will be measured at endpoint and studies will be classified in subgroup analyses as shorter-term (less or equal to three months) and medium-to-longer-term.
The effect sizes for continuous outcomes will be the standardized mean change (SMC, single-group) and the standardized mean difference as Hedges' g (SMD, treatment contrasts). SMCs will be preferably standardized to baseline standard deviations, and a pre-post correlation of 0.5 will be assumed for the primary analysis (correlations of 0.25 and 0.75 will be used in sensitivity analyses). The effect sizes for dichotomous outcomes will be response rates (single-group, logit transformed in the meta-analysis) and relative risks (treatment contrasts). Effect sizes will be accompanied by their 95% confidence intervals.

Additional outcome(s)
1) Internalizing associated symptoms (such as anxiety) as measured by appropriate scales.
2) Externalizing associated symptoms as well as ADHD symptoms and irritability, as measured by appropriate scales.
3) Number of participants with response to treatment, preferably defined by CGI-I at least much improved, but any study definition will be eligible for treatment comparisons.
4) Quality of life of participants as measured by appropriate scales (e.g. PedsQL).
5) Global functioning of participants as measured by appropriate scales (e.g. CGAS).

6) Parental stress as measured by appropriate scales (e.g. PSI).
7) Number of participants who prematurely discontinued due to any cause (as a measure of overall acceptability) and adverse events (as a measure of overall tolerability).
8) Important side effects defined as a) at least one adverse event, b) sedation, c) weight gain, d) extrapyramidal symptoms
* Measures of effect
As defined for the primary outcomes.

Data extraction (selection and coding)
Two authors will independently extract data from all selected trials in a Microsoft Access database. When disagreement arises we will resolve it by discussion and, if needed, involving a third senior author. Where this is not sufficient we will contact the study authors.

Data extraction will include characteristics of study (study citation, registration number to trials registries, year of publication, location, setting, number of centers, sample size, and funding/sponsor such as industry or academic), methodology (study design, number of arms and risk of bias), participants (age, sex, IQ, diagnosis, sample size), intervention (name, dose, application form) and outcome measure (including information on whether an intention-to-treat approach has been used and how it was defined)

For continuous outcomes, change scores will be preferred, but endpoint scores will also be eligible. Missing standard deviations (SD) will be calculated from the following options and following order by the 1) standard error, 2) CIs, t-value or p-value, 3) contacting original authors, 4) median-ranges, 5) pooling subscales with an assumed correlation of 0.5, 6) by SDs from other studies using a validated imputation method as described in the Cochrane Handbook. Intention-to-treat data will be used whenever possible and when imputation methods were used to handle missing data, they will be preferred to completers' data, giving preference to mixed-models of repeated measurement (MMRM) and multiple imputation over last-observation carried forward (LOCF). For dichotomous outcomes, if the original authors presented only the results of completer population, we will assume that those participants lost to follow-up would not have changed for a given outcome. When the number of responders was not reported, it will be imputed from mean and standard deviation (SD) of CGI-I using a validated method and studies with imputed responders will be excluded in a sensitivity analysis.

Risk of bias (quality) assessment
Two independent review authors will assess the risk of bias in the selected studies using the Cochrane Collaboration 'risk of bias' tool. When disagreement arises we will resolve it by discussion and, if needed, involving a third senior author. The following domains will be considered (classified as low, moderate or high): sequence generation, allocation concealment, blinding, completeness of outcome data, selective reporting and other biases. Similar to the GRISELDA NMA [3, 4], studies will be classified as having an overall low (no domain with high risk of bias and three or less with unclear risk), moderate (one with high risk of bias or none with high risk of bias but four or more with unclear risk) and high risk of bias (all other cases). Confidence in the results of the co-primary outcomes will be assessed using the approach of CINeMA [5] [6].

Strategy for data synthesis
1) For the first objective, single-group (placebo/drug response) and pairwise meta-analysis (drug-placebo differences) will be conducting for the co-primary outcomes by pooling placebo-controlled trials using random-effects models.
Heterogeneity will be investigated by visual inspection of forest plots, chi-squared and I-squared statistics.

2) For the second objective, as a first step of a network-meta-analysis (NMA), pairwise meta-analyses will be conducted using random-effects models by pooling each treatment comparison, separately in children/adolescents and adults.
We assume that participants eligible to our review have an equal likelihood to be randomized to any of the intervention of the NMA (transitivity assumption). The distribution of potential effect-modifiers will also be investigated, i.e. study duration, type of rater, associated conditions at inclusion, baseline severity.

In a second step and if the requirements of NMA are fulfilled, we will conduct NMA in a frequentist framework using a random-effects model and assuming a common variance (tau-squared) for each network. We will present relative effects and 95% confidence intervals for all pairwise comparisons.

Heterogeneity will be quantified with the tau-squared and we will compare it to empirical distributions. If the estimation of treatment effects is precise, we aim to obtain an hierarchy of treatments [7].

Incoherence will be evaluated both locally (with the 'separating indirect from direct evidence' approach) and globally (with a design-by-treatment interaction test) [8]. Tests for inconsistency are expected to have small statistical power, and therefore, sources of inconsistency will be explored even when evidence of inconsistency is lacking.

3) We will attempt to include unpublished studies. Small study and publication bias will be explored for both objectives with funnel plot analyses if at least 10 studies are available per comparison.

4) Statistical software: R (meta [9], netmeta [10], metafor [11] packages)

Analysis of subgroups or subsets
1) Meta-regressions of predictors of placebo/drug response or efficacy will be conducted similarly to our previous analyses in acute schizophrenia [12]. A priori, we plan exploratory univariable meta-regressions; multivariable meta-regressions will also be conducted, if there are enough data. Dependent variables will be SMC of placebo/drug response or SMD of efficacy in core symptoms. Independent variables will be the following potential predictors:

- Participants: a) associated symptoms, b) age c) sex (post-hoc), d) ethnicity (post-hoc), e) intellectual disability, f) baseline severity.
- Intervention: a) route of administration (oral versus other), b) type of intervention (pharmacological versus dietary supplements), c) fixed- versus flexible-designs.
- Study-design: a) study-duration (weeks), b) publication year, c) wash-out, c) lead-in with exclusion of placebo responders, d) rater (clinician versus caregiver), e) sample size, f) number of sites and academic sites, g) number of arms and medications, h) proportion of participants on placebo, i) country of origin (US vs not only US), j) sponsorship (industry-funded/patent application vs industry-independent), k) risk-of-bias domains

2) Sensitivity analysis of the co-primary outcomes will be conducted by excluding studies with a) implied randomization, b) genetic syndrome at inclusion, c) diagnosis using only diagnostic evaluation tools, d) open- or single-blind, e) duration of less than 4 weeks, f) presenting only completers data, g) imputed SDs, h) overall high or moderate risk-of-bias, i) by using fixed-effects model.

3) In NMA, subgroup analyses of the co-primary outcomes will investigate potential effect-modifiers, i.e. a) study-duration, b) rater, c) associated condition and d) baseline severity

Contact details for further information
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- Dr Johannes Schneider-Thoma. Department of Psychiatry and Psychotherapy, School of Medicine, Technische Universität München, Klinikum rechts der Isar
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- Professor Dimitris Mavridis, Department of Primary Education, University of Ioannina, Greece
- Mr Farhad Shokraneh. Cochrane Schizophrenia Group, The Institute of Mental Health, the University of Nottingham and Nottinghamshire Healthcare NHS Trust, Nottingham, UK

Type and method of review
Intervention, Meta-analysis, Systematic review

Anticipated or actual start date
01 June 2018

Anticipated completion date
31 May 2020

Funding sources/sponsors
This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777394. This Joint Undertaking receives support from the European

Union's Horizon 2020 research and innovation programme and EFPIA and AUTISM SPEAKS, Autistica, SFARI

Conflicts of interest

- In the last 3 years, Stefan Leucht has received honoraria for consulting or lectures from LB Pharma, Lundbeck, Otsuka, TEVA, LTS Lohmann, Geodon Richter, Recordati, Boehringer Ingelheim, Sandoz, Janssen, Lilly, SanofiAventis, Servier and Sunovion.
- David Fraguas has been a consultant and/or has received fees from Angelini, Eisai, IE4Lab, Janssen, Lundbeck, and Otsuka. He has also received grant support from Instituto de Salud Carlos III (Spanish Ministry of Science, Innovation and Universities) and from Fundación Alicia Koplowitz.
- Mara Parellada has received educational honoraria from Otsuka, research grants from FAK and Fundación Mutua Madrileña (FMM), Instituto de Salud Carlos III (Spanish Ministry of Science, Innovation and Universities) and European ERANET and H2020 calls, travel grants from Otsuka and Janssen. Consultant for Exeltis and Servier.

Language
English

Country
Germany
Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Autism Spectrum Disorder; Dietary Supplements; Humans

Date of registration in PROSPERO
15 March 2019

Date of publication of this version
15 March 2019

Stage of review at time of this submission
Preliminary searches: Started Yes Completed Yes
Piloting of the study selection process: Started Yes Completed Yes
Formal screening of search results against eligibility criteria: Started Yes Completed No
Data extraction: Started Yes Completed No
Risk of bias (quality) assessment: Started Yes Completed No
Data analysis: Started Yes Completed No

2.1.2 First version of the protocol (15.03.2019)

Placebo-controlled pharmacological and dietary supplement trials in autism spectrum disorders (ASD): systematic review, meta-analysis and meta-regression
Spyridon Siafis, Irene Bighelli, Johannes Schneider-Thoma, Stefan Leucht

Citation

Spyridon Siafis, Irene Bighelli, Johannes Schneider-Thoma, Stefan Leucht. Placebo-controlled pharmacological and dietary supplement trials in autism spectrum disorders (ASD): systematic review, meta-analysis and meta-regression. PROSPERO 2019 CRD42019125317 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019125317

Review question

To investigate predictors of efficacy and placebo response in placebo-controlled pharmacological and dietary supplement trials in ASD.

Searches

- Electronic databases: Comprehensive searches will be conducted in ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE, PsycINFO, PubMed, World Health Organization International Clinical Trials Registry Platform (WHO ICTRP). There will be no date/time, language, document type, and publication status limitations.
- Reference searching: Reference lists of included records will be hand-searched for potentially relevant studies.
- Previous reviews: Relevant reviews on pharmacological and dietary supplement treatments for ASD will be hand-searched for potentially relevant studies.
- Personal contact: In addition, we will contact the first and/or corresponding author of each included study published in the last 30 years for missing information.

Search strategy https://www.crd.york.ac.uk/PROSPEROFILES/125317_STRATEGY_20190213.pdf

Types of study to be included

Randomized controlled trials (RCT) in which participants with ASD received pharmacological treatments or dietary supplements compared to placebo will be eligible.

Inclusion:

- Both open and blinded RCTs.
- Randomization will be implied if not explicitly reported, when the study is stated as double-blind.
- In case of cross-over studies only data from the first phase before the crossover will be eligible, in order to avoid carry-over effects.
- No restriction in terms of language or country of origin.

Exclusion:

- Quasi-randomized trials and studies with high risk of bias in randomization as described in the Cochrane Handbook [13].
- Cluster randomized trials.
- Long-term studies with maintenance design, studies with placebo-controlled discontinuation or withdrawal design.
- Studies published before 1980 (see participants/population).
- Studies with less than 10 participants.

Condition or domain being studied

Autism spectrum disorders (ASD), including autistic disorder, Asperger's syndrome and pervasive developmental disorder-not otherwise specified, as they were previously classified as independent categorical entities in DSM-IV.

Participants/population

Inclusion:

- ASD as diagnosed by standardized diagnostic criteria (such as DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR,DSM-5, ICD-10) and/or validated diagnostic tools.
- Studies including participants with ASD and associated symptoms (e.g. ADHD symptoms, irritability) will be accepted.
- Studies with all or some of the participants having a genetic syndrome (such as Fragile X syndrome) will be accepted, when all participants had also ASD (defined by inclusion criteria).
- Trials in which less than 20% of participants had a developmental or psychiatric disorder other than ASD will be eligible.
- There will be no restriction in terms of age, sex, ethnicity, setting, initial severity of ASD symptoms.

Exclusion:

- Participants characterized as 'autistic' or with 'autistic behavior' and 'autistic traits' without using standardized diagnostic criteria or validated diagnostic tools for ASD. Studies published before 1980 will also be excluded, because ASD was clearly separated from childhood schizophrenia after the introduction of DSM-III (published in 1980). In addition, DSM-II and ICD-9 did not have standardized criteria.
- Studies requiring all participants to have a genetic syndrome, but not all of the participants had ASD defined by inclusion criteria.
- Studies focused on stable patients (controlled-discontinuation or withdrawal studies).

Intervention(s), exposure(s)

Any pharmacological treatment and dietary supplement will be eligible.

Inclusion:

- Any application form or route of administration (e.g. oral, intramuscular, intravenous, intranasal) - Both fixed- and flexible-dose designs.
- The minimum duration of treatment will be seven days.

Exclusion:

- Other interventions, such as psychological/behavioral, traditional medicine, homeopathic, dietary interventions, such as elimination diets (gluten/casein-free, ketogenic diets) or milk formulations.
- Augmentation treatments.
- Studies using single doses.

Comparator(s)/control

Placebo.

Context

Main outcome(s)

- Overall ASD core symptoms.
- Social communication/interaction deficits.
- Repetitive behaviors/restricted interests.

Timing and effect measures
Published and validated scales will be used. When scales filled by multiple informants are available, we will use the hierarchy: clinicians', parents/caregivers' and teachers' rating. Regarding core symptoms, separate analyses will be conducted for rating scales filled by parent/caregivers, teachers and clinicians as secondary outcomes. Change scores will be preferred, but we will also use endpoint scores if the former are not available.
We will take the endpoint results and pool all studies. In addition, studies will be classified as shorter-term (1-12 weeks) and longer-term (13 or more weeks).

Additional outcome(s)
- CGI-improvement and CGI-Severity.
- Overall ASD core symptoms as measured by rating scales filled by clinicians, caregivers or teachers.
- Social communication/interaction deficits as measured by rating scales filled by clinicians, caregivers or teachers.
- Repetitive behaviors/restricted interests as measured by rating scales filled by clinicians, caregivers or teachers.
- Internalizing associated symptoms (such as anxiety) as measured by appropriate scales.
- Externalizing associated symptoms as well as ADHD symptoms and irritability, as measured by appropriate scales.
- Number of participants with response to treatment, any study definition is eligible.
- Quality of life of participants as measured by appropriate scales (e.g. PedsQL)
- Global functioning of participants as measured by appropriate scales (e.g. CGAS)
- Parental stress as measured by appropriate scales (e.g. PSI)
- Number of participants who prematurely discontinued due to any cause (as a measure of overall acceptability), inefficacy (as a measure of global efficacy), adverse events (as a measure of overall tolerability).
- Important side effects.

Timing and effect measures
We will take the endpoint results and pool all studies. In addition, studies will be classified as shorter-term (1-12 weeks) and longer-term (13 or more weeks).

Data extraction (selection and coding)
Selection of trials: At least two reviewers will independently inspect the titles and abstracts of non-duplicated references identified through the search and will exclude those not pertinent. Discrepancies between the two reviewers will be resolved by discussion reaching consensus. If doubts still remain, the full-text will be obtained and eligibility will be assessed. Full-texts of included references will be obtained and independently assessed by two reviewers for eligibility. Again, disagreements will be resolved by discussion and, if needed, a third senior author will be involved. When required, further information will be requested from study authors.

Data extraction: Two authors will independently extract data from all selected trials in a Microsoft Access database. When disagreement arises we will resolve it by discussion and, if needed, involving a third senior author. Where this is not sufficient we will contact the study authors.
Data extraction will include:

- Study citation, registration number to trials registries, year of publication, location, setting, number of centers, sample size, and funding/sponsor (industry or academic).
- Methodology (study design, number of arms and risk of bias).
- Characteristics of study participants (age, sex, IQ, diagnosis, sample size).
- Characteristics of intervention (name, dose, application form).
- Outcome measures, including information on whether an intention-to-treat approach has been used and how it was defined.

Risk of bias (quality) assessment

Two independent review authors will assess the risk of bias in the selected studies using the Cochrane Collaboration 'risk of bias' tool. When disagreement arises we will resolve it by discussion and, if needed, involving a third senior author. The following domains will be considered (classified as low, moderate or high): sequence generation, allocation concealment, blinding, completeness of outcome data, selective reporting and other biases. Similar to the GRISELDA NMA [3, 4] studies will be classified as having an overall low (no domain with high risk of bias and three or less with unclear risk), moderate (one with high risk of bias or none with high risk of bias but four or more with unclear risk) and high risk of bias (all other cases). Quality of evidence for the primary outcome will be assessed by GRADE approach [14].

Strategy for data synthesis

The effect size for continuous outcomes will be the standardized mean difference as Hedges' g, and for dichotomous outcomes the relative risk, accompanied by their 95% confidence intervals. Intention-to-treat data will be used whenever possible. For dichotomous outcomes, if the original authors presented only the results of completer population, we will assume that those participants lost to follow-up would not have changed for a given outcome. Missing standard deviations (SD) will be calculated from the following options and following order by the 1) standard error, 2) CIs, t-value or p-value, 3) contacting original authors 4) by SDs from other studies using a validated imputation method as described in the Cochrane Handbook.

Pairwise meta-analyses of studies, separately for children/adolescents and adults, that compared the same intervention with placebo will be conducted using random effects models [15]. Meta-regressions of predictors of efficacy and placebo response will be conducted by using all studies. Meta-regressions for individual interventions will not be conducted due to small statistical power. Heterogeneity will be investigated by visual inspection of the forest plots, χ^2 test of homogeneity and I^2.

We will attempt to include unpublished studies. Small study and publication bias will be explored with funnel plot analyses if at least 10 studies are available for a comparison.

Sensitivity analyses of the primary outcomes will be performed: A) Exclusion of studies with implied randomization. B) Exclusion of studies including participants with associated symptoms or genetic syndrome. C) Exclusion of studies with a diagnosis based only on diagnostic evaluation tools. D) Exclusion of open and single-blinded trials. E) Exclusion of studies lasting less than 4 weeks. F) Using a fixed effects model. G) Exclusion of studies presenting only completers data. H) Exclusion of studies with imputed missing SD. I) Exclusion of studies with an overall high or unclear risk of bias.

Analysis of subgroups or subsets

Meta-regressions of predictors of efficacy and placebo response will be conducted for the primary outcomes using a similar approach to our previous meta-regressions in acute schizophrenia [16-18]. The dependent variables in the analyses will be 1) placebo response, 2) drug response and 3) effect sizes for the comparisons of interventions with placebo. The independent variables will be the following potential moderators. A priori, we plan exploratory univariate meta-regressions. Multivariable meta-regression models will be conducted, if there are enough available data, because a higher statistical power is required.

Potential moderators will be assessed:

1. Drug-related factors: A) Route of administration (oral versus other). B) Type of intervention: pharmacological versus dietary supplements. C) Fixed versus flexible designs.
2. Design-related factors: A.) Study duration (in weeks). B) Target symptom of the study: associated symptoms versus not. C) Publication year. D) Duration of wash-out (in days). E) Use of placebo-lead in phase with exclusion of placebo responders. F) Type of informant: parent/caregiver versus clinician or teacher. G) Sample size. H) Number of sites and proportion of academic sites. I) Number of arms and medications. J) Percentage of participants on placebo. K) Sponsorship (at least one site industry funded, no donation alone) versus not industry funded. L) Risk of bias for each domain.
3. Participant-related factors: A. Degree of placebo response (when efficacy or drug response are the dependent variables). B. Mean age. C. US population versus not US or mixed populations. D. Baseline severity. E. Intellectual impairment

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Conflicts of interest
- In the last 3 years, Stefan Leucht has received honoraria for consulting or lectures from LB Pharma, Lundbeck, Otsuka, TEVA, LTS Lohmann, Geodon Richter, Recordati, Boehringer Ingelheim, Sandoz, Janssen, Lilly, SanofiAventis, Servier and Sunovion.
- David Fraguas has been a consultant and/or has received fees from Angelini, Eisai, IE4Lab, Janssen, Lundbeck, and Otsuka. He has also received grant support from Instituto de Salud Carlos III (Spanish Ministry of Science, Innovation and Universities) and from Fundación Alicia Koplowitz.
- Mara Parellada has received educational honoraria from Otsuka, research grants from FAK and Fundación Mutua Madrileña (FMM), Instituto de Salud Carlos III (Spanish Ministry of Science, Innovation and Universities) and European ERANET and H2020 calls, travel grants from Otsuka and Janssen. Consultant for Exeltis and Servier.

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2.2 Methods clarifications and post-hoc decisions

- Exclusion of combination, augmentation or multimodal treatments: We excluded interventions aiming to idenrtify treatment effects of augmentation, combination or multimodal treatments, e.g., risperidone + memantine, atomoxetine + parental training, vitamin-D + omega-3, vitamin-D + perceptual-motor exercises.
- Exclusion of low fixed-doses: In case of fixed-doses, we excluded a low dose arm of risperidone (≤0.175mg/day; smaller than 0.25mg/day initial recommended dose by FDA) [19] and of balovaptan (1.5mg/day; a dose with limited pharmacodynamic effects that was used to provide initial safety) [20]. Multiple dose arms of the same intervention were combined according to the Cochrane Handbook [2].
- Exclusion of studies with high risk of bias in the randomization process: According to our protocol, we included studies with a low or unclear risk of bias in the randomization process, and we excluded studies with a high risk of bias in randomization, in accordance to the Cochrane Handbook [13, 21]. Sequence generation and allocation concealment are both components of the randomization process and the associated selection bias [22]. Therefore, we excluded studies with a high risk of bias in sequence generation (e.g., allocation by the day of the week, clinical judgment, patient preferences, laboratory values, or any other method without a random component of allocation etc.) or allocation concealment (e.g. allocation by alternation, non-opaque envelopes, open table of random tables, allocation by an unblinded investigator) according to the risk of bias tool [21]. Studies with high risk of bias in one of these two domains could inflate effect-sizes in favor of the interventions, e.g. [23].

  We a priori included studies with unclear risk of bias in random sequence generation or allocation concealment. This decision is according to the standards of the Cochrane Handbook [21], and supported by evidence from meta-epidemiological studies, e.g., [24-27]. These meta-epidemiological studies suggested that poor reporting does not necessarily reflect the actual methods conducted in the trials. One large meta-epidemiological study of 429 RCTs (and their protocols) found that from the trials with adequate random sequence generation and acllocation concealment, only 59% and 25% of them reported the exact methods in their publications [27]. Similar results were found in an older meta-epidemiological study of 56 RCTs in radiation oncology, which found that despite all trials had adequate allocation concealment, only 42% of them reported the exact method in their papers [26]. Another meta-epidemiological study of 98 RCTs (published in 29 medical journals before 2002) found that about 96% of RCTs with unclear reporting of allocation concealment had indeed concealed allocation [24]. In a similar vein, another meta-epidemiological study of 40 RCTs (also published before 2002) in rheumatology, which found that 76% and 78% of the studies with unclear reporting in random sequence generation and allocation concealment had indeed adequate methods [25]. This meta-epidemiological study included also non-drug trials (32.5% of the sample) that accounted for most of the trials with inadequately performed randomization methods [25].

  Most the included trials in our meta-analysis were very recently published (median publication year of 2015, interquartile range [2008-2019]) and only a few studies were published before the CONSORT statement (1996). A meta-epidemiological study found that the methodology of RCTs in psychopharmacology has improved in the last sixty years, yet there may be a disconnection between improvement in methodology and adequate reporting of the methodology [28]. Nevertheless, we acknowledge that there could be a few studies with unclear risk of bias in random sequence generation or allocation concealment, which could have had inadequate randomization methods. Therefore, we excluded these studies in a post-

hoc sensitivity analysis, and the results did not materially change (see eAppendix-6.6., Figure-S4).

- Including data from unpublished studies: We aimed to include studies with unpublished data, e.g., by contacting authors or using data from trial registries, conference abstracts, presentations or reviews. When more than one sources of data were available, preference was given to data and clarifications provided by authors, clinical study reports, published manuscripts, trial registries or conference abstracts, presentations and other reviews.
- Extraction of descriptive characteristics: A) About descriptive characteristics (e.g., age, sex), we preferred as randomized data per arm, but we also used completers' data per arm, or data from the total sample. B) Baseline severity was inconsistently assessed and reported in trials. CGI-S and ABC-Irritability were used as measures of global severity and serious problem behaviors, as well as they were used in other meta-analyses as measures of baseline severity [29-31]. C) Transitivity assumption was investigated with the distribution of potential effect-modifiers across interventions. In the predefined list of potential effect-modifiers, mean age was added post-hoc. D) We classified studies as industry sponsored or linked to a patent application, when 1. the study was funded by the industry (irrespective if the analysis was conducted centrally by the sponsor or independently), 2. at least an author of the manuscript was an industry employee, 3. at least an author of the manuscript had applied for a patent on the use of the intervention (e.g., as reported in the conflicts of interests). A study that was funded by the state or academia was not considered as industry-sponsored. We did not consider conflicts of interest in the forms of consultation of speaker fees or if the industry provided or donated the medications for the study.
- Imputation of responder rates: We analysed responder rates as a secondary outcome, since they are easily interpretable in comparison to standardized mean changes. We used response as defined by at least much improvement in the CGI-I (CGI-I=1 or 2), which is a rather homogenous definition (despite the use of different anchors, as well as CGI-I was frequently used in clinical trials of autism [32, 33]. We imputed the number of responders from mean and standard deviations of CGI-I, when they were not reported, using and validated method [34, 35]. In the imputation, a threshold of 2.5 was used instead of 2 to impute responders from an assumed normal distribution of the continuous CGI-I. This artificial threshold wa used, since CGI-I is a categorical scale with 7-points, so that we assumed that a participant with a value of 2.5 or less in the assumed underlying normal distribution would have been considered as at least much improved [36].
- Extraction of mean and standard deviations from median/ranges and from pooling subscales: When only medians and ranges were reported, we estimated means and standard deviations as reported in Shi et al 2020 [37] . When subscale scores were reported instead of eligible total scores, we pooled means and standard deviations of the subscales assuming a correlation of 0.5 [38]. In a predefined sensitivity analysis, we excluded studies with imputed standard deviations [13, 39], including studies with estimated means and standard deviations from medians/ranges or studies in which subscales scores were pooled.
- Extraction of change scores: In our protocol, we preferred change scores to endpoint scores, yet endpoint scores were used when the former were not reported. Since we found large baseline imbalances in some studies, which could have inflated effect sizes when endpoint scores were used, we estimated change scores when both endpoint and baseline scores were provided using a correlation of 0.5 [40] (see eAppendix-6.1.2 for further explanation). Therefore, we used the following hierarchy: 1) reported change scores, 2) estimated change scores when endpoint and baseline scores were reported, 3) endpoint scores (when baseline scores were not reported). In a sensitivity analysis, we used a correlation of 0.25 and 0.75.

- Using odds ratios instead of relative risks: Odds ratios (OR) were post-hoc used instead of relative risks (RR), since there is more recent evidence that ORs have better mathematical properties and should be preferred in meta-analysis [41, 42]. Nevertheless, we conducted a sensitivity analysis using relative risks, and the results did not materially change (Figure-S4). In addition, Figures 2-4 present the effect sizes of each medication in comparison to placebo for the continuous (measured with SMDs) and dichotomous outcomes (measured with ORs). In order to increase interpretability, we converted ORs to SMDs using the formula in the Cochrane Handbook (SMD=ln(OR)/1.81)[2].
- Changes in sensitivity analysis and subgroup analysis: A) Due to the disproportionate number of studies to interventions, we investigated a priori defined subgroup analyses as sensitivity analyses, i.e., 1. excluding studies with associated symptoms as inclusion criteria, 2. excluding studies shorter than four weeks, 3. excluding studies with non-clinician ratings. Baseline severity could not be assessed due to inconsistent reporting and large diversity of scales. B) In a sensitivity analysis, we post-hoc excluded studies with an overall high risk of bias, instead of the predefined sensitivity analysis of excluding studies with a high or moderate risk of bias. Since an important number of studies were rated with a moderate risk of bias, their exclusion would have led to a not meaningful sensitivity analysis. Nevertheless, we discussed the presence of risk of bias and risk of bias was incorporated in CINeMA approach for the primary outcomes. C) In a post-hoc sensitivity analysis, we excluded studies from less developed countries or countries with less tradition in clinical research (i.e. Azerbaijan, China, Egypt, India, Indonesia, Iran, Turkey, Ukrania), since there is evidence that treatment effects are on average more favourable in less developed countries [43]. D) In a post-hoc sensitivity analysis suggested by a reviewer, we used ABC-L/SW for social-communication difficulties and ABC-S for repetitive behaviors. E) In a post-hoc sensitivity analysis, we excluded studies with an unclear description of random sequence generation or allocation concealment.

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eAppendix-3 Database search strategy

3.1 Electronic search

3.1.1 Multiple electronic database search on the 8th July 2018

We searched the following resources on the 8th July 2018 with no date/time, language, document type, and publication status limitations:

- ClinicalTrials.Gov (Until search date)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Until search date)
- EMBASE (1974 to 2018 week 28)
- MEDLINE (1946 – search date)
- PsycINFO (1806 to July week 1 2018)
- PubMed (1946 – search date)
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (Until search date)

We followed the Cochrane Handbook [1] and MECIR [2] for conducting the search, PRISMA guideline [3] for reporting the search, and PRESS checklist for peer-reviewing the search strategies [4]. Keywords and search concepts were collected through experts' opinion, existing recent survey[5], controlled vocabulary (APA Thesaurus, Medical Subject Headings = MeSH, and Excerpta Medica Tree = EMTREE), text mining using the Yale MeSH Analyzer [6], and reviewing the primary search results. In addition, we utilized the report from Canadian Agency for Drugs and Technologies in Health (CADTH) to focus the search employing EMTREE [7]. We used existing search filters such as Eisinga's animal search filter to remove the non-human search results in EMBASE [8] and Cochrane's Randomized Controlled Trials search filters for EMBASE, MEDLINE, and PubMed [1]. Because of poor reporting of outcomes in medical research [9-13], we did not limit the search adding specific outcomes so that we could have all the outcomes. Search strategies, developed by assistance of a medical information specialist, were reported in eAppendix-3.2. The duplicate search results were detected based on title match and deleted after approval through manual check in EndNote X8.

The search found 13,803 references. Removing 6,455 duplicate records, we screened 7,348 records.

3.1.2 PubMed update search on the 4th July 2019

An update search on PubMed was conducted on 4th July 2019. The search found 191 new records, which were screened.

3.1.3 PubMed update search on the 4th July 2020

An update search on PubMed was conducted on the 30th April 2020. The search found 158 records, which were screened.

3.1.4 PubMed and CENTRAL update search on the 31st August 2020

An update search on PubMed and CENTRAL was conducted on 31st August 2020. The search found 70 records in PubMed and 599 in CENTRAL, which were screened.

3.1.5 PubMed and CENTRAL update on the 17th September 2021

An update search on PubMed and CENTRAL was conducted on the 17th September 2021. The search found 315 records in PubMed and 126 in CENTRAL, which were screened.

3.1.6 PubMed and CENTRAL update on the 3rd November 2021

An update search on PubMed and CENTRAL was conducted on the 3rd November 2021. The search found 32 records in PubMed and 28 in CENTRAL, which were screened.

3.2. Search Strategies

3.2.1 ClinicalTrials.Gov

Advanced Search

Condition or Disease: Autism Spectrum Disorder OR Autistic Disorder OR Asperger Syndrome OR Rett Syndrome OR "Child Development Disorders, Pervasive" OR Childhood Disintegrative Disorder OR Hyperammonemia

Study Type: Interventional Studies (Clinical Trials)

3.2.2 Cochrane Central Register of Controlled Trials (CENTRAL)

([mh "Autistic Disorder"] OR [mh "Autism Spectrum Disorder"] OR [mh "Asperger Syndrome"] OR [mh "Rett Syndrome"] OR [mh "Child Development Disorders, Pervasive"] OR (Autis* OR Kanner* OR Asperger* OR "Pervasive Child Development Disorder" OR "Pervasive Child Development Disorders" OR "Pervasive Developmental Disorder" OR "Pervasive Developmental Disorders" OR "Pervasive Development Disorder" OR "Pervasive Development Disorders" OR "Childhood Disintegrative Disorder" OR "Childhood Disintegrative Disorders" OR Rett* OR "Cerebroatrophic Hyperammonemia" OR "Cerebroatrophic Hyperammonemias"):ti,ab) AND ([mh ^"Pharmaceutical Preparations"] OR [mh "Drug Combinations"] OR [mh "Drugs, Chinese Herbal"] OR [mh "Drugs, Essential"] OR [mh "Drugs, Generic"] OR [mh "Drugs, Investigational"] OR [mh "Nonprescription Drugs"] OR [mh "Plant Extracts"] OR [mh "Prescription Drugs"] OR [mh Prodrugs] OR [mh "Pharmacologic Actions"] OR [mh "Drug Therapy"] OR [mh "Therapeutic Uses"] OR [mh "Physiological Effects of Drugs"] OR [mh Aripiprazole] OR [mh Clozapine] OR [mh Haloperidol] OR [mh Loxapine] OR [mh "Lurasidone Hydrochloride"] OR [mh "Paliperidone Palmitate"] OR [mh "Quetiapine Fumarate"] OR [mh Risperidone] OR [mh Sulpiride] OR [mh Citalopram] OR [mh Clomipramine] OR [mh Desipramine] OR [mh Fluoxetine] OR [mh Fluvoxamine] OR [mh Imipramine] OR [mh Mianserin] OR [mh Nortriptyline] OR [mh Paroxetine] OR [mh Sertraline] OR [mh "Venlafaxine Hydrochloride"] OR [mh "Atomoxetine Hydrochloride"] OR [mh Dextromethorphan] OR [mh Fenfluramine] OR [mh "Lisdexamfetamine Dimesylate"] OR [mh "Lithium Carbonate"] OR [mh Methylphenidate] OR [mh "N-Methyl-3,4-methylenedioxyamphetamine"] OR [mh "Valproic Acid"] OR [mh Betahistine] OR [mh Bromocriptine] OR [mh Buspirone] OR [mh Cyproheptadine] OR [mh Famotidine] OR [mh Levodopa] OR [mh Sumatriptan] OR [mh Clonidine] OR [mh Guanfacine] OR [mh Dexmedetomidine] OR [mh Propranolol] OR [mh Acetylcysteine] OR [mh Amantadine] OR [mh Ketamine] OR [mh Memantine] OR [mh Riluzole] OR [mh Baclofen] OR [mh Bumetanide] OR [mh Flumazenil] OR [mh Galantamine] OR [mh Mecamylamine] OR [mh Pregnenolone] OR [mh Rivastigmine] OR [mh Varenicline] OR [mh Cannabidiol] OR [mh Celecoxib] OR [mh Everolimus] OR [mh "Fingolimod Hydrochloride"] OR [mh Fluconazole] OR [mh "Glatiramer Acetate"] OR ([mh Immunoglobulins] AND [mh "Administration, Oral"]) OR [mh Minocycline] OR [mh Naltrexone] OR [mh Pentoxifylline] OR [mh Sirolimus] OR [mh Staurosporine] OR [mh Suramin] OR [mh Tacrolimus] OR [mh "Insulin-Like Growth Factor I"] OR [mh "Adrenal Cortex Hormones"] OR [mh "Adrenocorticotropic Hormone"] OR [mh Angiotensins] OR [mh Carnitine] OR [mh "Diet Therapy"] OR [mh "Dietary Supplements"] OR [mh "Fatty Acids, Omega-3"] OR [mh "Gastrin-Releasing Peptide"] OR [mh Ghrelin] OR [mh Hydrocortisone] OR [mh Lovastatin] OR [mh Melanocortins] OR [mh Melatonin] OR [mh Metformin] OR [mh Minerals] OR [mh "Nutrition Therapy"] OR [mh Oligosaccharides] OR [mh Oxytocin] OR [mh Prednisone] OR [mh Probiotics] OR [mh Pyridoxine] OR [mh Secretin] OR [mh "Thyroid Hormones"] OR [mh Thyroxine] OR [mh Triiodothyronine] OR [mh Vasopressins] OR [mh "Vitamin E"] OR [mh "Arachidonic Acid"] OR [mh "Ascorbic Acid"] OR

[mh Carnosine] OR [mh "Docosahexaenoic Acids"] OR [mh "Folic Acid"] OR [mh "Ginkgo biloba"] OR [mh Glutathione] OR [mh Glutens] OR [mh Inositol] OR [mh Leucovorin] OR [mh Magnesium] OR [mh "Magnesium Oxide"] OR [mh Milk] OR [mh Papain] OR [mh Succimer] OR [mh "Vitamin B 12"] OR [mh "Vitamin B 6"] OR [mh "Vitamin D"] OR [mh "Adrenergic alpha-2 Receptor Antagonists"] OR [mh "Antidepressive Agents, Second-Generation"] OR [mh "Anti-Dyskinesia Agents"] OR [mh Antiemetics] OR [mh "Antipsychotic Agents"] OR [mh "Dopamine Agonists"] OR [mh "Dopamine Antagonists"] OR [mh "Dopamine D2 Receptor Antagonists"] OR [mh "GABA Antagonists"] OR [mh "Serotonin 5-HT2 Receptor Antagonists"] OR [mh "Serotonin Agents"] OR [mh "Serotonin Antagonists"] OR [mh "Serotonin Uptake Inhibitors"] OR [mh "Adrenergic alpha-Antagonists"] OR [mh "Adrenergic Uptake Inhibitors"] OR [mh "Cytochrome P-450 CYP1A2 Inhibitors"] OR [mh "Cytochrome P-450 CYP2C19 Inhibitors"] OR [mh "Cytochrome P-450 CYP2D6 Inhibitors"] OR [mh "Enzyme Inhibitors"] OR [mh "Histamine H1 Antagonists"] OR [mh "Serotonin and Noradrenaline Reuptake Inhibitors"] OR [mh "Anti-Anxiety Agents"] OR [mh "Antidepressive Agents"] OR [mh "Antidepressive Agents, Tricyclic"] OR [mh "Psychotropic Drugs"] OR [mh Anticonvulsants] OR [mh "Antimanic Agents"] OR [mh "Calcium Channel Blockers"] OR [mh "Central Nervous System Stimulants"] OR [mh "Cytochrome P-450 CYP3A Inducers"] OR [mh "Dopamine Uptake Inhibitors"] OR [mh "Excitatory Amino Acid Antagonists"] OR [mh "GABA Agents"] OR [mh Hallucinogens] OR [mh "Neuroprotective Agents"] OR [mh "Nootropic Agents"] OR [mh "Serotonin Receptor Agonists"] OR [mh "Voltage-Gated Sodium Channel Blockers"] OR [mh "Antiparkinson Agents"] OR [mh "Dopamine Agents"] OR [mh "Histamine Agonists"] OR [mh "Histamine H2 Antagonists"] OR [mh "Hormone Antagonists"] OR [mh "Serotonin 5-HT1 Receptor Agonists"] OR [mh "Adrenergic alpha-2 Receptor Agonists"] OR [mh "Adrenergic beta-Antagonists"] OR [mh Sympatholytics] OR [mh "Excitatory Amino Acid Agonists"] OR [mh "Cholinesterase Inhibitors"] OR [mh "GABA Modulators"] OR [mh "GABA-B Receptor Agonists"] OR [mh "Ganglionic Blockers"] OR [mh "Nicotinic Agonists"] OR [mh "Nicotinic Antagonists"] OR [mh Parasympathomimetics] OR [mh "Sodium Potassium Chloride Symporter Inhibitors"] OR [mh "14-alpha Demethylase Inhibitors"] OR [mh "Adjuvants, Immunologic"] OR [mh "Anti-Bacterial Agents"] OR [mh "Antifungal Agents"] OR [mh "Cannabinoid Receptor Agonists"] OR [mh "Cannabinoid Receptor Antagonists"] OR [mh "Cannabinoid Receptor Modulators"] OR [mh "Central Nervous System Agents"] OR [mh "Cyclooxygenase 2 Inhibitors"] OR [mh "Cytochrome P-450 CYP2C9 Inhibitors"] OR [mh "Immunologic Factors"] OR [mh "Immunosuppressive Agents"] OR [mh "Narcotic Antagonists"] OR [mh "Neurotransmitter Agents"] OR [mh "Purinergic Agents"] OR [mh "Anti-Inflammatory Agents"] OR [mh Antioxidants] OR [mh "Central Nervous System Depressants"] OR [mh "Chelating Agents"] OR [mh Hormones] OR [mh Oxytocics] OR [mh "Vitamin B Complex"] OR [mh Vitamins] OR (Anticonvuls* OR Antiepilep* OR Antipsychotic* OR Psychotropic* OR "Anti-Anxiety" OR Anxiolytic* OR Antidepress* OR "Pharmaco-Therapy" OR "Pharmaco-Therapies" OR Chemotherapy OR Chemotherapies OR Pharmacotherapy OR Pharmacotherapies OR "Pharmacological Interventions" OR "Pharmacological Intervention" OR "Pharmacological Treatment" OR "Pharmacological Treatments" OR "Drug Therapy" OR "Drug Therapies" OR Amisulpride OR Aripiprazol* OR Abilify OR Brexpiprazole OR Clozapine OR Clozaril OR Leponex OR Haloperidol OR Haldol OR Loxapine OR Lurasidone OR Latuda OR Olanzapine OR Zyprexa OR Paliperidone OR Invega OR Quetiapine OR Seroquel OR Risperidone OR Risperdal OR Risperidal OR Sertindole OR Sulpiride OR Dogmatil OR Ziprasidone OR Geodon OR Ziprazidone OR Agomelatine OR Citalopram OR Clomipramine OR Desipramine OR Escitalopram OR Fluoxetine OR Prozac OR Fluvoxamine OR Imipramine OR Mianserin OR Milnacipran OR Mirtazapine OR Nortriptyline OR Paroxetine OR Sertraline OR Tianeptine OR Tianeptine OR Venlafaxine OR "m-chlorophenylpiperazine" OR "m-CPP" OR "1-(3-chlorophenyl)piperazine" OR Atomoxetine OR Strattera OR Dextromethorphan OR Fenfluramine OR Lamotrigine OR Levetiracetam OR Lisdexamfetamine OR Lithium OR MDMA OR "N-Methyl-3,4-methylenedioxyamphetamine" OR Ecstasy OR Methylenedioxymethamphetamine OR Methylphenidate OR Ritalin* OR Oxcarbazepine OR Topiramate OR Valproic Acid OR Divalproex OR Valproate OR Divalproate OR "(+)-5-FPT" OR

"PRX-07034" OR Betahistin* OR Bromocriptine OR Buspirone OR Cyproheptadine OR Famotidine OR Levodopa OR "L-Dopa" OR "LP-211" OR "N-(4-cyanophenylmethyl)-4-(2-diphenyl)-1-piperazinehexanamide" OR Sumatriptan OR Volinanserin OR "M100907" OR Clonidine OR Guanfacine OR Dexmedetomidine OR Propranolol OR Acetylcysteine OR "ADX71149" OR "JNJ-40411813" OR "1-butyl-3-chloro-4-(4-phenyl-1-piperidinyl)-(1H)-pyridone" OR Amantadine OR "AZD8529" OR Basimglurant OR "2-chloro-4-(1-(4-fluorophenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl)pyridine" OR "CDPPB" OR "3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide" OR "CX516" OR "BDP 12" OR "1-(quinoxalin-6-ylcarbonyl)piperidine" OR "D-Cycloserine" OR Eglumetad OR Fenobam OR "GRN-529" OR Ketamine OR "LY 341495" OR "LY341495" OR "LY 379268" OR "LY379268" OR "LY 487379" OR "LY487379" OR Mavoglurant OR Memantine OR "MGS0039" OR "MPEP" OR "6-methyl-2-(phenylethynyl)pyridine" OR "MPX-004" OR "MPX-007" OR "MTEP" OR "NCFP" OR Riluzole OR "RO4491533" OR "TASP0433864" OR "A 867744" OR "4-(5-(4-chlorophenyl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide" OR Acamprosate OR "ADX71441" OR Arbaclofen OR "AZD7325" OR Baclofen OR Bumetanide OR "DMXB A" OR "DMXBA" OR "GTS 21" OR "3-(2,4-dimethoxybenzylidene)anabaseine" OR Donepezil OR "EVP-6124" OR "7-chloro-N-quinuclidin-3-yl-benzo(b)thiophene-2-carboxamide" OR Flumazenil OR Galantamin* OR Mecamylamine OR "PNU 120596" OR "PNU120596" OR "1-(5-chloro-2,4-dimethoxyphenyl)-3-(5-methylisoxazol-3-yl)urea" OR Pregnenolone OR Rivastigmine OR "SSR180711" OR Varenicline OR "AF38469" OR "AR-A014418" OR "N-(4-methoxybenzyl)-N'-(5-nitro-1,3-thiazol-2-yl)urea" OR Cannabidiol OR Cannabidivarin OR Celecoxib OR Everolimus OR Fingolimod OR Fluconazole OR Glatiramer OR Hydroxyfasudil OR Lenalidomide OR Minocycline OR Naltrexone OR "NVP-BKM120" OR Buparlisib OR "Oral Human Immunoglobulin" OR Pentoxifylline OR "SB 216763" OR "SB216763" OR Sirolimus OR Rapamycin OR Staurosporine OR Suramin OR Tacrolimus OR "TAK-242" OR "TAK242" OR Temsirolimus OR Tideglusib OR "NP031112" OR Amastatin OR Angiotensin* OR Carnitine OR Levocarnitine OR "CM-AT" OR "Diet Therapy" OR "Diet Therapies" OR "Dietary Supplements" OR "Dietary Supplement" OR Dimethylglycine OR "EPI-743" OR "alpha-Tocotrienol Quinone" OR "Food Supplement" OR "Food Supplements" OR "Gastrin-Releasing Peptide" OR Ghrelin OR "Herbal Supplement" OR "Herbal Supplements" OR Hormone* OR Corticosteroid* OR Corticoid* OR Hydrocortisone OR "IGF-1" OR "Insulin-Like Growth Factor I" OR Lovastatin OR Melanocortin* OR Melatonin OR Metformin OR Mineral* OR "NNZ-2566" OR "NNZ2566" OR "Nutrition Therapy" OR "Nutritional Therapy" OR Oligosaccharide* OR "Omega-3" OR "Omega3" OR "n-3 Fatty" OR "n-3 Polyunsaturated Fatty" OR "n-3 PUFA" OR "n3 PUFA" OR "n 3 Oils" OR "n 3 Oil" OR "n3 Fatty" OR "ORG-2766" OR Oxytocin OR Syntocinon OR Pioglitazone OR Prednisone OR Probiotic* OR Bifidobacter* OR Pyridoxine OR "RG7713" OR "Ro27 3225" OR Secretin OR Sulforaphane OR Sulforafan OR Tetrahydrobiopterin OR Sapropterin OR Thyroxine OR Triiodothyronine OR "T3" OR Trofinetide OR Vasopressin* OR Vitamin* OR "WAY-267464" OR "WAY267464" OR Arachidonic OR Arachidonate OR Ascorbic OR Ascorbate OR Carnosine OR Cyanocobalamin OR Cobalamin* OR Cobamide* OR Hydroxocobalamin OR Docosahexaenoic OR Docosahexaenoate OR Ferrous OR Folic OR Folate OR Ginkgo* OR Gingko* OR Ginko* OR Maidenhair OR Glutathione OR Gluten OR Inositol OR Leucovorin OR Folinic OR Magnesium OR Milk OR Papain OR Pepsin OR Pyridoxal OR Pyridoxamine OR Succimer OR Dimercaptosuccinic Acid OR DMSA OR "Trichuris Suis" OR Ubiquinol):ti,ab)
In Trials

3.2.3 EMBASE

1. Exp Autism/ OR "Asperger Syndrome"/ OR "Childhood Disintegrative Disorder"/ OR "Pervasive Developmental Disorder Not Otherwise Specified"/ OR "Rett Syndrome"/ OR (Autis* OR Kanner* OR Asperger* OR "Pervasive Child Development Disorder" OR "Pervasive Child Development Disorders" OR "Pervasive Developmental Disorder" OR "Pervasive

Developmental Disorders" OR "Pervasive Development Disorder" OR "Pervasive Development Disorders" OR "Childhood Disintegrative Disorder" OR "Childhood Disintegrative Disorders" OR Rett* OR "Cerebroatrophic Hyperammonemia" OR "Cerebroatrophic Hyperammonemias").ti,ab.

2. Exp "Chemicals And Drugs"/ OR Exp *Drug/ OR *Behind the Counter Drug/ OR *Chinese Drug/ OR *Essential Drug/ OR *Generic Drug/ OR *Long Acting Drug/ OR *New Drug/ OR *Non Prescription Drug/ OR *Orphan Drug/ OR *Prescription Drug/ OR *Prodrug/ OR *Short Acting Drug/ OR *Unclassified Drug/ OR *Unindexed Drug/ OR Exp *Medicinal Plant/ OR Exp *Plant Extract/ OR Exp "Drug Combination"/ OR Exp *Drug Therapy/ OR Exp *Drug Effect/ OR Aripiprazole/ OR Clozapine/ OR Haloperidol/ OR Loxapine/ OR Lurasidone/ OR Paliperidone/ OR Quetiapine/ OR Risperidone/ OR Sulpiride/ OR Citalopram/ OR Clomipramine/ OR Desipramine/ OR Fluoxetine/ OR Fluvoxamine/ OR Imipramine/ OR Mianserin/ OR Nortriptyline/ OR Paroxetine/ OR Sertraline/ OR Venlafaxine/ OR Atomoxetine/ OR Dextromethorphan/ OR Fenfluramine/ OR Lisdexamfetamine/ OR "Lithium Carbonate"/ OR Methylphenidate/ OR Midomafetamine/ OR "Valproic Acid"/ OR Betahistine/ OR Bromocriptine/ OR Buspirone/ OR Cyproheptadine/ OR Famotidine/ OR Levodopa/ OR Sumatriptan/ OR Clonidine/ OR Guanfacine/ OR Dexmedetomidine/ OR Propranolol/ OR Acetylcysteine/ OR Amantadine/ OR Ketamine/ OR Memantine/ OR Riluzole/ OR Baclofen/ OR Bumetanide/ OR Flumazenil/ OR Galantamine/ OR Mecamylamine/ OR Pregnenolone/ OR Rivastigmine/ OR Varenicline/ OR Cannabidiol/ OR Celecoxib/ OR Everolimus/ OR Fingolimod/ OR Fluconazole/ OR Glatiramer/ OR (Immunoglobulin/ AND "Oral Drug Administration"/) OR Minocycline/ OR Naltrexone/ OR Pentoxifylline/ OR Rapamycin/ OR Staurosporine/ OR Suramin/ OR Tacrolimus/ OR "Somatomedin C"/ OR Exp *Corticosteroid/ OR Corticotropin/ OR Exp *Angiotensin Derivative/ OR Carnitine/ OR Exp *Diet Therapy/ OR *Diet Supplementation/ OR "Omega 3 Fatty Acid"/ OR "Gastrin Releasing Peptide"/ OR Ghrelin/ OR Hydrocortisone/ OR Mevinolin/ OR Melanocortin/ OR Melatonin/ OR Metformin/ OR Mineral/ OR Exp *Oligosaccharide/ OR Oxytocin/ OR Prednisone/ OR Probiotic Agent/ OR Pyridoxine/ OR Secretin/ OR Thyroid Hormone/ OR Thyroxine/ OR Liothyronine/ OR Exp *Vasopressin Derivative/ OR "alpha Tocopherol"/ OR "Arachidonic Acid"/ OR "Ascorbic Acid"/ OR Carnosine/ OR "Docosahexaenoic Acid"/ OR "Folic Acid"/ OR "Ginkgo biloba"/ OR Glutathione/ OR Gluten/ OR Inositol/ OR Folinic Acid/ OR Magnesium/ OR "Magnesium Oxide"/ OR Milk/ OR Papain/ OR Succimer/ OR Cyanocobalamin/ OR Pyridoxine/ OR "Vitamin D"/ OR Exp "alpha 2 Adrenergic Receptor Blocking Agent"/ OR Exp "Antidepressant Agent"/ OR Exp "Antiparkinson Agent"/ OR Exp "Antiemetic Agent"/ OR Exp "Neuroleptic Agent"/ OR Exp "Dopamine Receptor Stimulating Agent"/ OR Exp "Dopamine Receptor Blocking Agent"/ OR Exp "Dopamine 2 Receptor Blocking Agent"/ OR Exp "4 Aminobutyric Acid Receptor Blocking Agent"/ OR Exp "Serotonin 2 Antagonist"/ OR Exp "Serotonin Receptor Affecting Agent"/ OR Exp "Serotonin Antagonist"/ OR Exp "Serotonin Uptake Inhibitor"/ OR Exp "alpha Adrenergic Receptor Blocking Agent"/ OR Exp "Adrenergic Receptor Affecting Agent"/ OR Exp "Cytochrome P450 1A2 Inhibitor"/ OR Exp "Cytochrome P450 2C19 Inhibitor"/ OR Exp "Cytochrome P450 2D6 Inhibitor"/ OR Exp "Enzyme Inhibitor"/ OR Exp "Histamine H1 Receptor Antagonist"/ OR Exp Noradrenalin Uptake Inhibitor/ OR Exp "Serotonin Uptake Inhibitor"/ OR Exp "Anxiolytic Agent"/ OR Exp "Tricyclic Antidepressant Agent"/ OR Exp "Psychotropic Agent"/ OR Exp "Anticonvulsive Agent"/ OR Exp Tranquilizer/ OR Exp "Calcium Channel Blocking Agent"/ OR Exp "Central Stimulant Agent"/ OR Exp "Cytochrome P450 3A Inducer"/ OR Exp "Dopamine Uptake Inhibitor"/ OR Exp "Amino Acid Receptor Blocking Agent"/ OR Exp "GABAergic Receptor Affecting Agent"/ OR Exp "Psychedelic Agent"/ OR Exp "Neuroprotective Agent"/ OR Exp "Nootropic Agent"/ OR Exp "Serotonin Agonist"/ OR Exp "Voltage Gated Sodium Channel Blocking Agent"/ OR Exp "Histamine Agonist"/ OR Exp "Histamine H2 Receptor Antagonist"/ OR Exp "Hormone Antagonist"/ OR Exp "Serotonin 1 Agonist"/ OR Exp "alpha 2 Adrenergic Receptor Stimulating Agent"/ OR Exp "beta Adrenergic Receptor Blocking Agent"/ OR Exp "Adrenergic Receptor Blocking Agent"/ OR Exp "Amino

Acid Receptor Stimulating Agent"/ OR Exp "Cholinesterase Inhibitor"/ OR Exp "Benzodiazepine Receptor Affecting Agent"/ OR Exp "4 Aminobutyric Acid B Receptor Stimulating Agent"/ OR Exp "Ganglion Blocking Agent"/ OR Exp "Nicotinic Agent"/ OR Exp "Nicotinic Receptor Blocking Agent"/ OR Exp "Cholinergic Receptor Stimulating Agent"/ OR Exp "Loop Diuretic Agent"/ OR Exp "Sterol 14alpha Demethylase Inhibitor"/ OR Exp "Immunological Adjuvant"/ OR Exp "Antiinfective Agent"/ OR Exp "Antifungal Agent"/ OR Exp "Cannabinoid Receptor Agonist"/ OR Exp "Cannabinoid Receptor Antagonist"/ OR Exp "Cannabinoid Receptor Affecting Agent"/ OR Exp "Central Nervous System Agents"/ OR Exp "Cyclooxygenase 2 Inhibitor"/ OR Exp "Cytochrome P450 2C9 Inhibitor"/ OR Exp "Immunologic Factor"/ OR Exp "Immunosuppressive Agent"/ OR Exp "Narcotic Antagonist"/ OR Exp "Agents Interacting With Transmitter, Hormone OR Drug Receptors"/ OR Exp "Purinergic Receptor Affecting Agent"/ OR Exp "Antiinflammatory Agent"/ OR Exp Antioxidant/ OR Exp "Central Depressant Agent"/ OR Exp "Chelating Agent"/ OR Exp Hormone/ OR Exp "Oxytocic Agent"/ OR Exp "Vitamin B Complex"/ OR Exp Vitamin/ OR (Anticonvuls* OR Antiepilep* OR Antipsychotic* OR Psychotropic* OR "Anti-Anxiety" OR Anxiolytic* OR Antidepress* OR "Pharmaco-Therapy" OR "Pharmaco-Therapies" OR Chemotherapy OR Chemotherapies OR Pharmacotherapy OR Pharmacotherapies OR "Pharmacological Interventions" OR "Pharmacological Intervention" OR "Pharmacological Treatment" OR "Pharmacological Treatments" OR "Drug Therapy" OR "Drug Therapies" OR Amisulpride OR Aripiprazol* OR Abilify OR Brexpiprazole OR Clozapine OR Clozaril OR Leponex OR Haloperidol OR Haldol OR Loxapine OR Lurasidone OR Latuda OR Olanzapine OR Zyprexa OR Paliperidone OR Invega OR Quetiapine OR Seroquel OR Risperidone OR Risperdal OR Risperidal OR Sertindole OR Sulpiride OR Dogmatil OR Ziprasidone OR Geodon OR Ziprazidone OR Agomelatine OR Citalopram OR Clomipramine OR Desipramine OR Escitalopram OR Fluoxetine OR Prozac OR Fluvoxamine OR Imipramine OR Mianserin OR Milnacipran OR Mirtazapine OR Nortriptyline OR Paroxetine OR Sertraline OR Tianeptine OR Tianeptine OR Venlafaxine OR "m-chlorophenylpiperazine" OR "m-CPP" OR "1-(3-chlorophenyl)piperazine" OR Atomoxetine OR Strattera OR Dextromethorphan OR Fenfluramine OR Lamotrigine OR Levetiracetam OR Lisdexamfetamine OR Lithium OR MDMA OR "N-Methyl-3,4-methylenedioxyamphetamine" OR Ecstasy OR Methylenedioxymethamphetamine OR Methylphenidate OR Ritalin* OR Oxcarbazepine OR Topiramate OR Valproic Acid OR Divalproex OR Valproate OR Divalproate OR "(+)-5-FPT" OR "PRX-07034" OR Betahistin* OR Bromocriptine OR Buspirone OR Cyproheptadine OR Famotidine OR Levodopa OR "L-Dopa" OR "LP-211" OR "N-(4-cyanophenylmethyl)-4-(2-diphenyl)-1-piperazinehexanamide" OR Sumatriptan OR Volinanserin OR "M100907" OR Clonidine OR Guanfacine OR Dexmedetomidine OR Propanolol OR Acetylcysteine OR "ADX71149" OR "JNJ-40411813" OR "1-butyl-3-chloro-4-(4-phenyl-1-piperidinyl)-(1H)-pyridone" OR Amantadine OR "AZD8529" OR Basimglurant OR "2-chloro-4-(1-(4-fluorophenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl)pyridine" OR "CDPPB" OR "3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide" OR "CX516" OR "BDP 12" OR "1-(quinoxalin-6-ylcarbonyl)piperidine" OR "D-Cycloserine" OR Eglumetad OR Fenobam OR "GRN-529" OR Ketamine OR "LY 341495" OR "LY341495" OR "LY 379268" OR "LY379268" OR "LY 487379" OR "LY487379" OR Mavoglurant OR Memantine OR "MGS0039" OR "MPEP" OR "6-methyl-2-(phenylethynyl)pyridine" OR "MPX-004" OR "MPX-007" OR "MTEP" OR "NCFP" OR Riluzole OR "RO4491533" OR "TASP0433864" OR "A 867744" OR "4-(5-(4-chlorophenyl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide" OR Acamprosate OR "ADX71441" OR Arbaclofen OR "AZD7325" OR Baclofen OR Bumetanide OR "DMXB A" OR "DMXBA" OR "GTS 21" OR "3-(2,4-dimethoxybenzylidene)anabaseine" OR Donepezil OR "EVP-6124" OR "7-chloro-N-quinuclidin-3-yl-benzo(b)thiophene-2-carboxamide" OR Flumazenil OR Galantamin* OR Mecamylamine OR "PNU 120596" OR "PNU120596" OR "1-(5-chloro-2,4-dimethoxyphenyl)-3-(5-methylisoxazol-3-yl)urea" OR Pregnenolone OR Rivastigmine OR "SSR180711" OR Varenicline OR "AF38469" OR "AR-A014418" OR "N-(4-methoxybenzyl)-

N'-(5-nitro-1,3-thiazol-2-yl)urea" OR Cannabidiol OR Cannabidivarin OR Celecoxib OR Everolimus OR Fingolimod OR Fluconazole OR Glatiramer OR Hydroxyfasudil OR Lenalidomide OR Minocycline OR Naltrexone OR "NVP-BKM120" OR Buparlisib OR "Oral Human Immunoglobulin" OR Pentoxifylline OR "SB 216763" OR "SB216763" OR Sirolimus OR Rapamycin OR Staurosporine OR Suramin OR Tacrolimus OR "TAK-242" OR "TAK242" OR Temsirolimus OR Tideglusib OR "NP031112" OR Amastatin OR Angiotensin* OR Carnitine OR Levocarnitine OR "CM-AT" OR "Diet Therapy" OR "Diet Therapies" OR "Dietary Supplements" OR "Dietary Supplement" OR Dimethylglycine OR "EPI-743" OR "alpha-Tocotrienol Quinone" OR "Food Supplement" OR "Food Supplements" OR "Gastrin-Releasing Peptide" OR Ghrelin OR "Herbal Supplement" OR "Herbal Supplements" OR Hormone* OR Corticosteroid* OR Corticoid* OR Hydrocortisone OR "IGF-1" OR "Insulin-Like Growth Factor I" OR Lovastatin OR Melanocortin* OR Melatonin OR Metformin OR Mineral* OR "NNZ-2566" OR "NNZ2566" OR "Nutrition Therapy" OR "Nutritional Therapy" OR Oligosaccharide* OR "Omega-3" OR "Omega3" OR "n-3 Fatty" OR "n-3 Polyunsaturated Fatty" OR "n-3 PUFA" OR "n3 PUFA" OR "n 3 Oils" OR "n 3 Oil" OR "n3 Fatty" OR "ORG-2766" OR Oxytocin OR Syntocinon OR Pioglitazone OR Prednisone OR Probiotic* OR Bifidobacter* OR Pyridoxine OR "RG7713" OR "Ro27 3225" OR Secretin OR Sulforaphane OR Sulforafan OR Tetrahydrobiopterin OR Sapropterin OR Thyroxine OR Triiodothyronine OR "T3" OR Trofinetide OR Vasopressin* OR Vitamin* OR "WAY-267464" OR "WAY267464" OR Arachidonic OR Arachidonate OR Ascorbic OR Ascorbate OR Carnosine OR Cyanocobalamin OR Cobalamin* OR Cobamide* OR Hydroxocobalamin OR Docosahexaenoic OR Docosahexaenoate OR Ferrous OR Folic OR Folate OR Ginkgo* OR Gingko* OR Ginko* OR Maidenhair OR Glutathione OR Gluten OR Inositol OR Leucovorin OR Folinic OR Magnesium OR Milk OR Papain OR Pepsin OR Pyridoxal OR Pyridoxamine OR Succimer OR Dimercaptosuccinic Acid OR DMSA OR "Trichuris Suis" OR Ubiquinol).ti,ab.
3. Crossover Procedure/ OR Double Blind Procedure/ OR Randomized Controlled Trial/ OR Single Blind Procedure/ OR (Random* OR Factorial* OR Crossover* OR "Cross Over*" OR Placebo* OR (Doubl* adj Blind*) OR (Singl* adj Blind*) OR Assign* OR Allocat* OR Volunteer*).ti,ab.
4. 1 AND 2 AND 3
5. Exp Animals/ OR Exp Invertebrate/ OR Animal Experiment/ OR Animal Model/ OR Animal Tissue/ OR Animal Cell/ OR Nonhuman/
6. Human/ OR Normal Human/ OR Human Cell/
7. 5 AND 6
8. 5 NOT 7
9. 4 NOT 8

3.2.4 MEDLINE

1. "Autistic Disorder"/ OR "Autism Spectrum Disorder"/ OR "Asperger Syndrome"/ OR "Rett Syndrome"/ OR "Child Development Disorders, Pervasive"/ OR (Autis* OR Kanner* OR Asperger* OR "Pervasive Child Development Disorder" OR "Pervasive Child Development Disorders" OR "Pervasive Developmental Disorder" OR "Pervasive Developmental Disorders" OR "Pervasive Development Disorder" OR "Pervasive Development Disorders" OR "Childhood Disintegrative Disorder" OR "Childhood Disintegrative Disorders" OR Rett* OR "Cerebroatrophic Hyperammonemia" OR "Cerebroatrophic Hyperammonemias").ti,ab.
2. "Pharmaceutical Preparations"/ OR Exp "Drug Combinations"/ OR "Drugs, Chinese Herbal"/ OR "Drugs, Essential"/ OR "Drugs, Generic"/ OR "Drugs, Investigational"/ OR Exp "Nonprescription Drugs"/ OR Exp "Plant Extracts"/ OR "Prescription Drugs"/ OR Prodrugs/ OR "Pharmacologic Actions"/ OR Exp "Pharmacological Actions (Non MeSH)"/ OR Exp "Drug Therapy"/ OR Exp "Therapeutic Uses"/ OR Exp "Physiological Effects of Drugs"/ OR Aripiprazole/ OR Clozapine/ OR Haloperidol/ OR Loxapine/ OR "Lurasidone Hydrochloride"/ OR "Paliperidone Palmitate"/ OR "Quetiapine Fumarate"/ OR Risperidone/ OR Sulpiride/ OR

Citalopram/ OR Clomipramine/ OR Desipramine/ OR Fluoxetine/ OR Fluvoxamine/ OR Imipramine/ OR Mianserin/ OR Nortriptyline/ OR Paroxetine/ OR Sertraline/ OR "Venlafaxine Hydrochloride"/ OR "Atomoxetine Hydrochloride"/ OR Dextromethorphan/ OR Fenfluramine/ OR "Lisdexamfetamine Dimesylate"/ OR "Lithium Carbonate"/ OR Methylphenidate/ OR "N-Methyl-3,4-methylenedioxyamphetamine"/ OR "Valproic Acid"/ OR Betahistine/ OR Bromocriptine/ OR Buspirone/ OR Cyproheptadine/ OR Famotidine/ OR Levodopa/ OR Sumatriptan/ OR Clonidine/ OR Guanfacine/ OR Dexmedetomidine/ OR Propranolol/ OR Acetylcysteine/ OR Amantadine/ OR Ketamine/ OR Memantine/ OR Riluzole/ OR Baclofen/ OR Bumetanide/ OR Flumazenil/ OR Galantamine/ OR Mecamylamine/ OR Pregnenolone/ OR Rivastigmine/ OR Varenicline/ OR Cannabidiol/ OR Celecoxib/ OR Everolimus/ OR "Fingolimod Hydrochloride"/ OR Fluconazole/ OR "Glatiramer Acetate"/ OR (Immunoglobulins/ AND "Administration, Oral"/) OR Minocycline/ OR Naltrexone/ OR Pentoxifylline/ OR Sirolimus/ OR Staurosporine/ OR Suramin/ OR Tacrolimus/ OR "Insulin-Like Growth Factor I"/ OR "Adrenal Cortex Hormones"/ OR "Adrenocorticotropic Hormone"/ OR Angiotensins/ OR Carnitine/ OR "Diet Therapy"/ OR "Dietary Supplements"/ OR "Fatty Acids, Omega-3"/ OR "Gastrin-Releasing Peptide"/ OR Ghrelin/ OR Hydrocortisone/ OR Lovastatin/ OR Melanocortins/ OR Melatonin/ OR Metformin/ OR Minerals/ OR "Nutrition Therapy"/ OR Oligosaccharides/ OR Oxytocin/ OR Prednisone/ OR Probiotics/ OR Pyridoxine/ OR Secretin/ OR "Thyroid Hormones"/ OR Thyroxine/ OR Triiodothyronine/ OR Vasopressins/ OR "Vitamin E"/ OR "Arachidonic Acid"/ OR "Ascorbic Acid"/ OR Carnosine/ OR "Docosahexaenoic Acids"/ OR "Folic Acid"/ OR "Ginkgo biloba"/ OR Glutathione/ OR Glutens/ OR Inositol/ OR Leucovorin/ OR Magnesium/ OR "Magnesium Oxide"/ OR Milk/ OR Papain/ OR Succimer/ OR "Vitamin B 12"/ OR "Vitamin B 6"/ OR "Vitamin D"/ OR "Adrenergic alpha-2 Receptor Antagonists"/ OR "Antidepressive Agents, Second-Generation"/ OR "Anti-Dyskinesia Agents"/ OR Antiemetics/ OR "Antipsychotic Agents"/ OR "Dopamine Agonists"/ OR "Dopamine Antagonists"/ OR "Dopamine D2 Receptor Antagonists"/ OR "GABA Antagonists"/ OR "Serotonin 5-HT2 Receptor Antagonists"/ OR "Serotonin Agents"/ OR "Serotonin Antagonists"/ OR "Serotonin Uptake Inhibitors"/ OR "Adrenergic alpha-Antagonists"/ OR "Adrenergic Uptake Inhibitors"/ OR "Cytochrome P-450 CYP1A2 Inhibitors"/ OR "Cytochrome P-450 CYP2C19 Inhibitors"/ OR "Cytochrome P-450 CYP2D6 Inhibitors"/ OR "Enzyme Inhibitors"/ OR "Histamine H1 Antagonists"/ OR "Serotonin and Noradrenaline Reuptake Inhibitors"/ OR "Anti-Anxiety Agents"/ OR "Antidepressive Agents"/ OR "Antidepressive Agents, Tricyclic"/ OR "Psychotropic Drugs"/ OR Anticonvulsants/ OR "Antimanic Agents"/ OR "Calcium Channel Blockers"/ OR "Central Nervous System Stimulants"/ OR "Cytochrome P-450 CYP3A Inducers"/ OR "Dopamine Uptake Inhibitors"/ OR "Excitatory Amino Acid Antagonists"/ OR "GABA Agents"/ OR Hallucinogens/ OR "Neuroprotective Agents"/ OR "Nootropic Agents"/ OR "Serotonin Receptor Agonists"/ OR "Voltage-Gated Sodium Channel Blockers"/ OR "Antiparkinson Agents"/ OR "Dopamine Agents"/ OR "Histamine Agonists"/ OR "Histamine H2 Antagonists"/ OR "Hormone Antagonists"/ OR "Serotonin 5-HT1 Receptor Agonists"/ OR "Adrenergic alpha-2 Receptor Agonists"/ OR "Adrenergic beta-Antagonists"/ OR Sympatholytics/ OR "Excitatory Amino Acid Agonists"/ OR "Cholinesterase Inhibitors"/ OR "GABA Modulators"/ OR "GABA-B Receptor Agonists"/ OR "Ganglionic Blockers"/ OR "Nicotinic Agonists"/ OR "Nicotinic Antagonists"/ OR Parasympathomimetics/ OR "Sodium Potassium Chloride Symporter Inhibitors"/ OR "14-alpha Demethylase Inhibitors"/ OR "Adjuvants, Immunologic"/ OR "Anti-Bacterial Agents"/ OR "Antifungal Agents"/ OR "Cannabinoid Receptor Agonists"/ OR "Cannabinoid Receptor Antagonists"/ OR "Cannabinoid Receptor Modulators"/ OR "Central Nervous System Agents"/ OR "Cyclooxygenase 2 Inhibitors"/ OR "Cytochrome P-450 CYP2C9 Inhibitors"/ OR "Immunologic Factors"/ OR "Immunosuppressive Agents"/ OR "Narcotic Antagonists"/ OR "Neurotransmitter Agents"/ OR "Purinergic Agents"/ OR "Anti-Inflammatory Agents"/ OR Antioxidants/ OR "Central Nervous System Depressants"/ OR "Chelating Agents"/ OR Hormones/ OR Oxytocics/ OR "Vitamin B Complex"/ OR Vitamins/ OR "Diet Therapy".sh. OR (Brexpiprazole OR Olanzapine OR

Sertindole OR Ziprasidone OR Agomelatine OR Milnacipran OR Mirtazapine OR Tianeptine OR Tianeptine OR "1-(3-chlorophenyl)piperazine" OR Lamotrigine OR Levetiracetam OR Oxcarbazepine OR Topiramate OR "N-(4-cyanophenylmethyl)-4-(2-diphenyl)-1-piperazinehexanamide" OR Volinanserin OR "1-(quinoxalin-6-ylcarbonyl)piperidine" OR "1-butyl-3-chloro-4-(4-phenyl-1-piperidinyl)-(1H)-pyridone" OR "2-((4-tert-butylphenoxy)methyl)-5-methyl-2,3-dihydroimidazo(2,1-b)(1,3)oxazole-6-carboxamide" OR "2-amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo(3.1.0)hexane-2,6-dicarboxylic acid" OR "2-chloro-4-(1-(4-fluorophenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl)pyridine" OR "3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide" OR "4-(3-(2,6-dimethylpyridin-4-yl)phenyl)-7-methyl-8-trifluoromethyl-1,3-dihydrobenzo(b)(1,4)diazepin-2-one" OR "6-methyl-2-(phenylethynyl)pyridine" OR "AZD8529" OR Eglumetad OR Fenobam OR "GRN-529" OR "LY 341495" OR "LY 379268" OR Mavoglurant OR "MPX-004" OR "MPX-007" OR "N-(4-(2-methoxyphenoxy)phenyl)-N-(2,2,2-trifluoroethylsulfonyl)pyrid-3-ylmethylamine" OR "1-(5-chloro-2,4-dimethoxyphenyl)-3-(5-methylisoxazol-3-yl)urea" OR "3-(2,4-dimethoxybenzylidene)anabaseine" OR "4-(5-(4-chlorophenyl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide" OR "4-amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide" OR "7-chloro-N-quinuclidin-3-yl-benzo(b)thiophene-2-carboxamide" OR Acamprosate OR "ADX71441" OR "Arbaclofen Placarbil" OR Donepezil OR "SSR180711" OR "ethyl 6-(N-(2-chloro-4-fluorophenyl)sulfamoyl)cyclohex-1-ene-1-carboxylate" OR "N-(4-methoxybenzyl)-N'-(5-nitro-1,3-thiazol-2-yl)urea" OR "AF38469" OR Cannabidivarin OR Hydroxyfasudil OR Lenalidomide OR "NVP-BKM120" OR "SB 216763" OR Temsirolimus OR "NP 031112" OR "(6-chloro-1-(2-(dimethylamino)ethyl)indol-3-yl)-spiro(1H-isobenzofuran-3,4'-piperidine)-1'-yl-methanone" OR "4-(3,5-dihydroxybenzyl)-N-(2-methyl-4-((1-methyl-4,10-dihydropyrazolo(3,4-b)(1,5)benzodiazepin-5(1H)-yl)carbonyl)benzyl)piperazine-1-carboxamide" OR "alpha-tocotrienol quinone" OR "butir-His-Phe-Arg-Trp-Sar-NH2" OR Amastatin OR Dimethylglycine OR "NNZ 2566" OR "ORG 2766" OR Pioglitazone OR Sapropterin OR Sulforafan OR "Ferrous Sulfate" OR Ubiquinol).rn. OR (Anticonvuls* OR Antiepilep* OR Antipsychotic* OR Psychotropic* OR "Anti-Anxiety" OR Anxiolytic* OR Antidepress* OR "Pharmaco-Therapy" OR "Pharmaco-Therapies" OR Chemotherapy OR Chemotherapies OR Pharmacotherapy OR Pharmacotherapies OR "Pharmacological Interventions" OR "Pharmacological Intervention" OR "Pharmacological Treatment" OR "Pharmacological Treatments" OR "Drug Therapy" OR "Drug Therapies" OR Amisulpride OR Aripiprazol* OR Abilify OR Brexpiprazole OR Clozapine OR Clozaril OR Leponex OR Haloperidol OR Haldol OR Loxapine OR Lurasidone OR Latuda OR Olanzapine OR Zyprexa OR Paliperidone OR Invega OR Quetiapine OR Seroquel OR Risperidone OR Risperdal OR Risperidal OR Sertindole OR Sulpiride OR Dogmatil OR Ziprasidone OR Geodon OR Ziprazidone OR Agomelatine OR Citalopram OR Clomipramine OR Desipramine OR Escitalopram OR Fluoxetine OR Prozac OR Fluvoxamine OR Imipramine OR Mianserin OR Milnacipran OR Mirtazapine OR Nortriptyline OR Paroxetine OR Sertraline OR Tianeptine OR Tianeptine OR Venlafaxine OR "m-chlorophenylpiperazine" OR "m-CPP" OR "1-(3-chlorophenyl)piperazine" OR Atomoxetine OR Strattera OR Dextromethorphan OR Fenfluramine OR Lamotrigine OR Levetiracetam OR Lisdexamfetamine OR Lithium OR MDMA OR "N-Methyl-3,4-methylenedioxyamphetamine" OR Ecstasy OR Methylenedioxymethamphetamine OR Methylphenidate OR Ritalin* OR Oxcarbazepine OR Topiramate OR Valproic Acid OR Divalproex OR Valproate OR Divalproate OR "(+)-5-FPT" OR "PRX-07034" OR Betahistin* OR Bromocriptine OR Buspirone OR Cyproheptadine OR Famotidine OR Levodopa OR "L-Dopa" OR "LP-211" OR "N-(4-cyanophenylmethyl)-4-(2-diphenyl)-1-piperazinehexanamide" OR Sumatriptan OR Volinanserin OR "M100907" OR Clonidine OR Guanfacine OR Dexmedetomidine OR Propranolol OR Acetylcysteine OR "ADX71149" OR "JNJ-40411813" OR "1-butyl-3-chloro-4-(4-phenyl-1-piperidinyl)-(1H)-pyridone" OR Amantadine OR "AZD8529" OR Basimglurant OR "2-chloro-4-(1-(4-fluorophenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl)pyridine" OR "CDPPB" OR "3-cyano-N-

(1,3-diphenyl-1H-pyrazol-5-yl)benzamide" OR "CX516" OR "BDP 12" OR "1-(quinoxalin-6-ylcarbonyl)piperidine" OR "D-Cycloserine" OR Eglumetad OR Fenobam OR "GRN-529" OR Ketamine OR "LY 341495" OR "LY341495" OR "LY 379268" OR "LY379268" OR "LY 487379" OR "LY487379" OR Mavoglurant OR Memantine OR "MGS0039" OR "MPEP" OR "6-methyl-2-(phenylethynyl)pyridine" OR "MPX-004" OR "MPX-007" OR "MTEP" OR "NCFP" OR Riluzole OR "RO4491533" OR "TASP0433864" OR "A 867744" OR "4-(5-(4-chlorophenyl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide" OR Acamprosate OR "ADX71441" OR Arbaclofen OR "AZD7325" OR Baclofen OR Bumetanide OR "DMXB A" OR "DMXBA" OR "GTS 21" OR "3-(2,4-dimethoxybenzylidene)anabaseine" OR Donepezil OR "EVP-6124" OR "7-chloro-N-quinuclidin-3-yl-benzo(b)thiophene-2-carboxamide" OR Flumazenil OR Galantamin* OR Mecamylamine OR "PNU 120596" OR "PNU120596" OR "1-(5-chloro-2,4-dimethoxyphenyl)-3-(5-methylisoxazol-3-yl)urea" OR Pregnenolone OR Rivastigmine OR "SSR180711" OR Varenicline OR "AF38469" OR "AR-A014418" OR "N-(4-methoxybenzyl)-N'-(5-nitro-1,3-thiazol-2-yl)urea" OR Cannabidiol OR Cannabidivarin OR Celecoxib OR Everolimus OR Fingolimod OR Fluconazole OR Glatiramer OR Hydroxyfasudil OR Lenalidomide OR Minocycline OR Naltrexone OR "NVP-BKM120" OR Buparlisib OR "Oral Human Immunoglobulin" OR Pentoxifylline OR "SB 216763" OR "SB216763" OR Sirolimus OR Rapamycin OR Staurosporine OR Suramin OR Tacrolimus OR "TAK-242" OR "TAK242" OR Temsirolimus OR Tideglusib OR "NP031112" OR Amastatin OR Angiotensin* OR Carnitine OR Levocarnitine OR "CM-AT" OR "Diet Therapy" OR "Diet Therapies" OR "Dietary Supplements" OR "Dietary Supplement" OR Dimethylglycine OR "EPI-743" OR "alpha-Tocotrienol Quinone" OR "Food Supplement" OR "Food Supplements" OR "Gastrin-Releasing Peptide" OR Ghrelin OR "Herbal Supplement" OR "Herbal Supplements" OR Hormone* OR Corticosteroid* OR Corticoid* OR Hydrocortisone OR "IGF-1" OR "Insulin-Like Growth Factor I" OR Lovastatin OR Melanocortin* OR Melatonin OR Metformin OR Mineral* OR "NNZ-2566" OR "NNZ2566" OR "Nutrition Therapy" OR "Nutritional Therapy" OR Oligosaccharide* OR "Omega-3" OR "Omega3" OR "n-3 Fatty" OR "n-3 Polyunsaturated Fatty" OR "n-3 PUFA" OR "n3 PUFA" OR "n 3 Oils" OR "n 3 Oil" OR "n3 Fatty" OR "ORG-2766" OR Oxytocin OR Syntocinon OR Pioglitazone OR Prednisone OR Probiotic* OR Bifidobacter* OR Pyridoxine OR "RG7713" OR "Ro27 3225" OR Secretin OR Sulforaphane OR Sulforafan OR Tetrahydrobiopterin OR Sapropterin OR Thyroxine OR Triiodothyronine OR "T3" OR Trofinetide OR Vasopressin* OR Vitamin* OR "WAY-267464" OR "WAY267464" OR Arachidonic OR Arachidonate OR Ascorbic OR Ascorbate OR Carnosine OR Cyanocobalamin OR Cobalamin* OR Cobamide* OR Hydroxocobalamin OR Docosahexaenoic OR Docosahexaenoate OR Ferrous OR Folic OR Folate OR Ginkgo* OR Gingko* OR Ginko* OR Maidenhair OR Glutathione OR Gluten OR Inositol OR Leucovorin OR Folinic OR Magnesium OR Milk OR Papain OR Pepsin OR Pyridoxal OR Pyridoxamine OR Succimer OR Dimercaptosuccinic Acid OR DMSA OR "Trichuris Suis" OR Ubiquinol).ti,ab.

3. Randomized Controlled Trial.pt. OR Controlled Clinical Trial.pt. OR (Randomi?ed OR Placebo OR Randomly OR Trial OR Groups).ti,ab. OR Drug Therapy.fs. NOT (Exp Animals/ NOT Humans.sh.)
4. 1 AND 2 AND 3

3.2.5 PsycINFO

1. Autism Spectrum Disorders/ OR Rett Syndrome/ OR (Autis* OR Kanner* OR Asperger* OR "Pervasive Child Development Disorder" OR "Pervasive Child Development Disorders" OR "Pervasive Developmental Disorder" OR "Pervasive Developmental Disorders" OR "Pervasive Development Disorder" OR "Pervasive Development Disorders" OR "Childhood Disintegrative Disorder" OR "Childhood Disintegrative Disorders" OR Rett* OR "Cerebroatrophic Hyperammonemia" OR "Cerebroatrophic Hyperammonemias").ti,ab.
2. Exp Drugs/ OR Exp Drug Therapy/ OR Exp Adrenergic Blocking Drugs/ OR Exp Adrenergic Drugs/ OR Exp Anti Inflammatory Drugs/ OR Antiandrogens/ OR Exp Antibiotics/ OR Exp

Anticonvulsive Drugs/ OR Exp Antidepressant Drugs/ OR Exp Antiemetic Drugs/ OR Exp Antihistaminic Drugs/ OR Exp Antitremor Drugs/ OR Channel Blockers/ OR Exp Cholinergic Blocking Drugs/ OR Exp Cholinergic Drugs/ OR Exp Cholinomimetic Drugs/ OR Exp CNS Affecting Drugs/ OR Exp Dopamine Agonists/ OR Exp Enzyme Inhibitors/ OR Exp Ganglion Blocking Drugs/ OR Generic Drugs/ OR Exp Hallucinogenic Drugs/ OR Exp Narcotic Antagonists/ OR Exp Neurotransmitter Uptake Inhibitors/ OR Nonprescription Drugs/ OR Exp Nootropic Drugs/ OR Prescription Drugs/ OR Exp Psychotomimetic Drugs/ OR Exp Serotonin Agonists/ OR Exp Serotonin Antagonists/ OR Exp Sympatholytic Drugs/ OR Exp Sympathomimetic Drugs/ OR Exp Vitamins/ OR Exp Hormones/ OR Exp "Medicinal Herbs and Plants"/ OR Tricyclic Antidepressant Drugs/ OR Exp Neuroleptic Drugs/ OR Exp Dopamine Antagonists/ OR Exp Gamma Aminobutyric Acid Antagonists/ OR Exp Serotonin Reuptake Inhibitors/ OR Exp Serotonin Norepinephrine Reuptake Inhibitors/ OR Exp CNS Stimulating Drugs/ OR Exp Gamma Aminobutyric Acid Agonists/ OR Exp Cholinesterase Inhibitors/ OR Exp Immunologic Factors/ OR Exp Neurotransmitters/ OR Exp Antioxidants/ OR Exp CNS Depressant Drugs/ OR Aripiprazole/ OR Clozapine/ OR Haloperidol/ OR Loxapine/ OR Quetiapine/ OR Risperidone/ OR Sulpiride/ OR Citalopram/ OR Chlorimipramine/ OR Desipramine/ OR Fluoxetine/ OR Fluvoxamine/ OR Imipramine/ OR Mianserin/ OR Nortriptyline/ OR Paroxetine/ OR Sertraline/ OR Venlafaxine/ OR Atomoxetine/ OR Fenfluramine/ OR "Lithium Carbonate"/ OR Methylphenidate/ OR Methylenedioxymethamphetamine/ OR "Valproic Acid"/ OR Bromocriptine/ OR Buspirone/ OR Clonidine/ OR Propranolol/ OR Amantadine/ OR Ketamine/ OR Baclofen/ OR Galanthamine/ OR Mecamylamine/ OR (Immunoglobulins/ AND Oral*.ti,ab.) OR Naltrexone/ OR "Insulin-Like Growth Factor"/ OR "Adrenal Cortex Hormones"/ OR Corticotropin/ OR Angiotensin/ OR Diets/ OR "Dietary Supplements"/ OR Fatty Acids/ OR Ghrelin/ OR Hydrocortisone/ OR Melatonin/ OR Nutrition/ OR Oxytocin/ OR "Thyroid Hormones"/ OR Thyroxine/ OR Triiodothyronine/ OR Vasopressin/ OR Vitamin Therapy/ OR "Arachidonic Acid"/ OR "Ascorbic Acid"/ OR "Folic Acid"/ OR Magnesium/ OR (Anticonvuls* OR Antiepilep* OR Antipsychotic* OR Psychotropic* OR "Anti-Anxiety" OR Anxiolytic* OR Antidepress* OR "Pharmaco-Therapy" OR "Pharmaco-Therapies" OR Chemotherapy OR Chemotherapies OR Pharmacotherapy OR Pharmacotherapies OR "Pharmacological Interventions" OR "Pharmacological Intervention" OR "Pharmacological Treatment" OR "Pharmacological Treatments" OR "Drug Therapy" OR "Drug Therapies" OR Amisulpride OR Aripiprazol* OR Abilify OR Brexpiprazole OR Clozapine OR Clozaril OR Leponex OR Haloperidol OR Haldol OR Loxapine OR Lurasidone OR Latuda OR Olanzapine OR Zyprexa OR Paliperidone OR Invega OR Quetiapine OR Seroquel OR Risperidone OR Risperdal OR Risperidal OR Sertindole OR Sulpiride OR Dogmatil OR Ziprasidone OR Geodon OR Ziprazidone OR Agomelatine OR Citalopram OR Clomipramine OR Desipramine OR Escitalopram OR Fluoxetine OR Prozac OR Fluvoxamine OR Imipramine OR Mianserin OR Milnacipran OR Mirtazapine OR Nortriptyline OR Paroxetine OR Sertraline OR Tianeptine OR Tianeptine OR Venlafaxine OR "m-chlorophenylpiperazine" OR "m-CPP" OR "1-(3-chlorophenyl)piperazine" OR Atomoxetine OR Strattera OR Dextromethorphan OR Fenfluramine OR Lamotrigine OR Levetiracetam OR Lisdexamfetamine OR Lithium OR MDMA OR "N-Methyl-3,4-methylenedioxyamphetamine" OR Ecstasy OR Methylenedioxymethamphetamine OR Methylphenidate OR Ritalin* OR Oxcarbazepine OR Topiramate OR Valproic Acid OR Divalproex OR Valproate OR Divalproate OR "(+)-5-FPT" OR "PRX-07034" OR Betahistin* OR Bromocriptine OR Buspirone OR Cyproheptadine OR Famotidine OR Levodopa OR "L-Dopa" OR "LP-211" OR "N-(4-cyanophenylmethyl)-4-(2-diphenyl)-1-piperazinehexanamide" OR Sumatriptan OR Volinanserin OR "M100907" OR Clonidine OR Guanfacine OR Dexmedetomidine OR Propranolol OR Acetylcysteine OR "ADX71149" OR "JNJ-40411813" OR "1-butyl-3-chloro-4-(4-phenyl-1-piperidinyl)-(1H)-pyridone" OR Amantadine OR "AZD8529" OR Basimglurant OR "2-chloro-4-(1-(4-fluorophenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl)pyridine" OR "CDPPB" OR "3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide" OR "CX516" OR "BDP 12" OR "1-(quinoxalin-6-

ylcarbonyl)piperidine" OR "D-Cycloserine" OR Eglumetad OR Fenobam OR "GRN-529" OR Ketamine OR "LY 341495" OR "LY341495" OR "LY 379268" OR "LY379268" OR "LY 487379" OR "LY487379" OR Mavoglurant OR Memantine OR "MGS0039" OR "MPEP" OR "6-methyl-2-(phenylethynyl)pyridine" OR "MPX-004" OR "MPX-007" OR "MTEP" OR "NCFP" OR Riluzole OR "RO4491533" OR "TASP0433864" OR "A 867744" OR "4-(5-(4-chlorophenyl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide" OR Acamprosate OR "ADX71441" OR Arbaclofen OR "AZD7325" OR Baclofen OR Bumetanide OR "DMXB A" OR "DMXBA" OR "GTS 21" OR "3-(2,4-dimethoxybenzylidene)anabaseine" OR Donepezil OR "EVP-6124" OR "7-chloro-N-quinuclidin-3-yl-benzo(b)thiophene-2-carboxamide" OR Flumazenil OR Galantamin* OR Mecamylamine OR "PNU 120596" OR "PNU120596" OR "1-(5-chloro-2,4-dimethoxyphenyl)-3-(5-methylisoxazol-3-yl)urea" OR Pregnenolone OR Rivastigmine OR "SSR180711" OR Varenicline OR "AF38469" OR "AR-A014418" OR "N-(4-methoxybenzyl)-N'-(5-nitro-1,3-thiazol-2-yl)urea" OR Cannabidiol OR Cannabidivarin OR Celecoxib OR Everolimus OR Fingolimod OR Fluconazole OR Glatiramer OR Hydroxyfasudil OR Lenalidomide OR Minocycline OR Naltrexone OR "NVP-BKM120" OR Buparlisib OR "Oral Human Immunoglobulin" OR Pentoxifylline OR "SB 216763" OR "SB216763" OR Sirolimus OR Rapamycin OR Staurosporine OR Suramin OR Tacrolimus OR "TAK-242" OR "TAK242" OR Temsirolimus OR Tideglusib OR "NP031112" OR Amastatin OR Angiotensin* OR Carnitine OR Levocarnitine OR "CM-AT" OR "Diet Therapy" OR "Diet Therapies" OR "Dietary Supplements" OR "Dietary Supplement" OR Dimethylglycine OR "EPI-743" OR "alpha-Tocotrienol Quinone" OR "Food Supplement" OR "Food Supplements" OR "Gastrin-Releasing Peptide" OR Ghrelin OR "Herbal Supplement" OR "Herbal Supplements" OR Hormone* OR Corticosteroid* OR Corticoid* OR Hydrocortisone OR "IGF-1" OR "Insulin-Like Growth Factor I" OR Lovastatin OR Melanocortin* OR Melatonin OR Metformin OR Mineral* OR "NNZ-2566" OR "NNZ2566" OR "Nutrition Therapy" OR "Nutritional Therapy" OR Oligosaccharide* OR "Omega-3" OR "Omega3" OR "n-3 Fatty" OR "n-3 Polyunsaturated Fatty" OR "n-3 PUFA" OR "n3 PUFA" OR "n 3 Oils" OR "n 3 Oil" OR "n3 Fatty" OR "ORG-2766" OR Oxytocin OR Syntocinon OR Pioglitazone OR Prednisone OR Probiotic* OR Bifidobacter* OR Pyridoxine OR "RG7713" OR "Ro27 3225" OR Secretin OR Sulforaphane OR Sulforafan OR Tetrahydrobiopterin OR Sapropterin OR Thyroxine OR Triiodothyronine OR "T3" OR Trofinetide OR Vasopressin* OR Vitamin* OR "WAY-267464" OR "WAY267464" OR Arachidonic OR Arachidonate OR Ascorbic OR Ascorbate OR Carnosine OR Cyanocobalamin OR Cobalamin* OR Cobamide* OR Hydroxocobalamin OR Docosahexaenoic OR Docosahexaenoate OR Ferrous OR Folic OR Folate OR Ginkgo* OR Gingko* OR Ginko* OR Maidenhair OR Glutathione OR Gluten OR Inositol OR Leucovorin OR Folinic OR Magnesium OR Milk OR Papain OR Pepsin OR Pyridoxal OR Pyridoxamine OR Succimer OR Dimercaptosuccinic Acid OR DMSA OR "Trichuris Suis" OR Ubiquinol).ti,ab.

3. Exp Treatment Effectiveness Evaluation/ OR Clinical Trials/ OR Mental Health Program Evaluation/ OR Placebo/ OR (Random* OR Factorial* OR Crossover* OR Cross Over* OR Placebo* OR ((Singl* OR Doubl* OR Trebl* or Tripl*) adj (Mask* OR Blind*)) OR Assign* OR Allocat* OR Volunteer* OR Groups OR Trial*).ti,ab.
4. 1 AND 2 AND 3

3.2.6 PubMed

("Autistic Disorder"[MH] OR "Autism Spectrum Disorder"[MH] OR "Asperger Syndrome"[MH] OR "Rett Syndrome"[MH] OR "Child Development Disorders, Pervasive"[MH] OR Autis*[TIAB] OR Kanner*[TIAB] OR Asperger*[TIAB] OR "Pervasive Child Development Disorders"[TIAB] OR "Pervasive Developmental Disorder"[TIAB] OR "Pervasive Developmental Disorders"[TIAB] OR "Pervasive Development Disorder"[TIAB] OR "Pervasive Development Disorders"[TIAB] OR "Childhood Disintegrative Disorder"[TIAB] OR Rett*[TIAB]) AND ("Adrenergic alpha-2 Receptor Antagonists"[PA] OR "Antidepressive Agents, Second-Generation"[PA] OR "Anti-Dyskinesia Agents"[PA] OR Antiemetics[PA] OR "Antipsychotic Agents"[PA] OR "Dopamine Agonists"[PA]

OR "Dopamine Antagonists"[PA] OR "Dopamine D2 Receptor Antagonists"[PA] OR "GABA Antagonists"[PA] OR "Serotonin 5-HT2 Receptor Antagonists"[PA] OR "Serotonin Agents"[PA] OR "Serotonin Antagonists"[PA] OR "Serotonin Uptake Inhibitors"[PA] OR "Adrenergic alpha-Antagonists"[PA] OR "Adrenergic Uptake Inhibitors"[PA] OR "Cytochrome P-450 CYP1A2 Inhibitors"[PA] OR "Cytochrome P-450 CYP2C19 Inhibitors"[PA] OR "Cytochrome P-450 CYP2D6 Inhibitors"[PA] OR "Enzyme Inhibitors"[PA] OR "Histamine H1 Antagonists"[PA] OR "Serotonin and Noradrenaline Reuptake Inhibitors"[PA] OR "Anti-Anxiety Agents"[PA] OR "Antidepressive Agents"[PA] OR "Antidepressive Agents, Tricyclic"[PA] OR "Psychotropic Drugs"[PA] OR Anticonvulsants[PA] OR "Antimanic Agents"[PA] OR "Calcium Channel Blockers"[PA] OR "Central Nervous System Stimulants"[PA] OR "Cytochrome P-450 CYP3A Inducers"[PA] OR "Dopamine Uptake Inhibitors"[PA] OR "Excitatory Amino Acid Antagonists"[PA] OR "GABA Agents"[PA] OR Hallucinogens[PA] OR "Neuroprotective Agents"[PA] OR "Nootropic Agents"[PA] OR "Serotonin Receptor Agonists"[PA] OR "Voltage-Gated Sodium Channel Blockers"[PA] OR "Antiparkinson Agents"[PA] OR "Dopamine Agents"[PA] OR "Histamine Agonists"[PA] OR "Histamine H2 Antagonists"[PA] OR "Hormone Antagonists"[PA] OR "Serotonin 5-HT1 Receptor Agonists"[PA] OR "Adrenergic alpha-2 Receptor Agonists"[PA] OR "Adrenergic beta-Antagonists"[PA] OR Sympatholytics[PA] OR "Excitatory Amino Acid Agonists"[PA] OR "Cholinesterase Inhibitors"[PA] OR "GABA Modulators"[PA] OR "GABA-B Receptor Agonists"[PA] OR "Ganglionic Blockers"[PA] OR "Nicotinic Agonists"[PA] OR "Nicotinic Antagonists"[PA] OR Parasympathomimetics[PA] OR "Sodium Potassium Chloride Symporter Inhibitors"[PA] OR "14-alpha Demethylase Inhibitors"[PA] OR "Adjuvants, Immunologic"[PA] OR "Anti-Bacterial Agents"[PA] OR "Antifungal Agents"[PA] OR "Cannabinoid Receptor Agonists"[PA] OR "Cannabinoid Receptor Antagonists"[PA] OR "Cannabinoid Receptor Modulators"[PA] OR "Central Nervous System Agents"[PA] OR "Cyclooxygenase 2 Inhibitors"[PA] OR "Cytochrome P-450 CYP2C9 Inhibitors"[PA] OR "Immunologic Factors"[PA] OR "Immunosuppressive Agents"[PA] OR "Narcotic Antagonists"[PA] OR "Neurotransmitter Agents"[PA] OR "Purinergic Agents"[PA] OR "Anti-Inflammatory Agents"[PA] OR Antioxidants[PA] OR "Central Nervous System Depressants"[PA] OR "Chelating Agents"[PA] OR Hormones[PA] OR Oxytocics[PA] OR "Vitamin B Complex"[PA] OR Vitamins[PA] OR "Pharmaceutical Preparations"[MH:NoExp] OR "Drug Combinations"[MH] OR "Drugs, Chinese Herbal"[MH] OR "Drugs, Essential"[MH] OR "Drugs, Generic"[MH] OR "Drugs, Investigational"[MH] OR "Nonprescription Drugs"[MH] or "Plant Extracts"[MH] OR "Prescription Drugs"[MH] OR Prodrugs[MH] OR "Pharmacologic Actions"[MH] OR "Drug Therapy"[MH] OR "Therapeutic Uses"[MH] OR "Physiological Effects of Drugs"[MH] OR Aripiprazole[MH] OR Clozapine[MH] OR Haloperidol[MH] OR Loxapine[MH] OR "Lurasidone Hydrochloride"[MH] OR "Paliperidone Palmitate"[MH] OR "Quetiapine Fumarate"[MH] OR Risperidone[MH] OR Sulpiride[MH] OR Citalopram[MH] OR Clomipramine[MH] OR Desipramine[MH] OR Fluoxetine[MH] OR Fluvoxamine[MH] OR Imipramine[MH] OR Mianserin[MH] OR Nortriptyline[MH] OR Paroxetine[MH] OR Sertraline[MH] OR "Venlafaxine Hydrochloride"[MH] OR "Atomoxetine Hydrochloride"[MH] OR Dextromethorphan[MH] OR Fenfluramine[MH] OR "Lisdexamfetamine Dimesylate"[MH] OR "Lithium Carbonate"[MH] OR Methylphenidate[MH] OR "N-Methyl-3,4-methylenedioxyamphetamine"[MH] OR "Valproic Acid"[MH] OR Betahistine[MH] OR Bromocriptine[MH] OR Buspirone[MH] OR Cyproheptadine[MH] OR Famotidine[MH] OR Levodopa[MH] OR Sumatriptan[MH] OR Clonidine[MH] OR Guanfacine[MH] OR Dexmedetomidine[MH] OR Propranolol[MH] OR Acetylcysteine[MH] OR Amantadine[MH] OR Ketamine[MH] OR Memantine[MH] OR Riluzole[MH] OR Baclofen[MH] OR Bumetanide[MH] OR Flumazenil[MH] OR Galantamine[MH] OR Mecamylamine[MH] OR Pregnenolone[MH] OR Rivastigmine[MH] OR Varenicline[MH] OR Cannabidiol[MH] OR Celecoxib[MH] OR Everolimus[MH] OR "Fingolimod Hydrochloride"[MH] OR Fluconazole[MH] OR "Glatiramer Acetate"[MH] OR (Immunoglobulins[MH] AND "Administration, Oral"[MH]) OR Minocycline[MH] OR Naltrexone[MH] OR Pentoxifylline[MH] OR Sirolimus[MH] OR Staurosporine[MH] OR Suramin[MH] OR Tacrolimus[MH] OR "Insulin-Like Growth Factor I"[MH] OR"Adrenal Cortex Hormones"[MH] OR "Adrenocorticotropic Hormone"[MH] OR Angiotensins[MH] OR Carnitine[MH]

OR "Diet Therapy"[MH] OR "Dietary Supplements"[MH] OR "Fatty Acids, Omega-3"[MH] OR "Gastrin-Releasing Peptide"[MH] OR Ghrelin[MH] OR Hydrocortisone[MH] OR Lovastatin[MH] OR Melanocortins[MH] OR Melatonin[MH] OR Metformin[MH] OR Minerals[MH] OR "Nutrition Therapy"[MH] OR Oligosaccharides[MH] OR Oxytocin[MH] OR Prednisone[MH] OR Probiotics[MH] OR Pyridoxine[MH] OR Secretin[MH] OR "Thyroid Hormones"[MH] OR Thyroxine[MH] OR Triiodothyronine[MH] OR Vasopressins[MH] OR "Vitamin E"[MH] OR "Arachidonic Acid"[MH] OR "Ascorbic Acid"[MH] OR Carnosine[MH] OR "Docosahexaenoic Acids"[MH] OR "Folic Acid"[MH] OR "Ginkgo biloba"[MH] OR Glutathione[MH] OR Glutens[MH] OR Inositol[MH] OR Leucovorin[MH] OR Magnesium[MH] OR "Magnesium Oxide"[MH] OR Milk[MH] OR Papain[MH] OR Succimer[MH] OR "Vitamin B 12"[MH] OR "Vitamin B 6"[MH] OR "Vitamin D"[MH] OR "Adrenergic alpha-2 Receptor Antagonists"[MH] OR "Antidepressive Agents, Second-Generation"[MH] OR "Anti-Dyskinesia Agents"[MH] OR Antiemetics[MH] OR "Antipsychotic Agents"[MH] OR "Dopamine Agonists"[MH] OR "Dopamine Antagonists"[MH] OR "Dopamine D2 Receptor Antagonists"[MH] OR "GABA Antagonists"[MH] OR "Serotonin 5-HT2 Receptor Antagonists"[MH] OR "Serotonin Agents"[MH] OR "Serotonin Antagonists"[MH] OR "Serotonin Uptake Inhibitors"[MH] OR "Adrenergic alpha-Antagonists"[MH] OR "Adrenergic Uptake Inhibitors"[MH] OR "Cytochrome P-450 CYP1A2 Inhibitors"[MH] OR "Cytochrome P-450 CYP2C19 Inhibitors"[MH] OR "Cytochrome P-450 CYP2D6 Inhibitors"[MH] OR "Enzyme Inhibitors"[MH] OR "Histamine H1 Antagonists"[MH] OR "Serotonin and Noradrenaline Reuptake Inhibitors"[MH] OR "Anti-Anxiety Agents"[MH] OR "Antidepressive Agents"[MH] OR "Antidepressive Agents, Tricyclic"[MH] OR "Psychotropic Drugs"[MH] OR Anticonvulsants[MH] OR "Antimanic Agents"[MH] OR "Calcium Channel Blockers"[MH] OR "Central Nervous System Stimulants"[MH] OR "Cytochrome P-450 CYP3A Inducers"[MH] OR "Dopamine Uptake Inhibitors"[MH] OR "Excitatory Amino Acid Antagonists"[MH] OR "GABA Agents"[MH] OR Hallucinogens[MH] OR "Neuroprotective Agents"[MH] OR "Nootropic Agents"[MH] OR "Serotonin Receptor Agonists"[MH] OR "Voltage-Gated Sodium Channel Blockers"[MH] OR "Antiparkinson Agents"[MH] OR "Dopamine Agents"[MH] OR "Histamine Agonists"[MH] OR "Histamine H2 Antagonists"[MH] OR "Hormone Antagonists"[MH] OR "Serotonin 5-HT1 Receptor Agonists"[MH] OR "Adrenergic alpha-2 Receptor Agonists"[MH] OR "Adrenergic beta-Antagonists"[MH] OR Sympatholytics[MH] OR "Excitatory Amino Acid Agonists"[MH] OR "Cholinesterase Inhibitors"[MH] OR "GABA Modulators"[MH] OR "GABA-B Receptor Agonists"[MH] OR "Ganglionic Blockers"[MH] OR "Nicotinic Agonists"[MH] OR "Nicotinic Antagonists"[MH] OR Parasympathomimetics[MH] OR "Sodium Potassium Chloride Symporter Inhibitors"[MH] OR "14-alpha Demethylase Inhibitors"[MH] OR "Adjuvants, Immunologic"[MH] OR "Anti-Bacterial Agents"[MH] OR "Antifungal Agents"[MH] OR "Cannabinoid Receptor Agonists"[MH] OR "Cannabinoid Receptor Antagonists"[MH] OR "Cannabinoid Receptor Modulators"[MH] OR "Central Nervous System Agents"[MH] OR "Cyclooxygenase 2 Inhibitors"[MH] OR "Cytochrome P-450 CYP2C9 Inhibitors"[MH] OR "Immunologic Factors"[MH] OR "Immunosuppressive Agents"[MH] OR "Narcotic Antagonists"[MH] OR "Neurotransmitter Agents"[MH] OR "Purinergic Agents"[MH] OR "Anti-Inflammatory Agents"[MH] OR Antioxidants[MH] OR "Central Nervous System Depressants"[MH] OR "Chelating Agents"[MH] OR Hormones[MH] OR Oxytocics[MH] OR "Vitamin B Complex"[MH] OR Vitamins[MH] OR "Diet Therapy"[sh] OR Brexpiprazole[NM] OR Olanzapine[NM] OR Sertindole[NM] OR Ziprasidone[NM] OR Agomelatine[NM] OR Milnacipran[NM] OR Mirtazapine[NM] OR Tianeptine[NM] OR Tianeptine[NM] OR "1-(3-chlorophenyl)piperazine"[NM] OR Lamotrigine[NM] OR Levetiracetam[NM] OR Oxcarbazepine[NM] OR Topiramate[NM] OR "N-(4-cyanophenylmethyl)-4-(2-diphenyl)-1-piperazinehexanamide"[NM] OR Volinanserin[NM] OR "1-(quinoxalin-6-ylcarbonyl)piperidine"[NM] OR "1-butyl-3-chloro-4-(4-phenyl-1-piperidinyl)-(1H)-pyridone"[NM] OR "2-((4-tert-butylphenoxy)methyl)-5-methyl-2,3-dihydroimidazo(2,1-b)(1,3)oxazole-6-carboxamide"[NM] OR "2-amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo(3.1.0)hexane-2,6-dicarboxylic acid"[NM] OR "2-chloro-4-(1-(4-fluorophenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl)pyridine"[NM] OR "3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide"[NM] OR "4-(3-(2,6-dimethylpyridin-4-yl)phenyl)-7-

methyl-8-trifluoromethyl-1,3-dihydrobenzo(b)(1,4)diazepin-2-one"[NM] OR "6-methyl-2-(phenylethynyl)pyridine"[NM] OR "AZD8529"[NM] OR Eglumetad[NM] OR Fenobam[NM] OR "GRN-529"[NM] OR "LY 341495"[NM] OR "LY 379268"[NM] OR Mavoglurant[NM] OR "MPX-004"[NM] OR "MPX-007"[NM] OR "N-(4-(2-methoxyphenoxy)phenyl)-N-(2,2,2-trifluoroethylsulfonyl)pyrid-3-ylmethylamine"[NM] OR "1-(5-chloro-2,4-dimethoxyphenyl)-3-(5-methylisoxazol-3-yl)urea"[NM] OR "3-(2,4-dimethoxybenzylidene)anabaseine"[NM] OR "4-(5-(4-chlorophenyl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide"[NM] OR "4-amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide"[NM] OR "7-chloro-N-quinuclidin-3-yl-benzo(b)thiophene-2-carboxamide"[NM] OR Acamprosate[NM] OR "ADX71441"[NM] OR "Arbaclofen Placarbil"[NM] OR Donepezil[NM] OR "SSR180711"[NM] OR "ethyl 6-(N-(2-chloro-4-fluorophenyl)sulfamoyl)cyclohex-1-ene-1-carboxylate"[NM] OR "N-(4-methoxybenzyl)-N'-(5-nitro-1,3-thiazol-2-yl)urea"[NM] OR "AF38469"[NM] OR Cannabidivarin[NM] OR Hydroxyfasudil[NM] OR Lenalidomide[NM] OR "NVP-BKM120"[NM] OR "SB 216763"[NM] OR Temsirolimus[NM] OR "NP 031112"[NM] OR "(6-chloro-1-(2-(dimethylamino)ethyl)indol-3-yl)-spiro(1H-isobenzofuran-3,4'-piperidine)-1'-yl-methanone"[NM] OR "4-(3,5-dihydroxybenzyl)-N-(2-methyl-4-((1-methyl-4,10-dihydropyrazolo(3,4-b)(1,5)benzodiazepin-5(1H)-yl)carbonyl)benzyl)piperazine-1-carboxamide"[NM] OR "alpha-tocotrienol quinone"[NM] OR "butir-His-Phe-Arg-Trp-Sar-NH2"[NM] OR Amastatin[NM] OR Dimethylglycine[NM] OR "NNZ 2566"[NM] OR "ORG 2766"[NM] OR Pioglitazone[NM] OR Sapropterin[NM] OR Sulforafan[NM] OR "Ferrous Sulfate"[NM] OR Ubiquinol[NM] OR Anticonvuls*[TIAB] OR Antiepilep*[TIAB] OR Antipsychotic*[TIAB] OR Psychotropic*[TIAB] OR "Anti-Anxiety"[TIAB] OR Anxiolytic*[TIAB] OR Antidepress*[TIAB] OR "Pharmaco-Therapy"[TIAB] OR "Pharmaco-Therapies"[TIAB] OR Chemotherapy[TIAB] OR Chemotherapies[TIAB] OR Pharmacotherapy[TIAB] OR Pharmacotherapies[TIAB] OR "Pharmacological Interventions"[TIAB] OR "Pharmacological Intervention"[TIAB] OR "Pharmacological Treatment"[TIAB] OR "Pharmacological Treatments"[TIAB] OR "Drug Therapy"[TIAB] OR "Drug Therapies"[TIAB] OR Amisulpride[TIAB] OR Aripiprazol*[TIAB] OR Abilify[TIAB] OR Brexpiprazole[TIAB] OR Clozapine[TIAB] OR Clozaril[TIAB] OR Leponex[TIAB] OR Haloperidol[TIAB] OR Haldol[TIAB] OR Loxapine[TIAB] OR Lurasidone[TIAB] OR Latuda[TIAB] OR Olanzapine[TIAB] OR Zyprexa[TIAB] OR Paliperidone[TIAB] OR Invega[TIAB] OR Quetiapine[TIAB] OR Seroquel[TIAB] OR Risperidone[TIAB] OR Risperdal[TIAB] OR Risperidal[TIAB] OR Sertindole[TIAB] OR Sulpiride[TIAB] OR Dogmatil[TIAB] OR Ziprasidone[TIAB] OR Geodon[TIAB] OR Ziprazidone[TIAB] OR Agomelatine[TIAB] OR Citalopram[TIAB] OR Clomipramine[TIAB] OR Desipramine[TIAB] OR Escitalopram[TIAB] OR Fluoxetine[TIAB] OR Prozac[TIAB] OR Fluvoxamine[TIAB] OR Imipramine[TIAB] OR Mianserin[TIAB] OR Milnacipran[TIAB] OR Mirtazapine[TIAB] OR Nortriptyline[TIAB] OR Paroxetine[TIAB] OR Sertraline[TIAB] OR Tianeptine[TIAB] OR Tianeptine[TIAB] OR Venlafaxine[TIAB] OR "m-chlorophenylpiperazine"[TIAB] OR "m-CPP"[TIAB] OR "1-(3-chlorophenyl)piperazine"[TIAB] OR Atomoxetine[TIAB] OR Strattera[TIAB] OR Dextromethorphan[TIAB] OR Fenfluramine[TIAB] OR Lamotrigine[TIAB] OR Levetiracetam[TIAB] OR Lisdexamfetamine[TIAB] OR Lithium[TIAB] OR MDMA[TIAB] OR "N-Methyl-3,4-methylenedioxyamphetamine"[TIAB] OR Ecstasy[TIAB] OR Methylenedioxymethamphetamine[TIAB] OR Methylphenidate[TIAB] OR Ritalin*[TIAB] OR Oxcarbazepine[TIAB] OR Topiramate[TIAB] OR Valproic Acid[TIAB] OR Divalproex[TIAB] OR Valproate[TIAB] OR Divalproate[TIAB] OR "(+)-5-FPT"[TIAB] OR "PRX-07034"[TIAB] OR Betahistin*[TIAB] OR Bromocriptine[TIAB] OR Buspirone[TIAB] OR Cyproheptadine[TIAB] OR Famotidine[TIAB] OR Levodopa[TIAB] OR "L-Dopa"[TIAB] OR "LP-211"[TIAB] OR "N-(4-cyanophenylmethyl)-4-(2-diphenyl)-1-piperazinehexanamide"[TIAB] OR Sumatriptan[TIAB] OR Volinanserin[TIAB] OR "M100907"[TIAB] OR Clonidine[TIAB] OR Guanfacine[TIAB] OR Dexmedetomidine[TIAB] OR Propranolol[TIAB] OR Acetylcysteine[TIAB] OR "ADX71149"[TIAB] OR "JNJ-40411813"[TIAB] OR "1-butyl-3-chloro-4-(4-phenyl-1-piperidinyl)-(1H)-pyridone"[TIAB] OR Amantadine[TIAB] OR "AZD8529"[TIAB] OR Basimglurant[TIAB] OR "2-chloro-4-(1-(4-fluorophenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl)pyridine"[TIAB] OR "CDPPB"[TIAB] OR "3-

cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide"[TIAB] OR "CX516"[TIAB] OR "BDP 12"[TIAB] OR "1-(quinoxalin-6-ylcarbonyl)piperidine"[TIAB] OR "D-Cycloserine"[TIAB] OR Eglumetad[TIAB] OR Fenobam[TIAB] OR "GRN-529"[TIAB] OR Ketamine[TIAB] OR "LY 341495"[TIAB] OR "LY341495"[TIAB] OR "LY 379268"[TIAB] OR "LY379268"[TIAB] OR "LY 487379"[TIAB] OR "LY487379"[TIAB] OR Mavoglurant[TIAB] OR Memantine[TIAB] OR "MGS0039"[TIAB] OR "MPEP"[TIAB] OR "6-methyl-2-(phenylethynyl)pyridine"[TIAB] OR "MPX-004"[TIAB] OR "MPX-007"[TIAB] OR "MTEP"[TIAB] OR "NCFP"[TIAB] OR Riluzole[TIAB] OR "RO4491533"[TIAB] OR "TASP0433864"[TIAB] OR "A 867744"[TIAB] OR "4-(5-(4-chlorophenyl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide"[TIAB] OR Acamprosate[TIAB] OR "ADX71441"[TIAB] OR Arbaclofen[TIAB] OR "AZD7325"[TIAB] OR Baclofen[TIAB] OR Bumetanide[TIAB] OR "DMXBA"[TIAB] OR "DMXBA"[TIAB] OR "GTS 21"[TIAB] OR "3-(2,4-dimethoxybenzylidene)anabaseine"[TIAB] OR Donepezil[TIAB] OR "EVP-6124"[TIAB] OR "7-chloro-N-quinuclidin-3-yl-benzo(b)thiophene-2-carboxamide"[TIAB] OR Flumazenil[TIAB] OR Galantamin*[TIAB] OR Mecamylamine[TIAB] OR "PNU 120596"[TIAB] OR "PNU120596"[TIAB] OR "1-(5-chloro-2,4-dimethoxyphenyl)-3-(5-methylisoxazol-3-yl)urea"[TIAB] OR Pregnenolone[TIAB] OR Rivastigmine[TIAB] OR "SSR180711"[TIAB] OR Varenicline[TIAB] OR "AF38469"[TIAB] OR "AR-A014418"[TIAB] OR "N-(4-methoxybenzyl)-N'-(5-nitro-1,3-thiazol-2-yl)urea"[TIAB] OR Cannabidiol[TIAB] OR Cannabidivarin[TIAB] OR Celecoxib[TIAB] OR Everolimus[TIAB] OR Fingolimod[TIAB] OR Fluconazole[TIAB] OR Glatiramer[TIAB] OR Hydroxyfasudil[TIAB] OR Lenalidomide[TIAB] OR Minocycline[TIAB] OR Naltrexone[TIAB] OR "NVP-BKM120"[TIAB] OR Buparlisib[TIAB] OR "Oral Human Immunoglobulin"[TIAB] OR Pentoxifylline[TIAB] OR "SB 216763"[TIAB] OR "SB216763"[TIAB] OR Sirolimus[TIAB] OR Rapamycin[TIAB] OR Staurosporine[TIAB] OR Suramin[TIAB] OR Tacrolimus[TIAB] OR "TAK-242"[TIAB] OR "TAK242"[TIAB] OR Temsirolimus[TIAB] OR Tideglusib[TIAB] OR "NP031112"[TIAB] OR Amastatin[TIAB] OR Angiotensin*[TIAB] OR Carnitine[TIAB] OR Levocarnitine[TIAB] OR "CM-AT"[TIAB] OR "Diet Therapy"[TIAB] OR "Diet Therapies"[TIAB] OR "Dietary Supplements"[TIAB] OR "Dietary Supplement"[TIAB] OR Dimethylglycine[TIAB] OR "EPI-743"[TIAB] OR "alpha-Tocotrienol Quinone"[TIAB] OR "Food Supplement"[TIAB] OR "Food Supplements"[TIAB] OR "Gastrin-Releasing Peptide"[TIAB] OR Ghrelin[TIAB] OR "Herbal Supplement"[TIAB] OR "Herbal Supplements"[TIAB] OR Hormone*[TIAB] OR Corticosteroid*[TIAB] OR Corticoid*[TIAB] OR Hydrocortisone[TIAB] OR "IGF-1"[TIAB] OR "Insulin-Like Growth Factor I"[TIAB] OR Lovastatin[TIAB] OR Melanocortin*[TIAB] OR Melatonin[TIAB] OR Metformin[TIAB] OR Mineral*[TIAB] OR "NNZ-2566"[TIAB] OR "NNZ2566"[TIAB] OR "Nutrition Therapy"[TIAB] OR "Nutritional Therapy"[TIAB] OR Oligosaccharide*[TIAB] OR "Omega-3"[TIAB] OR "Omega3"[TIAB] OR "n-3 Fatty"[TIAB] OR "n-3 Polyunsaturated Fatty"[TIAB] OR "n-3 PUFA"[TIAB] OR "n3 PUFA"[TIAB] OR "n 3 Oils"[TIAB] OR "n 3 Oil"[TIAB] OR "n3 Fatty"[TIAB] OR "ORG-2766"[TIAB] OR Oxytocin[TIAB] OR Syntocinon[TIAB] OR Pioglitazone[TIAB] OR Prednisone[TIAB] OR Probiotic*[TIAB] OR Bifidobacter*[TIAB] OR Pyridoxine[TIAB] OR "RG7713"[TIAB] OR "Ro27 3225"[TIAB] OR Secretin[TIAB] OR Sulforaphane[TIAB] OR Sulforafan[TIAB] OR Tetrahydrobiopterin[TIAB] OR Sapropterin[TIAB] OR Thyroxine[TIAB] OR Triiodothyronine[TIAB] OR "T3"[TIAB] OR Trofinetide[TIAB] OR Vasopressin*[TIAB] OR Vitamin*[TIAB] OR "WAY-267464"[TIAB] OR "WAY267464"[TIAB] OR Arachidonic[TIAB] OR Arachidonate[TIAB] OR Ascorbic[TIAB] OR Ascorbate[TIAB] OR Carnosine[TIAB] OR Cyanocobalamin[TIAB] OR Cobalamin*[TIAB] OR Cobamide*[TIAB] OR Hydroxocobalamin[TIAB] OR Docosahexaenoic[TIAB] OR Docosahexaenoate[TIAB] OR Ferrous[TIAB] OR Folic[TIAB] OR Folate[TIAB] OR Ginkgo*[TIAB] OR Gingko*[TIAB] OR Ginko*[TIAB] OR Maidenhair[TIAB] OR Glutathione[TIAB] OR Gluten[TIAB] OR Inositol[TIAB] OR Leucovorin[TIAB] OR Folinic[TIAB] OR Magnesium[TIAB] OR Milk[TIAB] OR Papain[TIAB] OR Pepsin[TIAB] OR Pyridoxal[TIAB] OR Pyridoxamine[TIAB] OR Succimer[TIAB] OR Dimercaptosuccinic Acid[TIAB] OR DMSA[TIAB] OR "Trichuris Suis"[TIAB] OR Ubiquinol[TIAB]) AND ("Randomized Controlled Trial"[PT] OR "Controlled Clinical Trial"[PT]

OR Randomized[TIAB] OR Randomised[TIAB] OR Placebo*[TIAB] OR "Drug Therapy"[SH] OR Randomly[TIAB] OR Trial[TIAB] OR Groups[TIAB]) NOT (Animals[MH] NOT Humans[MH])

3.2.7 World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)

Including:

- Australian New Zealand Clinical Trials Registry, last data file imported on 2 July 2018
- Chinese Clinical Trial Registry, last data file imported on 2 July 2018
- ClinicalTrials.gov, last data file imported on 2 July 2018
- EU Clinical Trials Register (EU-CTR), last data file imported on 25 June 2018
- ISRCTN, last data file imported on 2 July 2018
- The Netherlands National Trial Register, last data file imported on 2 July 2018
- Brazilian Clinical Trials Registry (ReBec), last data file imported on 20 June 2018
- Clinical Trials Registry - India, last data file imported on 18 June 2018
- Clinical Research Information Service - Republic of Korea, last data file imported on 18 June 2018
- Cuban Public Registry of Clinical Trials, last data file imported on 18 June 2018
- German Clinical Trials Register, last data file imported on 18 June 2018
- Iranian Registry of Clinical Trials, last data file imported on 20 June 2018
- Japan Primary Registries Network, last data file imported on 20 June 2018
- Pan African Clinical Trial Registry, last data file imported on 22 May 2018
- Sri Lanka Clinical Trials Registry, last data file imported on 18 June 2018
- Thai Clinical Trials Registry (TCTR), last data file imported on 20 June 2018
- Peruvian Clinical Trials Registry (REPEC), last data file imported on 18 June 2018

Advanced Search

Autism OR Autistic OR Asperger OR Rett OR Pervasive OR Disintegrative OR Hyperammonemia OR Hyperammonaemia in the Condition

Recruitment status is ALL

3.3 References

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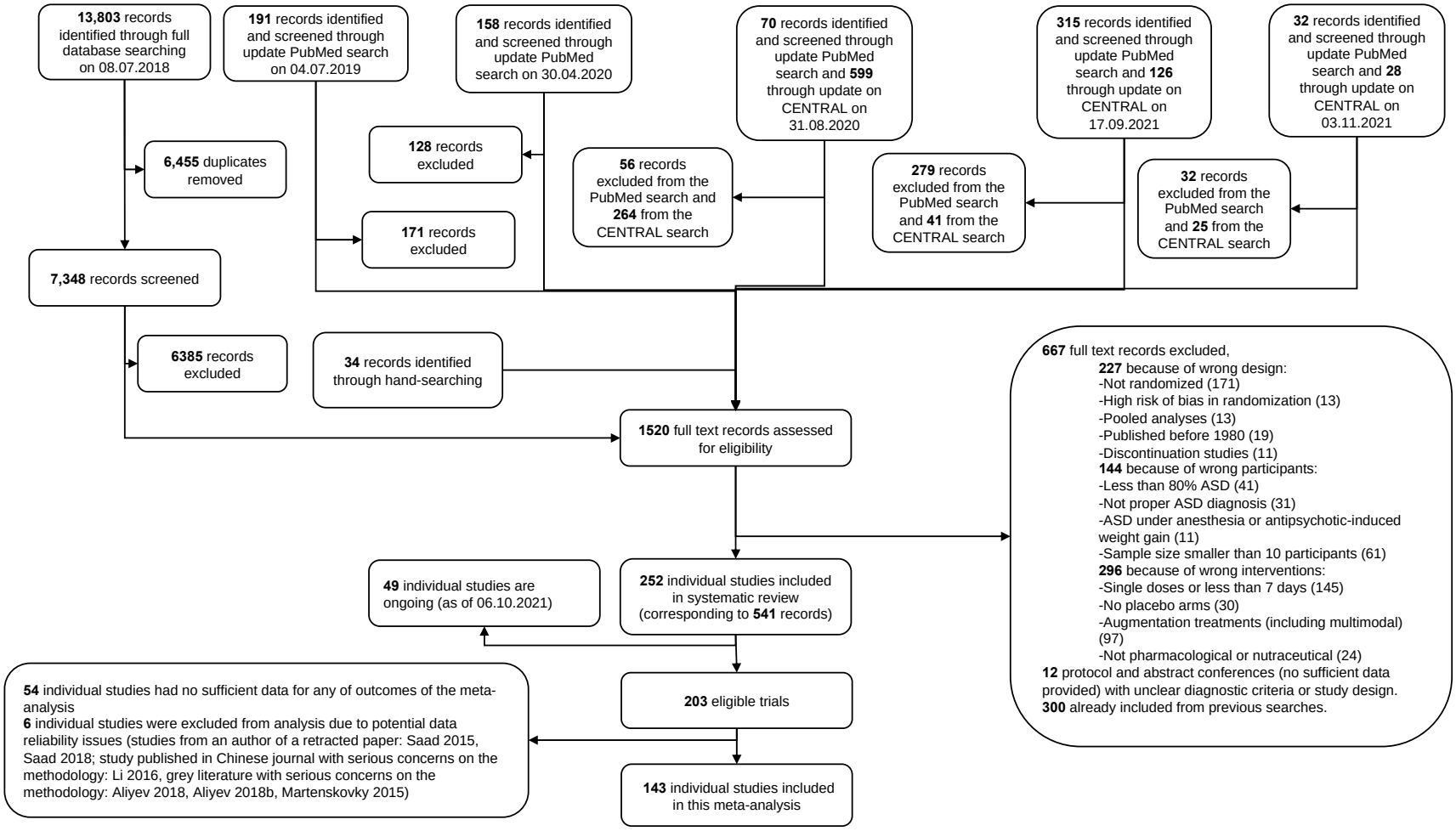
eAppendix-4 Study selection

4.1 PRISMA flow diagram of study selection



4.2 Excluded records

4.2.1 Excluded records

1) Excluded records (*k= 667*)
   a) Wrong design (k=227):
      i) not randomized (k=171):[1–159, 866-873, 880-882, 950]
      ii) high risk of bias in randomization (sequence generation or allocation concealment, k=13):[160–170, 877-878]
      iii) pooled analyses (k=13):[171–181, 837-838, 951]
      iv) placebo-discontinuation studies (k=11):[182–189, 836, 834, 981]
      v) published before 1980 (k=19):[190–208]
   b) Wrong participants (k=144):
      i) Less than 80% had ASD (k=41):[209–245, 954-957]
      ii) Inappropriate ASD diagnosis (standardized diagnostic criteria or validated diagnostic tools were not used for diagnosis, or not a diagnosis of ASD by inclusion criteria, k=31): [246–263, 854-865, 953]
      iii) ASD under anesthesia or antipsychotic-induced weight gain (combination treatment) (k=11):[264–272, 819, 952]
      iv) Sample size smaller than 10 participants (including withdrawn studies, k=61):[273-274, 276–333, 978]
   c) Wrong interventions (k=296):
      i) Single dose interventions or less than seven days of treatments (k=145):[333–456, 820-833, 963-969]
      ii) Different dose of the same medication or no treatment control groups (k=30):[457–476, 874-876, 958-962, 980, 982]
      iii) Combination and multimodal treatments (k=97):[477–553, 835, 839-853, 974-977]
      iv) Not pharmacological or dietary supplement interventions (k=24):[554-572, 879, 970-973]
2) Protocol and abstract conferences (no sufficient data provided) with unclear diagnostic criteria or study design (*k=12*):[573, 575-577, 579–586]
3) Already included or excluded from the previous searches (*k=300*):[587–818, 883-949, 979]

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4.3 Eligible trials, included and ongoing

4.3.1 Included records in the systematic review

From the 203 eligible trials, 143 were included in the quantitative analysis, i.e. data for at least an outcome (underlined). Six studies were not included in the quantitative in spite of availability of data (*italics*), becauase of data reliability issues and retraction of the paper (k=2), or important concerns on methodology and reported data (k=4). Fifty-four studies did not provide appropriate data, due to crossover design, insufficient reporting, use of not appropriate scales for our review, assessment of outcomes not in the interest of our review.

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    - ACTRN12619000615189 (2019): Prebiotic supplement use, the gut microbiome and behaviour change in children with autism spectrum disorder (ASD). Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01974264/full.
17. UMIN000035172 (ongoing; last update posted on 10.06.2021)
    - JPRN-JMA-IIA00438 (2020): The efficacy and safety of pyridoxamine in patients with autism spectrum disorder; Exploratory physician-led Phase 2 trial. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02172398/full.
    - JPRN-jRCT2021200001 (2020): The efficacy and safety of pyridoxamine in patients with autism spectrum disorder; Exploratory physician-led Phase 2 trial. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02172414/full.
    - JPRN-UMIN000035172 (2018): The efficacy and safety of pyridoxamine in patients with autism spectrum disorder; Exploratory physician-led Phase II trial. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01946502/full.
18. UMIN000035175 (ongoing; last update posted on 17.12.2018)
    - JPRN-jRCTs031180411 (2019): Rare sugar in the patient with autism. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01971045/full.
    - JPRN-UMIN000035175 (2018): Safety and efficacy of rare sugar in children with autism spectrum disorder. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01946503/full.
19. JPRCTS051190017 (ongoing; last update posted on 17.05.2021)
    - JPRN-jRCTs051190017 (2019): Double blinded randomized placebo controlled trial to examine if intake of 5-aminolevulinic acid supplement can improve clinical symptoms of individuals with Autism Spectrum Disorder. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01972240/full.
20. UMIN000033113 (ongoing; last update posted on 01.08.2019)
    - JPRN-UMIN000033113 (2018): RCT of Autism spectrum disorder and probiotics. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01910855/full.
21. NCT03682978 (ongoing; last update posted on 28.08.2021)
    - NCT03682978 (2018): Arbaclofen in Children and Adolescents With ASD. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01663564/full.
    - Parellada M; San José Cáceres A; Palmer M; Delorme R; Jones EJH; Parr JR et al. (2021): A Phase II Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy, Safety, and Tolerability of Arbaclofen Administered for the Treatment of Social Function in Children and Adolescents With Autism Spectrum Disorders: Study Protocol for AIMS-2-TRIALS-CT1. In *Frontiers in psychiatry* 12, p. 701729. Available online at https://pubmed.ncbi.nlm.nih.gov/34504446/
22. NCT03757585 (ongoing; last update posted on 24.02.2021)
    - NCT03757585 (2018): Management of Emotional Dysregulation in Youth With Non-verbal Learning Disability (NVLD) and/or Autism Spectrum Disorders (ASD) Using Telepsychiatry of Complementary and Alternative Treatments. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01918501/full.
23. NCT03887676 (ongoing; last update posted on 13.08.2021)

- NCT03887676 (2019): Arbaclofen vs. Placebo in the Treatment of Children and Adolescents With ASD (ARBA). Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01919372/full.

24. NCT04031755 (ongoing; last update posted on 10.03.2021)
    - NCT04060017 (2019): Early Treatment of Language Impairment in Young Children With Autism Spectrum Disorder With Leucovorin Calcium. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01983530/full.
25. NCT04174365 (ongoing; last update posted on 28.05.202)

NCT04174365 (2019): Brexpiprazole in Treatment of Children and Adolescents With Irritability Associated With Autism Spectrum Disorder. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02004225/full

26. NCT04060030 (ongoing; last update posted on 10.03.2021)
    - NCT04060030 (2019): Treatment of Social and Language Deficits With Leucovorin for Young Children With Autism. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01983531/full.
27. NCT04293783 (ongoing; last update posted on 03.03.2020)
    - NCT04293783 (2020): Randomized Double-blind Clinical Trial With L.Reuteri Supplementation in Children With Autism Spectrum Disorder. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02088723/full.
28. NCT04312152 (ongoing; last update posted on 18.03.2020)
    - NCT04312152 (2020): Q10 Ubiquinol in Autism Spectrum Disorder and in Phelan-McDermid Syndrome. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02089167/full.
29. NCT04312932 (ongoing; last update posted on 09.09.2021)
    - NCT04312932 (2020): Fatty Acid Supplementation in Children With ASD (Study 2). Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02089174/full.
30. NCT04517799 (ongoing; last update posted on 05.09.2021)
    - NCT04517799 (2020): Trial of Cannabidiol to Treat Severe Behavior Problems in Children With Autism. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02162910/full.
31. NCT04520685 (ongoing; last update posted on 23.07.2021)
    - NCT04520685 (2020): CAnnabidiol Study in Children With Autism Spectrum DisordEr. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02162969/full.
32. NCT04623398 (ongoing; last update posted on 16.09.2021)
    - NCT04623398 (2020): Effect of Lithium in Patients With Autism Spectrum Disorder and Phelan-McDermid Syndrome (SHANK3 Haploinsufficiency). Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02197416/full.
33. TCTR20200522003 (ongoing; last update posted on)
    - TCTR20200522003 (2020): Folate receptor alpha autoantibody in children with autism spectrum disorder: establishment of in-house ELISA and efficacy of folinic acid â?? a randomized controlled trial. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02189820/full.
34. ACTRN12621000801819 (ongoing; version 2 of the protocol posted on 24.06.2021)
    - ACTRN12621000801819 (2021): SerTRaline for AnxieTy in adults with a diagnosis of Autism (STRATA) A randomised controlled trial. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02280170/full.

- ISRCTN15984604 (2021): Sertraline for anxiety in adults with a diagnosis of autism. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02238056/full.

35. ACTRN12621000029897 (ongoing; last update posted on 12.04.2021)
- ACTRN12621000029897 (2021): Effect of Probiotic supplementation on gut bacteria in children with autism - a pilot randomized controlled trial. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02241654/full.

36. ChiCTR2000037941 (last update posted on 30.03.2021)
- ChiCTR2000037941 (2020): The role of probiotics in children with autism spectrum disorders: a randomized controlled trial. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02241091/full.

37. ChiCTR2000040336 (last update posted on 16.02.2021)
- ChiCTR2000040336 (2020): Lithium treatment for children with autism. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02239734/full.

38. ChiCTR2100042512 (ongoing; last update posted on 03.05.2021)
- ChiCTR2100042512 (2021): A randomized, double-blind, controlled study of nutrition intervention in children with autism with bifidobacterium lactate M8+ low carbon balanced diet. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02280595/full.

39. CTRI/2020/12/030101 (ongoing; last update posted on 28.12.2020)
- CTRI/2020/12/030101 (2020): Studying vitamin D status and the efficacy of vitamin D supplementation in autistic children in Bangladesh. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02238940/full.

40. JPRN-UMIN000034939 (ongoing; last update posted on 31.03.2021)
- JPRN-UMIN000034939 (2021): Double blinded randomized placebo controlled trial to examine if intake of 5-aminolevulinic acid supplement can improve clinical symptoms of individuals with Autism Spectrum Disorder. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02255864/full.

41. NCT04745026 (ongoing; last update posted on 11.06.2021)
- NCT04745026 (2021): Trial to Investigate the Safety and Efficacy of Cannabidiol Oral Solution (GWP42003-P; CBD-OS) in Children and Adolescents With Autism Spectrum Disorder. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02218356/full.

42. NCT04766177 (ongoing; last update posted on 23.02.2021)
- NCT04766177 (2021): Role of Bumetanide in Treatment of Autism. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02236565/full.

43. NCT04878198 (ongoing; last update posted on 11.05.2021)
- NCT04878198 (2021): Treatment of Sleep Disturbance in Children With ASD. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02270250/full.

44. NCT04903353 (ongoing; last update posted on 21.09.2021)
- NCT04903353 (2021): Pragmatic Trial Comparing Weight Gain in Children With Autism Taking Risperidone Versus Aripiprazole. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02289599/full.

45. NCT04939974 (ongoing; last update posted on 25.06.2021)
- NCT04939974 (2021): Probiotic in Autism. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02279189/full.

46. NCT04942522 (ongoing; last update posted on 28.06.2021)
- NCT04942522 (2021): Application of Probiotic PS128 in Children With ASD. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02279247/full.

47. RBR-5wr2cqq (ongoing; last update posted on 17.12.2020)

- RBR-5wr2cqq (2021): Evaluation of the efficacy and safety of medicinal cannabis in children with autism. Available online at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02241594/full

48. CTRI/2021/07/034901
- CTRI/2021/07/34901. Evaluation of the efficacy of oral Folinic acid supplementation in children with Autism Spectrum disorders: a randomized double blind, placebo controlled trial - FIAT

49. NCT05015439
- NCT05015439. Cannabidiol (CBD) in Adults With ASD.

4.4 Contacting corresponding authors for additional data/clarifications

Study authors of eligible and unclear studies were contacted in our previous analysis of placebo-controlled studies (Siafis et al 2018, *Molecular Autism*). In this analysis, we contacted study authors of 18 head-to-head not placebo-controlled as well as newly identified studies that we had no contacted before, from which we acquired additional data and clarifications for two (except for studies identified during the update searches of August 2020 and September 2021).

	Study name	In the review	Contacted	Replied	Provided additional data and clarifications	Comment (up to 16.09.2020)
1	DeVane_2019	Included in the analysis	Yes	Yes	No	
2	EUCTR2014-001560-35	Included in the analysis	Yes	Yes	No	Most of the data were available in the manuscript
3	Ghanizadeh_2014	Included in the analysis	Yes	Yes	No	No access to the data
4	IRCT2012111011421N1	Unpublished protocol	Yes	No	No	
5	ISRCTN04516575	Unpublished protocol	No	No	No	No working email was found
6	Lamberti_2016	Included in the analysis	Yes	Yes	No	
7	Li_2016	Excluded from the analysis due to unclear methdoology	Yes	No	No	
8	Miral_2008	Included in the analysis	Yes	No	No	
9	NCT00467818	Unpublished protocol	No	No	No	No working email was found
10	NCT02385799	Including in the analysis	Yes	Yes	Yes	
11	NCT02551380	Including in the analysis	Yes	No	No	
12	NCT02674984	Unclear trial for inclusion and ongoing	Yes	No	No	Recruiting
13	NCT02909959	Included in the analysis	Yes	Yes	Yes	
14	NCT03550209	Unpublished protocol	Yes	Yes	No	Data were not shared before publication of the trial
15	Nikvharz_2017	Included in the analysis	Yes	No	No	
16	Reynolds_2019	Included in the analysis	Yes	Yes	No	
17	Vasconcelos_2014	Included in the analysis	Yes	Yes	No	Further analysis of the data is planned
18	Wang_2020	Included in the analysis	Yes	No	No	

eAppendix-5 Study characteristics

5.1 Tables of study characteristics

5.1.1 Summary of characteristics of the sample

k=143 studies, n=8554 participants			
Age group		**Children/adolescents (k=125, n=7450)**	**Adults or mixed populations (k=18, n=1104)**
Study design	Publication year	2015 [2006-2019], min/max=1984-2021	2016 [2012-2019], min/max=1996-2021
	Design	Parallel (k=97), crossover (k=28) * Double blind (k=120), single-blind (k=2), open (k=3) Placebo-controlled (k=119), no placebo control (k=6)	Parallel(k=13), crossover (k=5) * Double-blind (k=18) Placebo-controlled (k=18)
	Sites	Single-site (k=71) Number of sites in multi-center studies: 5 [3-16], min/max 2-50, n.i. or unclear (k=13) Only academic sites (k=87), for the rest of the studies the percentage of academic sites ranged between 0%-75% with median 47% [5%-61%], n.i. or unclear (k=24)	Single-site (k=14) Number of sites in multi-center studies: 15 [4-32], min/max:2-51 Only academic sites (k=15), for the rest of the studies the percentage of academic sites ranged between 0%-67% with median 62% [31%-64%]
	Duration of treatment	12 weeks [8-13], min/max 1-52 weeks Shorter-term studies (1 to 3 weeks, k=7), medium-term studies (4 to 13 weeks, k=89), longer-term studies (>13 weeks, k=29)	12 weeks [6-12], min/max 2-24 weeks Shorter-term studies (1 to 3 weeks, k=1), medium-term studies (4 to 13 weeks, k=15), longer-term studies (>13 weeks, k=2)
	Number of arms and medications	Two arms (k=110), three arms (k=7), four arms (k=9), All of the studies investigated two medications (including placebo or different doses of the same drug) apart from one study that investigated four medications (placebo, omega-3, vitamin-D, vitamin-D + omega-3 in Mazahery 2019).	Two arms (k=15), three arms (k=2), four arms (k=1), All of the studies investigated two medications (including placebo or different doses of the same drug) apart from one study that investigated three medications (clomipramine, haloperidol, placebo in Remington 2001)
	Sample size	42 [24-80], min/max 10-308	34 [20-47], min/max 10-322
	Sponsorship	Academic sponsorship (k=76), financial interest due to industry sponsorship (k=37) or patent application (k=3), n.i. or unclear sponsorship (k=9)	Academic sponsorship (k=9), financial interest due to industry sponsorship (k=6) or patent application (k=3)
Intervention	Experimental intervention	<u>Pharmacological (k=84):</u> amantadine (k=1), arbaclofen (k=1), aripiprazole (k=8), atomoxetine (k=4, while two arms with atomoxetine + parental training and parental training were not analyzed), balovaptan (k=1), bumetanide (k=4), buspirone (k=1), cannabinoids (k=1), citalopram (k=2), donepezil (k=2, including one study with donepezil + choline), fenfluramine (k=4), fluoxetine (k=4), fluvoxamine (k=1), guanfacine (k=1), haloperidol (k=4), IGOH (k=1), ketamine (k=1), L1-79 (k=1), lamotrigine (k=1), levetiracetam (k=1), lurasidone (k=1), mecamylamine (k=1), melatonin (k=4, while two arms with melatonin + CBT and CBT were not investigated), memantine (k=4), methylphenidate (k=3), mirtazapine (k=1), naltrexone (k=5), olanzapine (k=2), ORG-2766 (k=2), oxytocin	<u>Pharmacological (k=16)</u> balovaptan (k=2), citalopram (k=1), clomipramine (k=1), dextromethorphan/quinidine (k=1), haloperidol (k=1), ketamine (k=1), milnacipran (k=1), oxytocin (k=6), risperidone (k=1) <u>Dietary supplements (k=2)</u> sulforaphane (k=2)

		(k=6), prednisolone (k=1), riluzole (k=1), risperidone (k=10), sertraline (k=1), simvastatin (k=1), tianeptine (k=1), tideglusib (k=1), valproate/divalproex (k=3) <u>Dietary supplements (k=41)</u>: carnitine/carnosine (k=4), cholesterol (k=1), digestive enzymes (k=1), dimethylglycine (k=1), ferrous (k=1), folinic acid (k=2), gluten-casein supplement (k=1), inositol (k=1), n-acetylcysteine (k=3), pre/probiotics (k=5), omega-3 (k=11, while an arm with vitamin-D + omega-3 was not analyzed), pyridoxine+Mg (k=1), saproptertin (k=2), sulforaphane (k=1), vitamin-B12 (k=2), vitamin-D (k=4, while three arms with vitamin-D + omega-3, perceptual exercise + vitamin D and perceptual exercise were not analyzed), whey-protein (k=1)	
	Dose administration	Flexible schedule (k=52), fixed (k=70), n.i. (k=4)	Flexible schedule (k=8), fixed (k=10), n.i. (k=4)
	Route of administration	Oral (k=117), intranasal (k=6), subcutaneous (k=2)	Oral (k=11), intranasal (k=7)
Participants	Diagnosis	<u>Standardized diagnostic criteria (k=118):</u> DSM-III (k=15), DSM-IV (k=66), DSM-5 (k=29), ICD-10 (k=4), DSM version n.i. (k=2), DSM was assumed (k=2) *Studies could have used more than one diagnostic criteria* <u>Studies that used only diagnostic tools (k=7):</u> ADI-R and/or ADOS (k=3), CARS (k=3), SCQ + clinical diagnosis (k=1, validation of the method was reported**)	<u>Standardized diagnostic criteria (k=18):</u> DSM-III (k=1), DSM-IV (k=13), DSM-5 (k=4)
	Age	8.23 years [6.26-9.51], min/max of mean age 3.62-14.64 years, n.i. (k=5)	24.55 years [21.92-27.91], min/max of mean age 16.33-34.31 years, n.i. (k=1)
	Sex	Percentage of female participants was 16.37% [11.95-20.42%], min/max 0-50%, n.i. (k=7)	Percentage of female participants was 10% [0-20.25%], min/max 0-30%, n.i. (k=1)
	Intellectual disability	Percentage of participants with intellectual impairment was 56% [31.74-83.77%], min/max 0-100%, n.i. (k=87). The mean IQ was 71.6 [62.44-84.31], min/max 40-102.5, n.i. (k= 86). Different scales and versions were used within and between studies.	Percentage of participants with intellectual impairment was 0% [0-8.11%], min/max 0-100%, n.i. (k=5). The mean IQ was 102.14 [79.9-105.55], min/max 30.98-108, n.i. (k=5). Different scales and versions were used within and between studies.
	Associated symptoms	Associated symptoms as inclusion criteria (k=45): Irritability (k=15), ADHD symptoms (k=10), irritability and hyperactivity (k=1), anxiety (k=1), disruptive behaviors (k=1), difficulty in motor skills (k=1), gastrointestinal symptoms (k=1), gastrointestinal symptoms and anxiety (k=1), language impairment (k=2), lower scores in executive functions (k=1), lower levels of vitamin-D (k=2), lower levels of cholesterol (k=1), lower levels of tetrahydrobiopterin in CSF (k=1), maladaptive behaviors and high urine levels of I-FABP (k=1), sleep disorders (k=5), sleep disorders and low levels of ferritin (k=1). Not indicated or unclear (k=2) Genetic syndrome as inclusion criteria (k=1, neurofibromatosis type 1)	Associated symptoms as inclusion criteria (k=2): Irritability or labile emotional state (k=1), self-injurious behavior (k=1)

	Baseline severity	Baseline CGI-Severity 4.87 [4.52-5.13], min/max 3.74-5.8, n.i. (k=82) Baseline ABC-Irritability 18.23 [13.99-23.24], min/max 11.01-29.91, n.i, (k=86) Minimum threshold of ASD core symptoms for inclusion (k=9): SRS (k=2), ABC-L/SW (k=2), CARS (k=1), CPRS items (k=1), C-YBOCS, C-YBOCS-PDD (k=3)***	Baseline CGI-Severity 4.4 [4.2-4.5], min/max 4.1-5.9, n.i. (k=9) Baseline ABC-Irritability 11.41 [8.73-14.04], min/max 8.07-14.56, n.i, (k=14) Minimum threshold of ASD core symptoms for inclusion (k=5): SRS (k=2), ABC-L/SW (k=1), CYBOCS or YBOCS (k=1), YBOCS, RLRS or SIBQ (k=1)***
Scales	Social-communication difficulties	69 studies: ABC-L/SW or ABC-SW (k=38), ADOS-SI (k=5), ATEC-S (k=3), BASC-S (k=1), CBCL-Social (k=1), CCC-2-SIDC (k=2), GARS—SI (k=2), SRS-SC (k=4), VABS-S (k=13)	8 studies: ABC-L/SW (k=4), ADOS-SI (k=2), VABS-S (k=2)
	Repetitive behaviors and restricted interests	60 studies: ABC-S (k=30), ADOS-RRBI (k=4), CYBOCS-PDD or similar versions (k=14), GARS-S (k=3), PDDBI-RRBI (k=1), RBS (k=5), SRS-RRBI (k=3)	14 studies: ABC-S (k=5), ADOS-RRBI (k=2), YBOCS or modifications (k=6), RBS (k=1)
	Overall core symptoms	55 studies: ADOS (k=7), CARS (k=12), CPRS-AF (k=2), CSBQ (k=1), GARS (k=2), PDDBI (k=2), RLRS (k=4), SRS (k=25)	9 studies: ADOS (k=1), CARS (k=2), RLRS (k=1), SRS (k=5)
	Irritability	59 studies: ABC-I (k=50), CBCL-Aggression (k=3), CPRS-Anger or Conduct problems (k=2), DBC-Disruptive (k=2), HSQ (k=1), SDQ-CP (k=1)	7 studies: ABC-I (k=5), POMS-Anger (k=1), SIB-Q (k=1)
	ADHD symptoms	50 studies: ABC-H (k=38), ADHD-RS (k=5), CBCL-ADHD (k=1), CPRS-H (k=3), DBC-ADHD (k=1), SDQ-H (k=1), SNAP-IV-ADHD (k=1)	7 studies: ABC-H (k=7)
	Anxiety or depressive symptoms	18 studies: BASC-I (k=2), CASI (k=2), CBCL-I (k=3), DBC-Anxiety (k=2), NCBRF-insecure/anxious (k=1), PARS (k=2), PAS-R (k=1), PRAS-ASD (k=1), SCAS (k=2), SDQ-Emotional (k=1), VAS-Anxiety (k=1)	7 studies: HAM-A (k=1), POMS-Depression (k=1), STAI-State (k=4), VAS-Anxiety (k=1)
	Caregiver stress	14 studies: APSI (k=1), CGSQ (k=2), CSQ (k=3), NOSI (k=1), PedsQL-Family Impact (k=1), PSI (k=5), WHO-5 (k=1)	2 studies: PedsQL-Family Impact (k=2)
	Global functioning	6 studies: CGAS or similar versions (k=6)	3 studies: GAF (k=3)
	Quality of life	5 studies: PedsQL or similar versions (k=5)	5 studies: PedsQL (k=2), WHO-QOL (k=3)

The median of values are presented (of summary data), [] = interquartile ranges, min/max =minimum and maximum of the study-level average values are presented, k= number of studies, n.i. = not indicated or unclear, IGOH= oral human immunoglobulin, CBT=Cognitive-behavioral therapy, PT=Parent Training

*only crossover studies with available data before the crossover

**Lee H, Marvin AR, Watson T, et al. Accuracy of phenotyping of autistic children based on Internet implemented parent report. Am J Med Genet B Neuropsychiatr Genet. 2010;153B(6):1119-1126.

***When scales used only for the confirmation of a diagnosis (such as SRS T-score of 60, CARS score of 30) were not considered as a minimum threshold of symptoms.

5.1.2 Characteristics of included studies for quantitative analysis

ID	Study name	Intervention	n	Duration (weeks)	Blinding (0: open, 1: single-blind, 2: double-blind)	Diagnostic criteria or tools	Age (years)	Participant subgroup defined per inclusion criteria (associated condition, intellectual function, genetic syndrome)
1	Akkok_1995	placebo	9	2	1	DSM-III-R	6.3	
		naltrexone	11				6.3	
2	Aman_2017	placebo	61	12	2	DSM-IV-TR	8.9	participants with irritability were excluded
		memantine	60				9	
3	Amminger_2007	placebo	6	6	2	DSM-IV	12.1	Irritability and no other psychotropic medication
		omega-3	7				10.5	
4	Anagnostou_2012	placebo	9	6	2	DSM-IV-TR	32.9	high functioning
		oxytocin	10				33.8	
5	Anderson_1989	placebo	30	4	2	DSM-III	4.5	hypoactive or low energic participants were excluded
		haloperidol	15				4.5	
6	Arnold_2006	placebo	7	6	2	DSM-IV	9.3	ADHD symptoms
		atomoxetine	9				9.3	
7	Arnold_2012	placebo	8	14	2	DSM-IV	8.4	
		mecamylamine	12				6.8	
8	Arnold_2019	placebo	4	8	2	DSM-5	8.8	gastrointestinal symptoms and anxiety
		probiotics	6				8.8	
9	Barthelemy_1989	placebo	6	4	2	DSM-III	6.3	intellectual disability and no other psychotropic medication
		fenfluramine	7				6.3	
10	Belsito_2001	placebo	16	12	2	(ADI-R, ADOS, CARS)	6.1	
		lamotrigine	19				5.6	
11	Bent_2011	placebo	13	12	2	DSM-IV-TR	5.8	
		omega-3	14				5.8	
12	Bent_2014	placebo	28	6	2	(SCQ and a previous	7.1	ADHD symptoms
		omega-3	29				7.3	

						clinical diagnosis)		
13	Bernaerts_2020	placebo	18	4	2	DSM-IV-TR	24	high functioning
		oxytocin	22				25	
14	Bertoglio_2010	placebo	17	6	2	DSM-IV-TR	(3-8)	
		vitamin-B12	13				(3-8)	
15	Bolognani_2019	placebo	75	12	2	DSM-5, ICD-10	24.7	high functioning
		balovaptan 1.5 mg/d	32				28.2	
		balovaptan 4 mg/d	77				24.5	
		balovaptan 10 mg/d	39				23.9	
16	Bouvard_1995	placebo	5	4	2	DSM-III-R, ICD-10	9.5	
		naltrexone	5				9.5	
17	Buietlaar_1990	placebo	7	4	2	DSM-III-R	8.8	
		ORG-2766	7				8.7	
18	Buitelaar_1992	placebo	11	8	2	DSM-III-R	10.3	
		ORG-2766	10				10.3	
19	Campbell_1982	placebo	20	4	2	DSM-III	4.6	hypoactive or low energic participants were excluded
		haloperidol	20				4.6	
20	Campbell_1987	placebo	14	8	2	DSM-III	4.6	
		fenfluramine	14				4.6	
21	Campbell_1993	placebo	18	3	2	DSM-III-R	4.9	
		naltrexone	23				4.9	
22	Chez_2017	placebo	7	8	2	DSM-IV-TR	21.9	Irritability or emotional lability
		dextromethorphan + quinidine	7				21.9	
23	Chugani_2016	placebo	57	24	2	DSM-IV-TR	3.6	
		buspirone 2.5mg/day	54				3.5	
		buspirone 5 mg/day	55				3.8	
24	Cortesi_2012	placebo	40	12	2	DSM-IV-TR	6.3	sleep disorders
		CBT	40				7.1	
		melatonin	40				6.8	

		melatonin+CBT	40				6.4	
25	Danfors_2005	placebo	6	26	2	DSM-IV	4.9	low tetrahydrobiopterin levels in CSF
		sapropterin	6				5.7	
26	Dean_2017	placebo	51	24	2	DSM-IV-TR	6.2	
		n-acetylcysteine	51				6.5	
27	DeVane_2019	aripiprazole	31	10	2	DSM-IV	8.5	irritability
		risperidone	30				8.3	
28	Ekman_1989	placebo	10	16	2	DSM-III, DSM-III-R	6.2	
		fenfluramine	10				6.2	
29	EUCTR2014-001560-35	placebo	45	13	2	DSM-IV-TR, DSM-5	10.2	
		bumetanide	47				10.5	
30	Fahmy_2013	placebo	14	26	2	(CARS)	5.7	
		carnosine	16				5.8	
31	Findling_1997	placebo	5	4	2	DSM-III-R	6.3	
		pyridoxine+Mg	5				6.3	
32	Frye_2018	placebo	25	12	2	DSM (version not specified)	7.2	language impairment and participants with irritability were excluded
		folinic acid	23				7.6	
33	Gabis_2019	placebo	31	12	2	DSM-IV-TR, DSM-5	9.5	
		donepezil+choline	29				9.5	
34	Geier_2011	placebo	11	13	2	(CARS)	6.7	
		carnosine	19				6.3	
35	Ghanizadeh_2014	aripiprazole	29	8	2	DSM-IV-TR	9.6	
		risperidone	30				9.5	
36	Ghodsi_2018	placebo	22	8	2	DSM-5	8.4	
		carnosine	22				8.9	
37	Ghuman_2009	placebo	6	2	2	DSM-IV-TR	4.8	ADHD symptoms
		methylphenidate	6				4.8	
38	Gringras_2017	placebo	65	13	2	DSM-IV-TR, DSM-5, ICD-10	8.4	sleep disorders
		melatonin	60				9	
39	Guastella_2015	placebo	24	8	2	DSM-IV-TR	14	

		oxytocin	26				13.8	
40	Handen_2000	placebo	4	1	2	(CARS)	7.4	ADHD symptoms
		methylphenidate 0.3mg/kg/d	9				7.4	
41	Handen_2009	placebo	31	12	2	DSM-IV-TR	6.2	gastrointestinal symptoms
		IGOH 140mg/day	32				7.4	
		IGOH 420mg/day	31				8	
		IGOH 840mg/day	31				7.6	
42	Handen_2012	placebo	16	10	2	DSM-IV-TR	11.7	high functioning and lower scores in executive function system
		donepezil	18				11.5	
43	Handen_2015	placebo	32	10	2	DSM-IV-TR	8.2	ADHD symptoms
		atomoextine+PT	32				8	
		atomoxetine	32				8.6	
		PT	32				7.7	
44	Hardan_2012	placebo	18	12	2	DSM-IV-TR	7.2	irritability
		n-acetylcysteine	15				7	
45	Harfterkamp_2013	placebo	49	8	2	DSM-IV-TR	10	ADHD symptoms
		atomoxetine	48				9.9	
46	Hellings_2005	placebo	14	8	2	DSM-IV	12.1	Irritability
		valproate	16				10.3	
47	Hendren_2016	placebo	29	8	2	DSM-IV	4.8	
		vitamin-B12	28				5.6	
48	Herscu_2019	placebo	80	14	2	DSM-IV-TR	8.9	participants with irritability were excluded
		fluoxetine	78				9.1	
49	Hollander_2005	placebo	20	8	2	DSM-IV-TR	7.3	
		fluoxetine	19				9.1	
50	Hollander_2006	placebo	4	8	2	DSM-IV	9.5	
		divalproex	9				9.5	
51	Hollander_2006b	placebo	5	8	2	DSM-IV	8.9	
		olanzapine	6				9.2	

52	Hollander_2010	placebo	11	12	2	DSM-IV-TR	9	Irritability
		divalproex	16				9.7	
53	Hollander_2012	placebo	15	12	2	DSM-IV	38	
		fluoxetine	22				31.8	
54	Ichikawa_2017	placebo	45	8	2	DSM-IV-TR	9.9	Irritability
		aripiprazole	47				10.3	
55	Kent_2013	placebo	35	6	2	DSM-IV-TR	9	Irritability
		risperidone 0.125mg/day	30				10	
		risperidone 1.25mg/day	31				9	
56	Kerley_2017	placebo	20	20	2	DSM (version not specified)	6.9	
		vitamin-D	22				7.9	
57	Kern_2001	placebo	19	4	2	DSM-IV	(3-11)	
		dimethylglycine	18				(3-11)	
58	King_2001	placebo	20	4	2	DSM-IV, ICD-10	7	irritability and ADHD symptoms
		amantadine	19				7	
59	King_2009	placebo	76	12	2	DSM-IV-TR	9.6	participants with irritability were excluded
		citalopram	73				9.1	
60	Klaiman_2013	placebo	23	16	2	DSM-IV-TR	5	participants with irritability were excluded
		sapropterin	23				5	
61	Kosaka_2016	placebo	20	12	2	DSM-IV-TR	24.9	high functioning
		oxytocin 16IU/day	20				23.3	
		oxytocin 32IU/day	20				24.8	
62	Lamberti_2016	aripiprazole	22	24	0	DSM-5	8.4	ADHD symptoms
		risperidone	22				7.9	
63	Lemonnier_2012	placebo	30	13	2	ICD-10	7.1	
		bumetanide	30				6.9	
64	Lemonnier_2017	placebo	23	13	2	ICD-10	8.9	
		bumetanide 1mg/day	20				7.8	
		bumetanide 2mg/day	23				7.9	
		bumetanide 4mg/day	22				8.4	

65	Leventhal_1993	placebo	8	16	2	DSM-III	7.6	intellectual disability
		fenfluramine	7				7.6	
66	Levine_1997	placebo	5	4	2	DSM-III-R	6	intellectual disability
		inositol	5				5.2	
67	Liu_2019	placebo	41	4	2	DSM-5	9.9	
		probiotic	39				10.1	
68	Loebel_2016	placebo	50	6	2	DSM-IV-TR	11	Irritability
		lurasidone 20mg/day	49				10.5	
		lurasidone 60mg/day	51				10.5	
69	Malone_2001	haloperidol	6	6	0	DSM-IV	7.3	Irritability
		olanzapine	6				8.5	
70	Mankad_2015	placebo	19	24	2	DSM-IV-TR	3.5	
		omega-3	19				3.9	
71	Marcus_2009	placebo	52	8	2	DSM-IV-TR	10.2	Irritability
		aripiprazole 5mg/day	53				9	
		aripiprazole 10mg/day	59				10	
		aripiprazole 15mg/day	54				9.5	
72	Mazahery_2019	placebo	29	52	2	DSM-5	5.5	low vitamin-D in serum
		omega-3	29				5	
		vitamin-D	31				5.2	
		vitamin-D+omega-3	28				5.2	
73	McDougle_1996	placebo	15	12	2	DSM-III-R	30.1	
		fluvoxamine	15				30.1	
74	McDougle_1998	placebo	16	12	2	DSM-IV	29.7	YBOCS, RLRS or SIBQ for inclusion (not considered for indirectness)
		risperidone	15				26	
75	McDougle_2000	placebo	16	12	2	(diagnosis not specified; most probably with DSM-IV)	9.5	
		fluvoxamine	18				9.5	
76	Mehrazad_2018	placebo	25	8	2	DSM-V	8.3	sleep disorders
		carnosine	25				8.6	

77	Miral_2008	haloperidol	15	10	2	DSM-IV	10.9	
		risperidone	15				10	
78	Moradi_2018	placebo	25	13	2	DSM-5	7.2	high functioning and low levels of vitamin-D in serum
		perceptual exercise	25				7.6	
		vitamin-D	25				8	
		vitamin-D + perceptual exercise	25				7.6	
79	Munasinghe_2010	placebo	22	13	2	DSM-IV-TR	5.8	
		digestive enzymes	21				5.7	
80	Munesue_2016	placebo	14	8	2	DSM-IV-TR	22.4	intellectual disability
		oxytocin	15				22.6	
81	Nagaraj_2006	placebo	21	24	2	DSM-IV	5.2	
		risperidone	19				4.8	
82	NCT00183339	placebo	10	52	2	DSM-IV-TR	3.7	
		fluoxetine	8				3.5	
83	NCT00198107	placebo	41	8	2	DSM-IV	9.4	Irritability
		aripiprazole	40				9	
84	NCT00498173	placebo	31	8	2	DSM-IV	8.4	ADHD symptoms and exclusion of extreme aggression or self-injury
		atomoxetine	29				9.3	
85	NCT00609531	placebo	6	12	2	DSM-IV-TR	(10-55)	high functionin
		citalopram	6				(10-55)	
86	NCT00870727	placebo	16	8	2	DSM-IV-TR	9.5	Irritability
		aripiprazole	17				9.8	
87	NCT01302964	placebo	10	10	2	DSM-IV-TR	11.3	anxiety
		mirtazapine	20				10.9	
88	NCT01308749	placebo	13	8	2	DSM-IV	10	
		oxytocin	12				10.6	
89	NCT01624675	placebo	18	8	2	DSM-IV-TR	7	irritability
		risperidone	21				8	
90	NCT01661855	placebo	29	12	2	DSM-IV	11.5	

		riluzole	29				11.6	
91	NCT01908205	placebo	30	12	2	DSM-IV	12.4	high functioning
		oxytocin	30				12.5	
92	NCT01972074	placebo	21	12	2	DSM-5	13.3	high functioning
		memantine	22				13.2	
93	NCT02385799	placebo	26	26	2	DSM-5	3.7	
		sertraline	32				4.3	
94	NCT02551380	placebo	10	12	1	(ADOS)	6.4	language impairment and participants with irritability were excluded
		folinic acid	9				6.4	
95	NCT02586935	placebo	40	12	2	DSM-5	(12-17)	
		tideglusib	40				(12-17)	
96	NCT02909959	placebo	24	12	2	DSM-5	17.7	
		sulforaphane	24				16.8	
97	NCT02947048	placebo	10	4	2	DSM-5	(13-21)	
		L1-79 300mg/d	10				(13-21)	
		L1-79 600mg/day	10				(13-21)	
98	NCT02956226	placebo	50	12	2	DSM-5	11.8	disruptive behaviors
		cannabinoids pure mix	50				11.8	
		cannabinoids whole plant	50				11.8	
99	Niederhofer_2003	placebo	6	6	2	ICD-10	7.3	No tolerance or response to previous psychopharmacological treatments
		tianeptine	6				7.3	
100	Nikvarz_2017	memantine	18	8	0	DSM-IV-TR	6.8	
		risperidone	16				6.6	
101	Noone_2014	placebo	5	12	2	DSM-IV-TR	25.2	high functioning
		milnacipran	5				25	
102	Owen_2009	placebo	51	8	2	DSM-IV-TR	8.8	irritability
		aripiprazole	47				9.7	
103	Parellada_2017	placebo	37	8	2	DSM-IV-TR	10	
		omega-3	40				9.4	
104	Parker_2017	placebo	18	4	2		8.1	

		oxytocin	17			DSM-IV-TR, DSM-5	9.3	
105	Pearson_2013	placebo	6	1	2	DSM-IV-TR	8.8	ADHD symptoms
		methylphenidate low dose	6				8.8	
		methylphenidate medium dose	6				8.8	
		methylphenidate high dose	6				8.8	
106	Pusponegoro_2015	placebo	36	1	2	DSM-IV-TR	5.1	maladaptive behaviors and high levels of I-FABP in urine
		gluten-casein	38				5.4	
107	Reddihough_2019	placebo	71	16	2	DSM-IV-TR, DSM-5	11.2	
		fluoxetine	75				11.3	
108	Remington_2001	placebo	10	6	2	DSM-IV	18.5	
		clomipramine	13				16.8	
		haloperidol	13				14.2	
109	Reynold_2019	placebo	11	12	2	DSM-IV-TR	5.7	sleep disorders and low level of ferritin
		ferrous	9				6	
110	RUPP_2002	placebo	52	8	2	DSM-IV	9.1	irritability
		risperidone	49				8.6	
111	Scahill_2015	placebo	32	8	2	DSM-IV	8.5	ADHD symptoms
		guanfacine	30				8.5	
112	Scifo_1991	placebo	6	15	2	DSM-III-R	11.2	intellectual disability
		naltrexone	6				11.2	
113	Shea_2004	placebo	39	8	2	DSM-IV	7.3	
		risperidone	41				7.6	
114	Singh_2014	placebo	15	18	2	DSM-IV-TR	16.6	
		sulforaphane	29				17.9	
115	Stivaros_2018	placebo	16	12	2	(ADI-R, ADOS, SRS)	8.3	genetic syndrome (neurofibromatosis type I)
		simvastatin	14				7.9	
116	Vasconcelos_2014	placebo	20	24	2	DSM-IV-TR	4.6	
		prednisolone	20				4.8	
117	VeenstraVanderWeele_2017	placebo	74	12	2	DSM-IV-TR	11.7	

		arbaclofen	76				11.4	
118	Voigt_2014	placebo	24	26	2	DSM-IV	6.5	
		omega-3	24				5.8	
119	Wang_2020	placebo	10	15	2	CCMD-3, DSM-5	4.3	participants with hyperactivity were excluded
		probiotics	16				4.3	
120	Wasserman_2006	placebo	10	10	2	DSM-IV	9.8	
		levetiracetam	10				7.6	
121	Watanabe_2015	placebo	10	6	2	DSM-IV-TR	29.3	high functioning
		oxytocin	10				35.1	
122	Willemsen_1996	placebo	12	4	2	DSM-III-R	5.5	
		naltrexone	11				5.5	
123	Wink_2016	placebo	15	12	2	DSM-IV	8.2	
		n-acetylcysteine	16				7.6	
124	Wink_2020	placebo	10	2	2	DSM-5	19.5	
		ketamine	11				19.5	
125	Wright_2011	placebo	11	13	2	ICD-10	9	sleep disorders
		melatonin	9				9	
126	Yamasue_2018	placebo	53	6	2	DSM-IV-TR	26.3	high functioning
		oxytocin	53				27.6	
127	Yatawara_2016	placebo	22	5	2	DSM-IV-TR	6.7	
		oxytocin	17				5.7	
128	Yui_2013	placebo	6	16	2	DSM-IV	15.5	high functioning
		omega-3	7				13.9	
129	IRCT20131013014994N5	placebo	26	15	2	DSM-5	8.95	
		Vitamin-D	26				8.88	
130	Santocchi_2019	placebo	43	26	2	DSM-5	4.13	
		probiotics	42				4.16	
131	NCT01372449	placebo	11	24	2	DSM-IV-TR, DSM-5	9.64	difficulty in motor skills and participants with irritability were excluded
		memantine	12				9.25	
132	NCT01944046	placebo	144	24	2	DSM-5	10.4	

		oxytocin	146				10.4	
133	NCT02901431	placebo	81	24	2	DSM-5, ICD-10	12.5	high functioning
		balovaptan 4mg/d (unclear information for this arm, not included in the analysis)	n.i.				n.i.	
		balovaptan 10mg/d	86				12.53	
134	NCT03156153	placebo	60	13	2	DSM-5	4.22	
		bumetanide	60				4.03	
135	NCT03337035	placebo	18	16	2	DSM-IV-TR, DSM-5	9.85	
		probiotics	17				10.7	
136	NCT03504917	placebo	158	24	2	DSM-5	27.6	high functioning
		balovaptan	163				27.9	
137	NCT00965068	placebo	7	12	2	DSM-IV	6.3	low levels of cholesterol
		cholesterol	8				6.9	
138	NCT03550209	placebo	35	13	2	DSM-5	(2-6)	
		omega-3 25mg/d	12					
		omega-3 50mg/d	12					
		omega-3 75mg/d	13					
139	Doaei_2021	placebo	26	8	2	DSM-IV-TR	8.2	
		omega-3	28				8.1	
140	Hayashi_2021	placebo	66	2	2	DSM-5	10.8	sleep difficulties
		melatonin 1mg/d	65				10.8	
		melatonin 4mg/d	65				12	
141	Zimmerman_2021	placebo	29	15	2	DSM-5	7	
		sulforaphane	28				7.4	
142	NCT00467818	placebo	8	12	2	(diagnosis not specified; most probably with DSM-IV)	10.6	
		omega-3	9				11.7	
143	Castejon_2021	whey protein	22	1	2	DSM-IV, DSM-5	3.9	
		placebo	24				3.9	

Arms in *italics* were excluded from the analysis irrespective of data availability: parental treatment, atomoxetine + parental treatment, CBT, melatonin + CBT, vitamin-D + omega-3, perceptual exercise, perceptual exercise + vitamin-D

5.2 Risk of bias

5.2.1 Risk of bias of included studies

	Study name	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting	Other biases	Overall
children/adolescents	Akkok_1995	unclear	unclear	high	unclear	low	low	unclear	moderate
	Aman_2017	low	low	unclear	unclear	low	low	unclear	moderate
	Amminger_2007	unclear	unclear	low	low	high	low	high	high
	Anderson_1989	unclear	unclear	low	low	unclear	unclear	unclear	moderate
	Arnold_2006	unclear	unclear	low	low	low	high	unclear	moderate
	Arnold_2012	low	low	unclear	unclear	low	low	high	moderate
	Arnold_2019	low	low	low	low	high	low	low	moderate
	Barthelemy_1989	unclear	unclear	unclear	unclear	low	high	unclear	moderate
	Belsito_2001	low	low	low	low	high	high	unclear	high
	Bent_2011	low	low	low	low	low	low	low	low
	Bent_2014	low	low	low	low	low	low	unclear	low
	Bertoglio_2010	low	low	unclear	unclear	low	high	unclear	moderate
	Bouvard_1995	unclear	unclear	unclear	unclear	low	high	unclear	moderate
	Buietlaar_1990	unclear	unclear	low	low	low	high	low	moderate
	Buitelaar_1992	unclear	unclear	low	low	high	high	unclear	high
	Campbell_1982	unclear	unclear	low	low	unclear	high	unclear	moderate
	Campbell_1987	unclear	unclear	low	low	unclear	high	high	high
	Campbell_1993	unclear	unclear	unclear	unclear	unclear	high	unclear	moderate
	Castejon_2021	low	low	unclear	unclear	high	high	high	high
	Chugani_2016	low	unclear	unclear	unclear	low	low	high	moderate
	Cortesi_2012	low	low	low	low	high	high	unclear	high
	Danfors_2005	unclear	low	low	low	low	high	high	high
	Dean_2017	low	low	low	low	low	low	low	low
	DeVane_2019	unclear	unclear	low	low	high	high	low	high

	Doaei_2021	low	low	unclear	unclear	low	low	low	low
	Ekman_1989	unclear	unclear	unclear	unclear	high	unclear	unclear	moderate
	EUCTR2014-001560-35	low	low	low	low	high	low	low	moderate
	Fahmy_2013	low	unclear	low	low	unclear	low	high	moderate
	Findling_1997	unclear	unclear	low	low	low	high	unclear	moderate
	Frye_2018	low	low	low	low	low	low	high	moderate
	Gabis_2019	unclear	low	low	low	high	high	unclear	high
	Geier_2011	low	unclear	low	low	high	low	low	moderate
	Ghanizadeh_2014	unclear	unclear	high	unclear	low	low	low	moderate
	Ghodsi_2018	low	unclear	unclear	unclear	high	high	unclear	high
	Ghuman_2009	unclear	unclear	low	low	low	high	unclear	moderate
	Gringras_2017	low	low	low	low	low	high	low	moderate
	Guastella_2015	low	low	low	low	low	low	low	low
	Handen_2000	unclear	unclear	unclear	unclear	low	high	unclear	moderate
	Handen_2009	low	unclear	low	low	low	high	unclear	moderate
	Handen_2012	unclear	low	unclear	unclear	low	low	low	moderate
	Handen_2015	low	low	low	low	low	low	low	low
	Hardan_2012	low	low	low	low	low	low	low	low
	Harfterkamp_2013	low	low	low	low	low	low	high	moderate
	Hayashi_2021	low	low	low	low	low	low	unclear	low
	Hellings_2005	unclear	low	unclear	unclear	unclear	high	low	moderate
	Hendren_2016	low	low	unclear	unclear	low	low	low	low
	Herscu_2019	low	low	low	low	low	low	low	low
	Hollander_2005	unclear	unclear	unclear	unclear	unclear	unclear	low	moderate
	Hollander_2006	unclear	unclear	low	low	low	unclear	low	moderate
	Hollander_2006b	unclear	unclear	low	low	unclear	high	unclear	moderate
	Hollander_2010	unclear	unclear	low	low	low	high	unclear	moderate
	Ichikawa_2017	unclear	low	unclear	unclear	low	low	low	moderate

	IRCT20131013014994N5	low	low	low	low	high	low	low	moderate
	Kent_2013	low	unclear	low	low	low	high	low	moderate
	Kerley_2017	unclear	low	low	low	high	low	low	moderate
	Kern_2001	unclear	low	low	low	high	high	high	high
	King_2001	unclear	unclear	low	low	low	high	low	moderate
	King_2009	low	unclear	low	low	low	low	low	low
	Klaiman_2013	low	low	low	low	low	low	high	moderate
	Lamberti_2016	low	unclear	high	high	unclear	high	low	high
	Lemonnier_2012	low	low	low	low	high	low	low	moderate
	Lemonnier_2017	low	low	low	low	low	low	low	low
	Leventhal_1993	unclear	unclear	unclear	unclear	low	high	unclear	moderate
	Levine_1997	low	low	low	low	low	low	low	low
	Liu_2019	low	low	low	low	high	low	low	moderate
	Loebel_2016	low	unclear	low	low	low	low	low	low
	Malone_2001	low	unclear	high	high	low	low	low	high
	Mankad_2015	low	low	low	low	low	low	low	low
	Marcus_2009	low	low	unclear	unclear	low	low	low	low
	Mazahery_2019	low	low	low	low	high	low	high	high
	McDougle_2000	unclear	unclear	unclear	unclear	unclear	unclear	unclear	moderate
	Mehrazad_2018	low	unclear	low	low	high	low	low	moderate
	Miral_2008	unclear	unclear	unclear	unclear	high	high	low	high
	Moradi_2018	unclear	unclear	unclear	unclear	unclear	high	unclear	moderate
	Munasinghe_2010	low	low	low	low	high	high	unclear	high
	Nagaraj_2006	low	low	low	low	low	low	low	low
	NCT00183339	unclear	unclear	unclear	unclear	unclear	high	unclear	moderate
	NCT00198107	unclear	unclear	unclear	unclear	low	low	unclear	moderate
	NCT00467818	unclear	unclear	unclear	unclear	unclear	unclear	unclear	moderate
	NCT00498173	unclear	unclear	low	low	unclear	low	unclear	moderate
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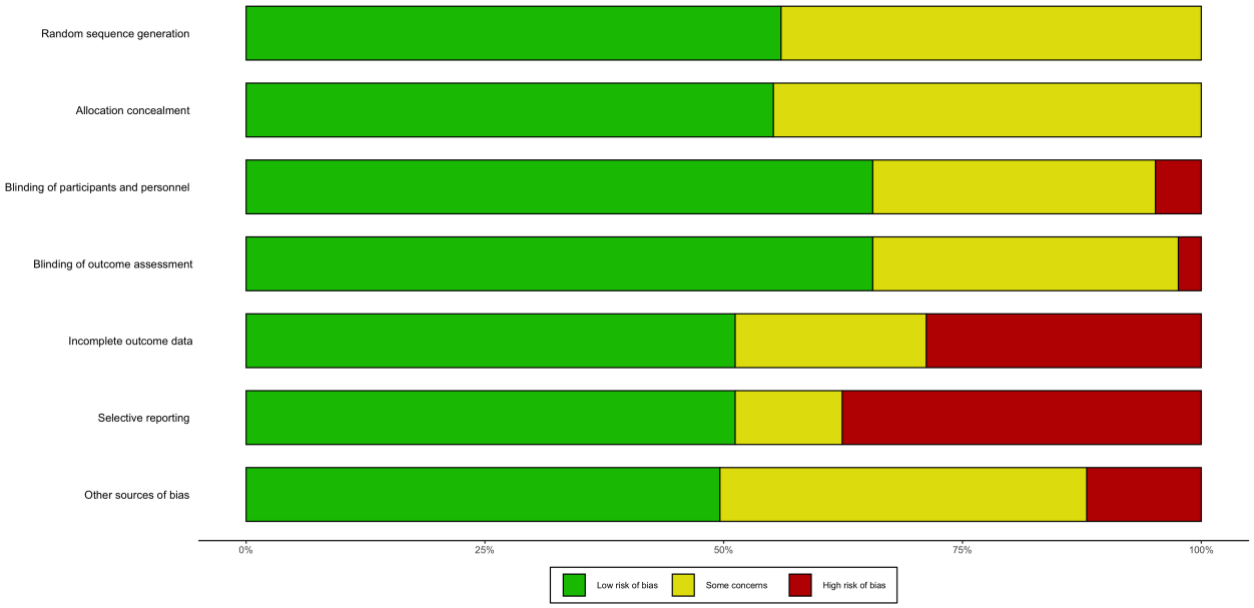
	NCT00965068	unclear	unclear	unclear	unclear	unclear	low	high	moderate
	NCT01302964	unclear	unclear	low	low	low	high	unclear	moderate
	NCT01308749	unclear	unclear	unclear	unclear	low	low	unclear	moderate
	NCT01372449	low	low	low	low	low	high	low	moderate
	NCT01624675	unclear	low	low	low	low	high	low	moderate
	NCT01661855	unclear	unclear	unclear	unclear	unclear	unclear	unclear	moderate
	NCT01908205	unclear	unclear	unclear	unclear	unclear	unclear	unclear	moderate
	NCT01944046	low	low	low	low	low	low	low	low
	NCT01972074	low	low	low	low	low	unclear	unclear	low
	NCT02385799	low	low	low	low	low	low	low	low
	NCT02551380	unclear	unclear	high	unclear	low	high	low	high
	NCT02586935	unclear	unclear	unclear	unclear	unclear	unclear	unclear	moderate
	NCT02901431	low	low	low	low	high	unclear	high	high
	NCT02947048	unclear	unclear	unclear	unclear	unclear	unclear	unclear	moderate
	NCT02956226	low	low	low	low	high	high	low	high
	NCT03156153	low	low	low	low	low	low	low	low
	NCT03337035	low	low	low	low	unclear	low	low	low
	NCT03550209	low	low	low	low	unclear	unclear	unclear	moderate
	Niederhofer_2003	unclear	unclear	low	low	unclear	high	unclear	moderate
	Nikvarz_2017	unclear	unclear	high	high	high	low	low	high
	Owen_2009	low	low	unclear	unclear	low	low	low	low
	Parellada_2017	low	low	low	low	high	low	low	moderate
	Parker_2017	low	low	low	low	high	low	low	moderate
	Pearson_2013	unclear	unclear	unclear	unclear	low	high	unclear	moderate
	Pusponegoro_2015	unclear	low	low	low	high	low	low	moderate
	Reddihough_2019	low	low	low	low	high	low	high	high
	Reynold_2019	low	low	low	low	low	high	low	moderate
	RUPP_2002	low	low	low	low	low	low	low	low
	Santocchi_2019	low	low	low	low	high	low	low	moderate

	Scahill_2015	low	low	low	low	low	low	low	low
	Scifo_1991	low	low	low	low	unclear	unclear	unclear	moderate
	Shea_2004	low	low	unclear	unclear	low	low	low	low
	Stivaros_2018	low	low	unclear	unclear	low	low	low	low
	Vasconcelos_2014	low	low	low	low	high	high	unclear	high
	VeenstraVanderWeele_2017	low	low	low	low	low	low	low	low
	Voigt_2014	low	low	low	low	high	high	unclear	high
	Wang_2020	low	unclear	unclear	unclear	high	low	low	moderate
	Wasserman_2006	unclear	unclear	low	low	unclear	high	unclear	moderate
	Willemsen_1996	unclear	unclear	unclear	unclear	low	high	unclear	moderate
	Wink_2016	low	low	low	low	high	low	low	moderate
	Wright_2011	unclear	low	low	low	high	high	unclear	high
	Yatawara_2016	low	low	low	low	high	low	low	moderate
	Yui_2013	unclear	low	low	low	unclear	low	low	low
	Zimmerman_2021	low	low	low	low	high	high	low	high
adults/mixed populations	Anagnostou_2012	low	low	unclear	unclear	low	low	low	low
	Bernaerts_2020	low	low	low	low	low	low	low	low
	Bolognani_2019	low	low	low	low	low	low	low	low
	Chez_2017	unclear	low	unclear	unclear	low	high	low	moderate
	Hollander_2012	unclear	unclear	unclear	low	low	unclear	low	moderate
	Kosaka_2016	low	low	unclear	unclear	low	low	low	low
	McDougle_1996	unclear	unclear	low	low	low	high	low	moderate
	McDougle_1998	low	unclear	low	low	low	low	low	low
	Munesue_2016	low	low	low	low	low	low	low	low
	NCT00609531	unclear	low	unclear	unclear	unclear	unclear	unclear	moderate
	NCT02909959	low	low	low	low	low	low	unclear	low
	NCT03504917	low	low	low	low	low	unclear	high	moderate
	Noone_2014	unclear	unclear	unclear	unclear	low	unclear	high	moderate

	Remington_2001	unclear	unclear	low	low	unclear	high	unclear	moderate
	Singh_2014	low	low	low	low	low	low	low	low
	Watanabe_2015	low	low	low	low	high	low	low	moderate
	Wink_2020	unclear	low	low	low	high	high	unclear	high
	Yamasue_2018	low	low	low	low	low	low	low	low

5.2.2 Risk of bias summary of included studies

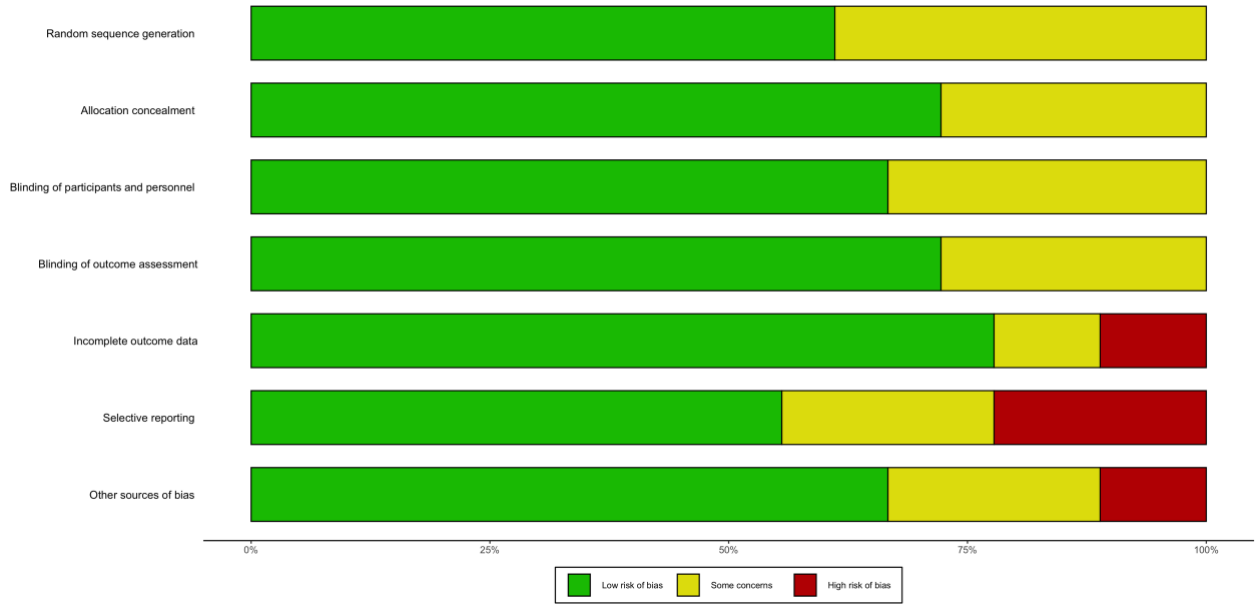
5.2.2.1 Children/adolescents



The table below presents the number and percentage of studiesin children/adolescnets (from 125 studies including in the meta-analysis of at least an outcome) with low/unclear/high risk of bias per domain.

Domain	Low risk	Unclear risk	High risk
Random sequence generation	70 (56%)	55 (44%)	0 (0%)
Allocation concealment	69 (55.2%)	56 (44.8%)	0 (0%)
Blinding of participants and personnel	82 (65.6%)	37 (29.6%)	6 (4.8%)
Blinding of outcome assessment	82 (65.6%)	40 (32%)	3 (2.4%)
Incomplete outcome data	64 (51.2%)	25 (20%)	36 (28.8%)
Selective reporting	64 (51.2%)	14 (11.2%)	47 (37.6%)
Other bias	62 (49.6%)	48 (38.4%)	15 (12%)
	Low risk	**Moderate risk**	**High risk**
Overall	29 (23.2%)	71 (56.8%)	25 (20%)

5.2.2.2 Adults/mixed populations



The table below presents the number and percentage of studies in adults or mixed populations (from 18 studies including in the meta-analysis of at least an outcome) with low/unclear/high risk of bias per domain.

Domain	Low risk	Unclear risk	High risk
Random sequence generation	11 (61.1%)	7 (38.9%)	0 (0%)
Allocation concealment	13 (72.2%)	5 (27.8%)	0 (0%)
Blinding of participants and personnel	12 (66.7%)	6 (33.3%)	0 (0%)
Blinding of outcome assessment	13 (72.2%)	5 (27.8%)	0 (0%)
Incomplete outcome data	14 (77.8%)	2 (11.1%)	2 (11.1%)
Selective reporting	10 (55.6%)	4 (22.2%)	4 (22.2%)
Other bias	12 (66.7%)	4 (22.2%)	2 (11.1%)
	Low risk	**Moderate risk**	**High risk**
Overall	9 (50%)	8 (44.4%)	1 (5.6%)

5.3. Eligible scales

5.3.1 General strategy

Data from clinicians' (observations or semi-structured interviews), caregivers' and teachers' rating scales were extracted separately for the primary outcomes and we preferred clinician's scales for the secondary outcomes. Self-reporting scales were also used when scores of other raters were not available. Usually one scale per type of informant was reported, but

- Regarding caregivers' and teachers' ratings, we preferred the frequently used scores of ABC-Lethargy/Social Withdrawal [1], ABC-Stereotypic behavior [2], SRS total score [3], ABC-Irritability [4], ABC-Hyperactivity [4], CASI-Anxiety [5]. SRS subscales were also eligible when data from other scales were not available [6, 7].
- Regarding clinicians' ratings, we preferred the frequently used Vineland-Socialization domain (semi-structured interview) [1], CYBOCS-PDD (or C-YBOCS-Compulsion subscale) [2], CARS [3], CPRS [4] and ADHD-RS (clinician-scored version) [8] as well as PARS [5].
- Self-reported scales (e.g. versions of SRS and RBS) were only rarely used in clinical trials, and they were used when scores of other raters were not available.
- No priority was given for any of the scales measuring quality of life, parental stress and global functioning, since up to one scale for each of these outcomes was usually used in the trials.

A note about SRS: The five original subscales of SRS were based on expert consensus rather appropriate factorial analyses. However, a more recent confirmatory factor analysis suggested that a two-factor structure consisting of social-communication difficulties and repetitive behaviors/restricted interests (RRBI) could be acceptable [9]. Therefore, we decided that SRS subscales would be eligible when data from other scales were not available for social-communication deficits or RRBI. We followed the two-factor structure whenever possible, and when the five original SRS subscales were reported, we used as a) measure of RRBI the subscale 'Autistic Mannerism' and as b) measure of social-communication difficulties, we calculated a total score (or average for T-standardized scores) using the four subscales Social Awareness, Social cognition, Social Communication, Social Motivation [7]. To calculate the standard deviation of a total or average score, we assumed a correlation of 0.5 between the subscales [10, 11].

5.3.2 Table of eligible scales

Social-communication difficulties	**Repetitive behaviors and restricted interests**	**Overall core symptoms**
Preferred: • ABC-Lethargy/Social Withdrawal • ADOS-Social • AIM-Social reciprocity/ AIM-Peer interaction • ASQ-Social • ATEC-Sociability • BASC-Social skills/BASC-Withdrawal • BOSCC-Social communication • CBCL-Social Problems • GARS-Social	• ABC-Stereotypic behavior • ADOS-Repetitive behaviors • AIM-Repetitive behaviors • ASQ-Stereotyped behavior • BOSCC-Repetitive behaviors • CYBOCS-PDD • CYBOCS/YBOCS-Compulsion subscale (total score also eligible)	• ADOS-CSS (total score also eligible, if the calibrated severity score not available) • BOSCC total score • AIM-Frequency/AIM-Impact • ASQ total score • AUBC total score • BSE-Autism factor • CARS total score • CBCL-PDD scale • CPRS-Autism factor • CBSQ • GARS total score

• PDD-BI-Social approach behaviors/PDD-BI-Social Pragmatic Problems • VABS-Socialization Also eligible, when the former not available: • ADOS-Communication • AIM-Communication • ASQ-Communication • BASC-Functional communication • GARS communication • PDD-BI-Receptive/expressive social communication abilities • VABS-Communication • CCC-2 Social interaction deviance index • SRS-Social communication composite score	• GARS-Stereotyped behavior • PDD-BI-Sensory perceptual approach behaviors/PDDBI-Stereotyped restricted behavior • RBQ • RBS-R total score • SRS-Autistic Mannerisms (when another scale was not available)	• PDD-BI-Autism composite score/ PDD-BI-Approach/Withdrawal problems • RF total score • SRS total score (standardized scores preferred to raw)
Irritability	**ADHD symptoms**	**Internalizing symptoms (anxiety and depressive symptoms)**
• ABC-Irritability • CBCL-Aggression • CPRS-Anger/uncooperativeness • CPRS-Conduct Problems factor • DBC-Disruptive/Antisocial subscale • HSQ-ASD • POMS-Anger • SDQ-Conduct Problems subscale • SIB-Q	• ABC-Hyperactivity • ADHD-Rating Scale • CBCL-ADHD • CPRS-Hyperactivity factor • DBC-ADHD • SDQ-H subscale • SNAP-IV-ADHD	• BASC-Internalizing • CASI • CBCL-Internalizing • DBC-Anxiety subscale • NCBRF-Insecure/anxious • PARS • PAS-R • POMS-Depression • PRAS-ASD • SCAS • SDQ-Emotional • STAI-State anxiety • VAS-Anxiety
Quality of life	**Global functioning**	**Parental stress**
• PedsQL-Generic Core • WHO-QoL	• CGAS • CGAS-DD • GAF	• APSI • CGSQ • CSQ • NOSI • PedsQL-Family Impact • PSI • WHO-5 for well-being of caregivers

Abbreviations:
ABC, Aberrant Behavior Checklist; ADOS, Autism Diagnostic Observation Scale; AIM, Autism Impact Measure; APSI: Autism Parenting Stress Index; ASQ, Autism Symptoms Questionnaires;

ATEC, Autism Treatment Evaluation Checklist; AUBC, Krug's Autism Behavior Checklist; BASC, Behavior Assessment System for Children; BSE, Behavior Summarized Evaluation; BOSCC, Brief Observation of Social Communication Change; CARS, Childhood Autism Rating Scale; CASI, Childhood Anxiety Senstvity Index; CBCL, Child Behavior Checklist; CBSQ, Children's Social Behavior Questionnaire; CCC-2, Children Communication Checklist; CGAS(-DD), Children Global Assessment Scale (-Developmental Disorders); CGSQ, Caregiver Strain Questionnaire; CPRS, Children's Psychiatric Rating Scale; (C)YBOCS-PDD, (Children) Yale Obsessive Compulsive Scale-Pervasive Developmental Disorders; CSQ, Client Satisfaction Questionnaire; DBC, Developmental Behavior Checklist; GAF, Global Assessment of Functioning; GARS, Gilliam Autism Rating Scale; HSQ-ASD: Home Situation Questionnaire-Autism Spectrum Disorder; NCBR, Nisonger Child Behavior Rating Form; NOSI, Nijmeegse Ouderlijke Stress Index; PAS-R, Preschool Anxiety Scale-Revised; PARS, Pediatric Anxiety Rating Scale; PedsQL, Pediatric Quality of Life Invenotry; PDD-BI, Pervasive Developmental Disorders Behavioral Inventory; POMS, Profile of Mood States; PRAS-ASD, Parent-Rated Anxiety Scale for ASD; RBQ, Repetitive Behaviour Questionnaire; PSI, Parental Stress Index; RBS-R, Repetitive Behavior Scale - Revised; RF, Ritvo-Freeman Real Life Rating Scale; SCAS, Spence Children's Anxiety Scale; SDQ, Strengths and Difficulties Questionnaire; SIB-Q, Self-Injurious Questionnaire; SRS, Social Responsiveness Scale; STAI, State-Trait Anxiety Inventory; VABS, Vineland Adaptive Behavior Scale; VAS, Visual Analogue Scale, WHO-QoL, World Health Organization-Quality of Life; WHO-5, World Healt Organization-Five Well-Being Index

5.4 References

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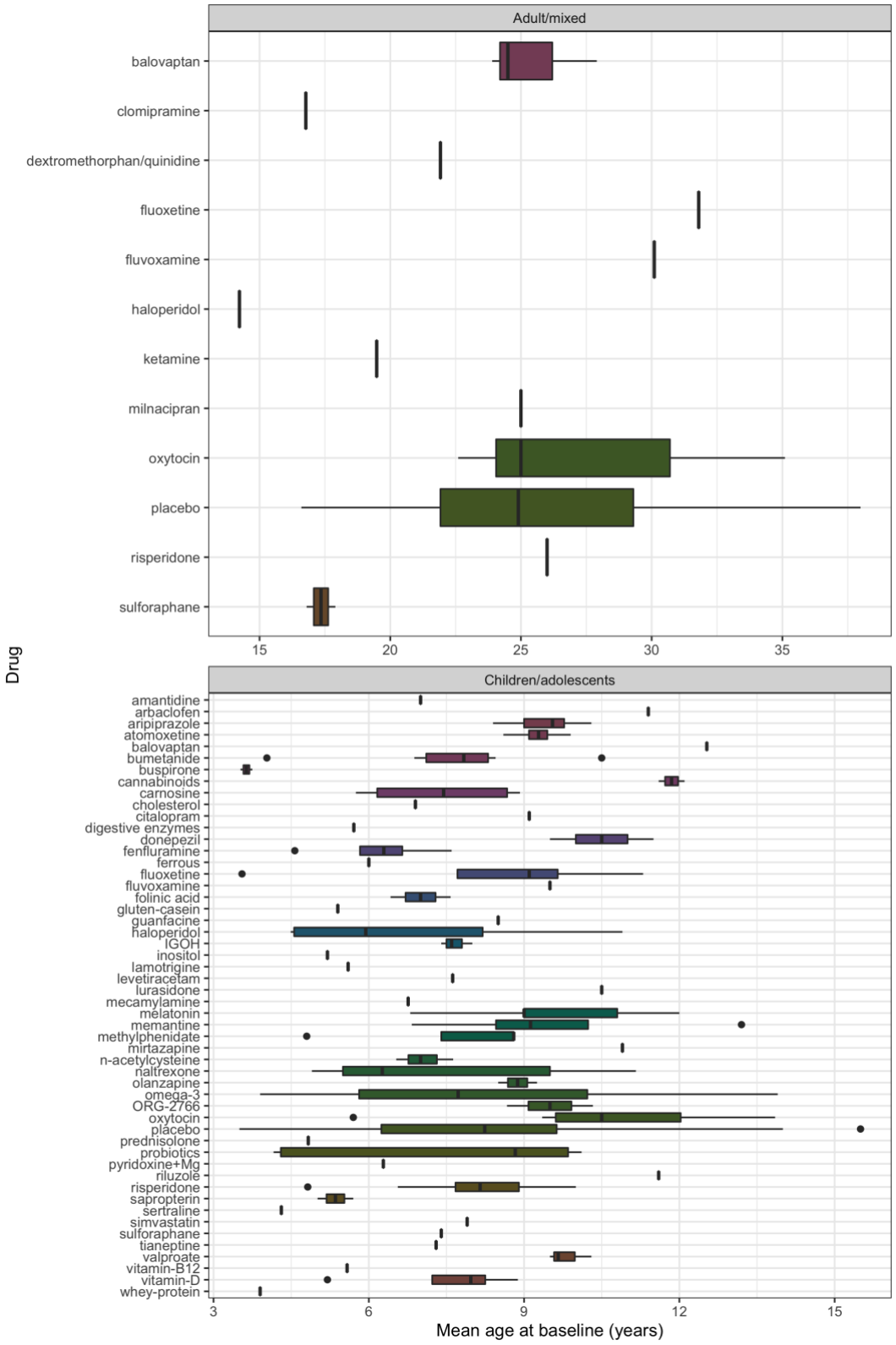
eAppendix-6 Results

6.1 Assessment of transitivity and baseline imbalance

6.1.1 Assessment of transitivity assumption

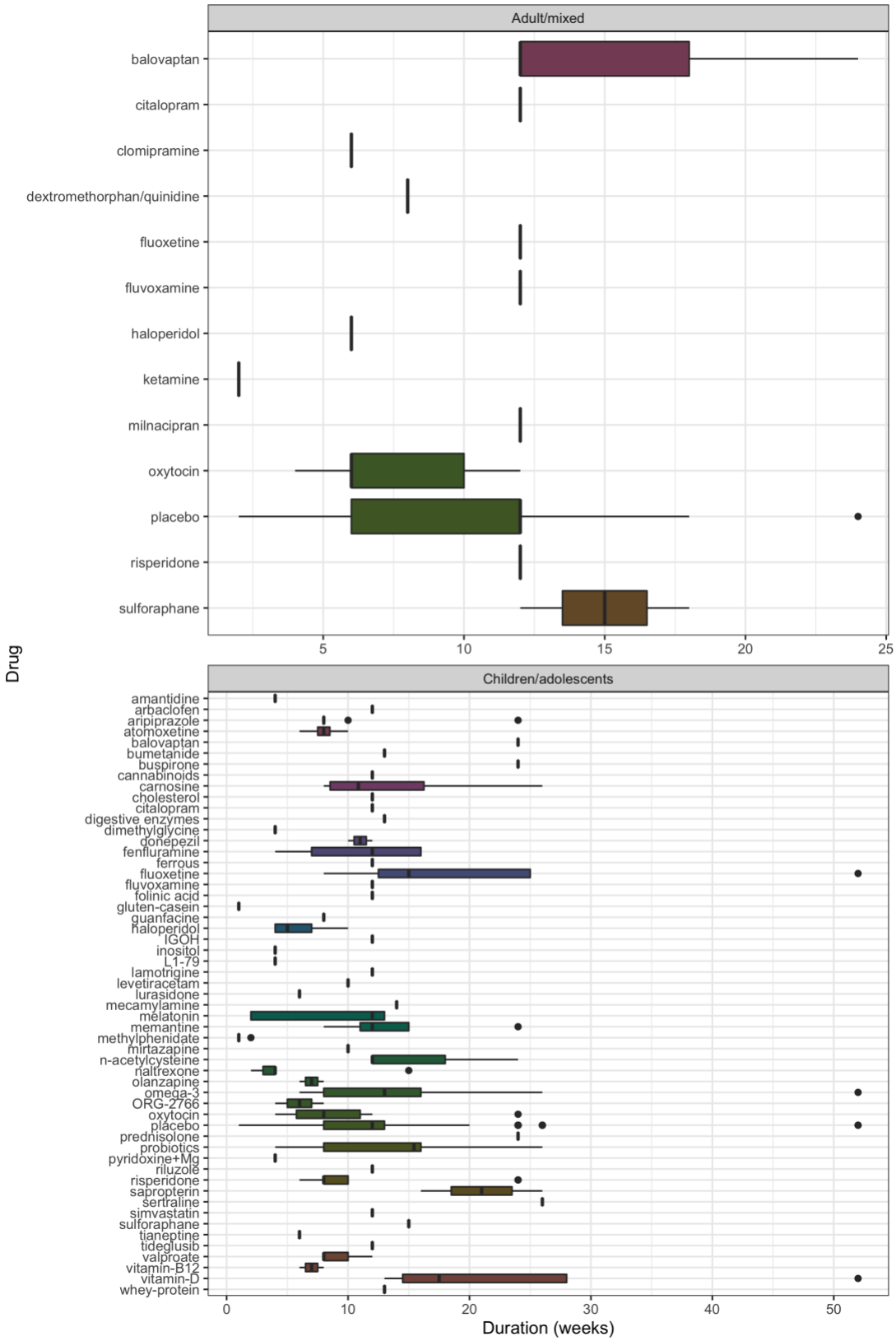
We assessed transitivity assumption by examining the distribution of potential effect-modifiers (age, trial duration, baseline ABC-irritability, baseline CGI-Severity, type of rater for the primary outcomes and the presence of associated symptoms as inclusion criteria) across treatments, since most of the comparisons were placebo-controlled. Summary statistics (as median, interquartile ranges IQR) are also presented.

6.1.1.1 Age (years)



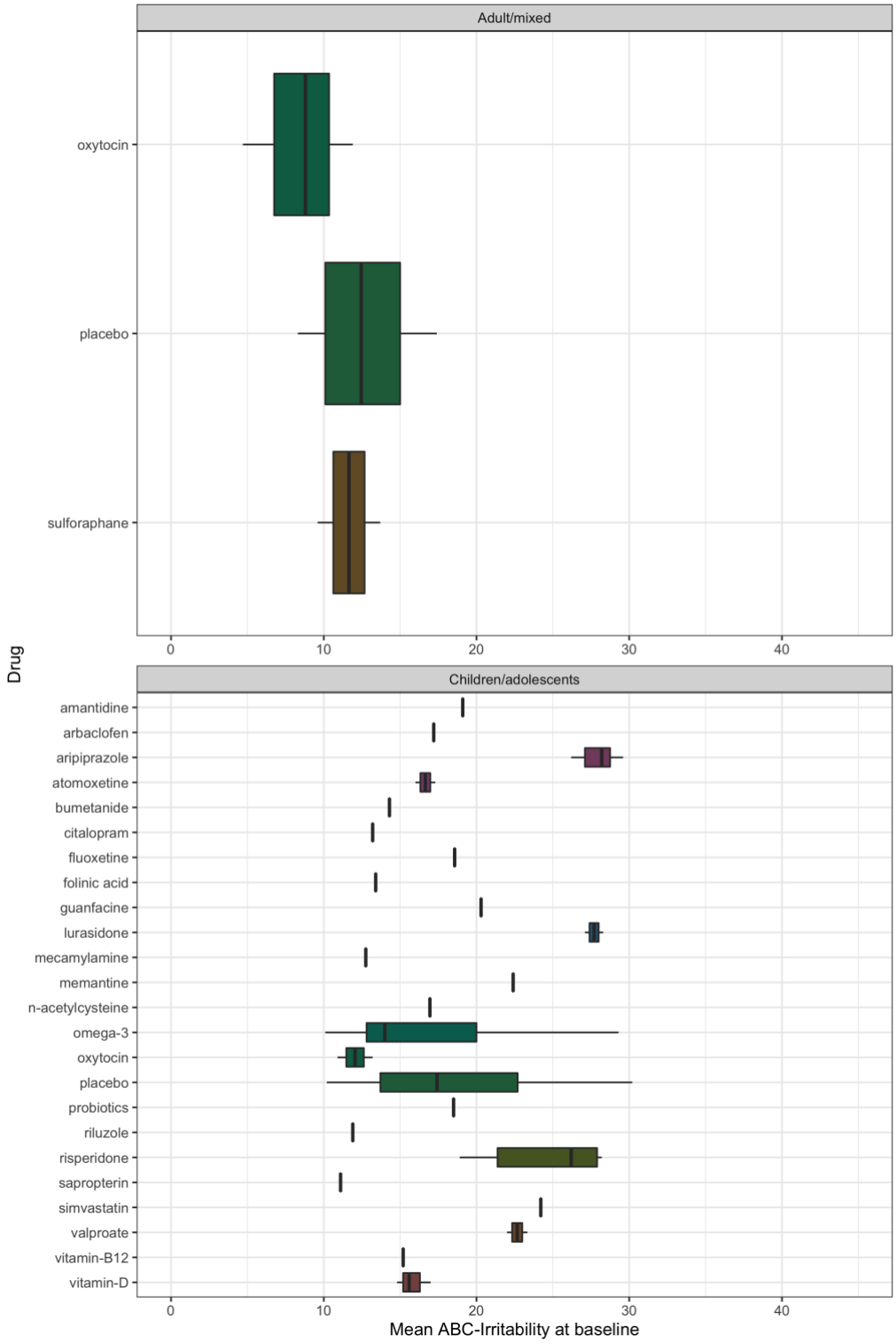
The median [IQR] of mean age was 8.23 [6.26, 9.5] in children/adolescents studies (missing in 5 arms) and 24.6 [21.92, 27.91] in adult/mixed studies (missing in 1 arms).

6.1.1.2 Trial duration (weeks)



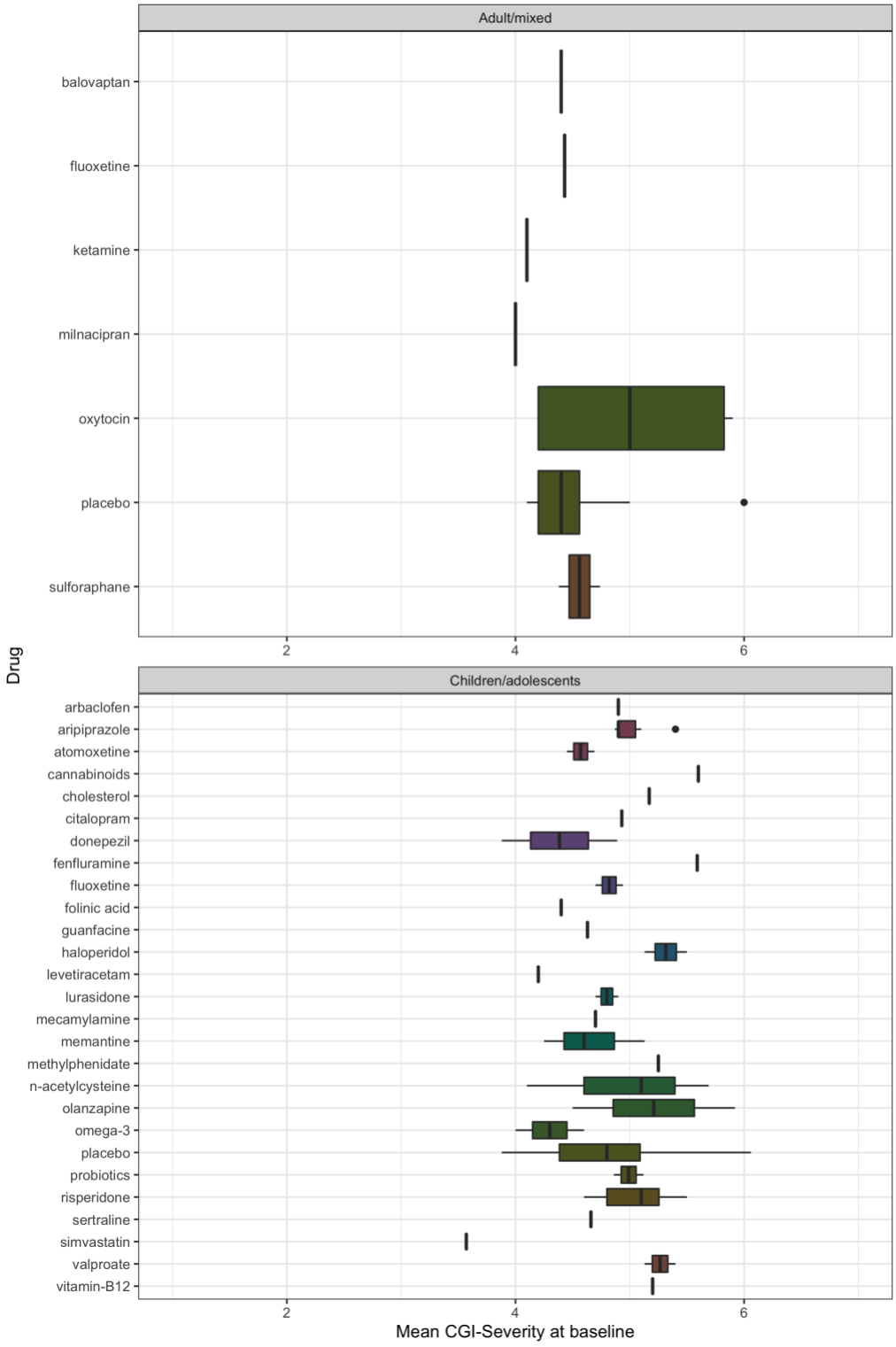
The median [IQR] of duration was 12 [8, 13] weeks in children/adolescents studies and 12 [6, 12] weeks in adult/mixed studies.

6.1.1.3 Baseline ABC-Irritability



The median [IQR] of baseline ABC-Irritability was 18.23 [13.99, 23.24] in children/adolescents studies (missing in 86 arms) and 11.41 [8.73, 14.04] in adult/mixed studies (missing in 14 arms).

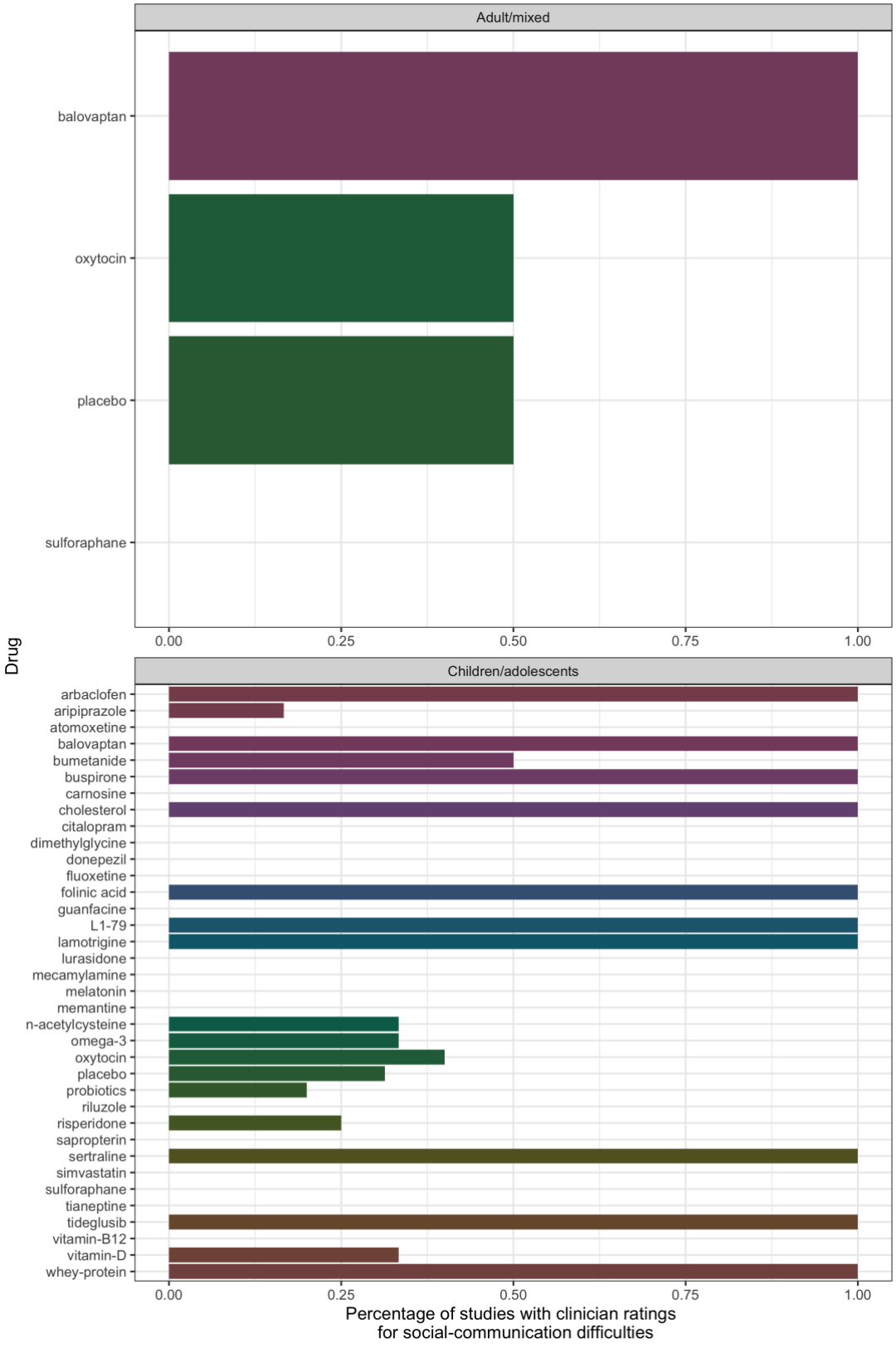
6.1.1.4 Baseline CGI-Severity



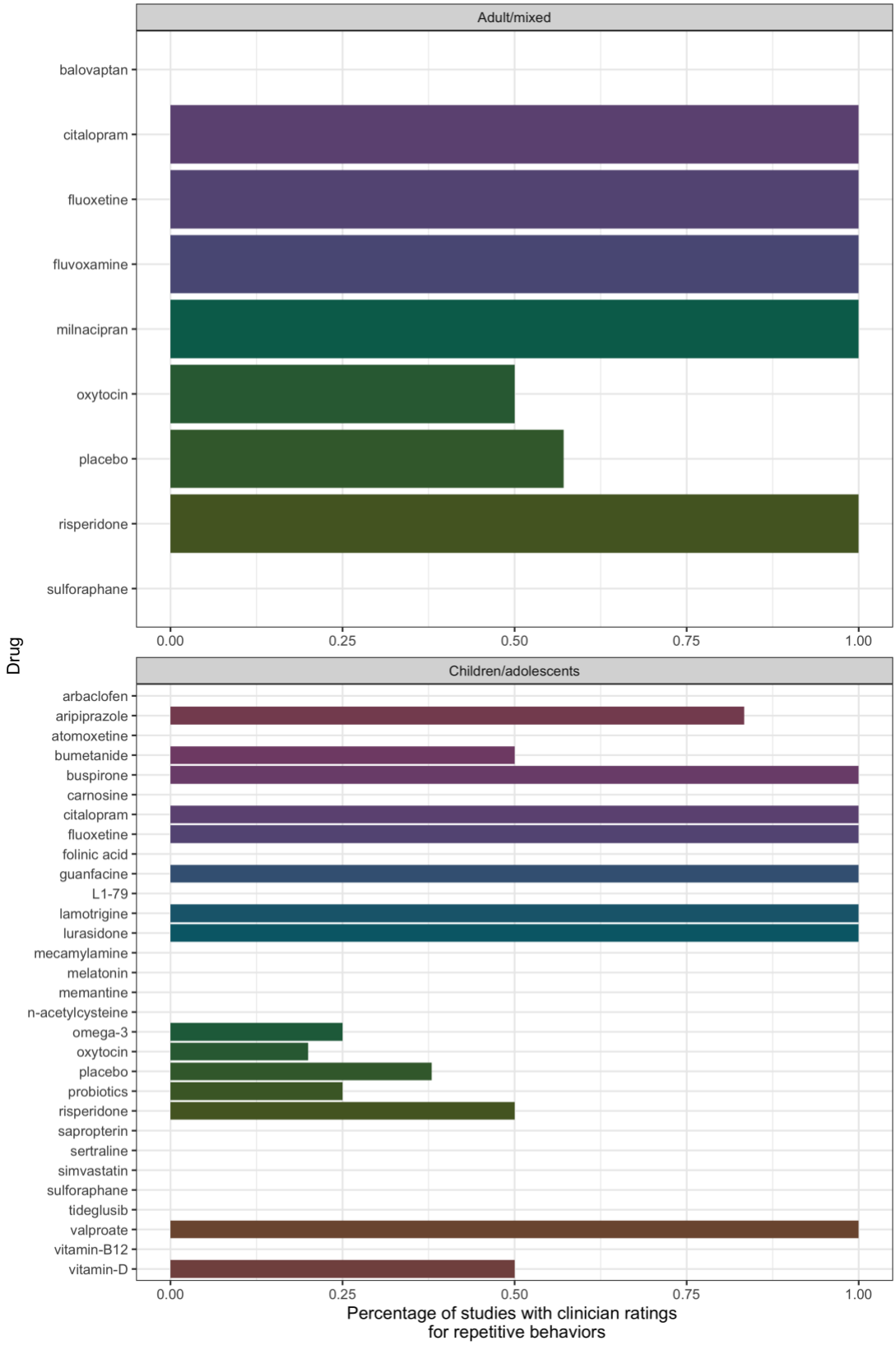
The median [IQR] of baseline CGI-S was 4.87 [4.52, 5.13] in children/adolescents studies (missing in 82 arms) and 4.4 [4.2, 4.5] in adult/mixed studies (missing in 9 arms).

6.1.1.5 Type of rater

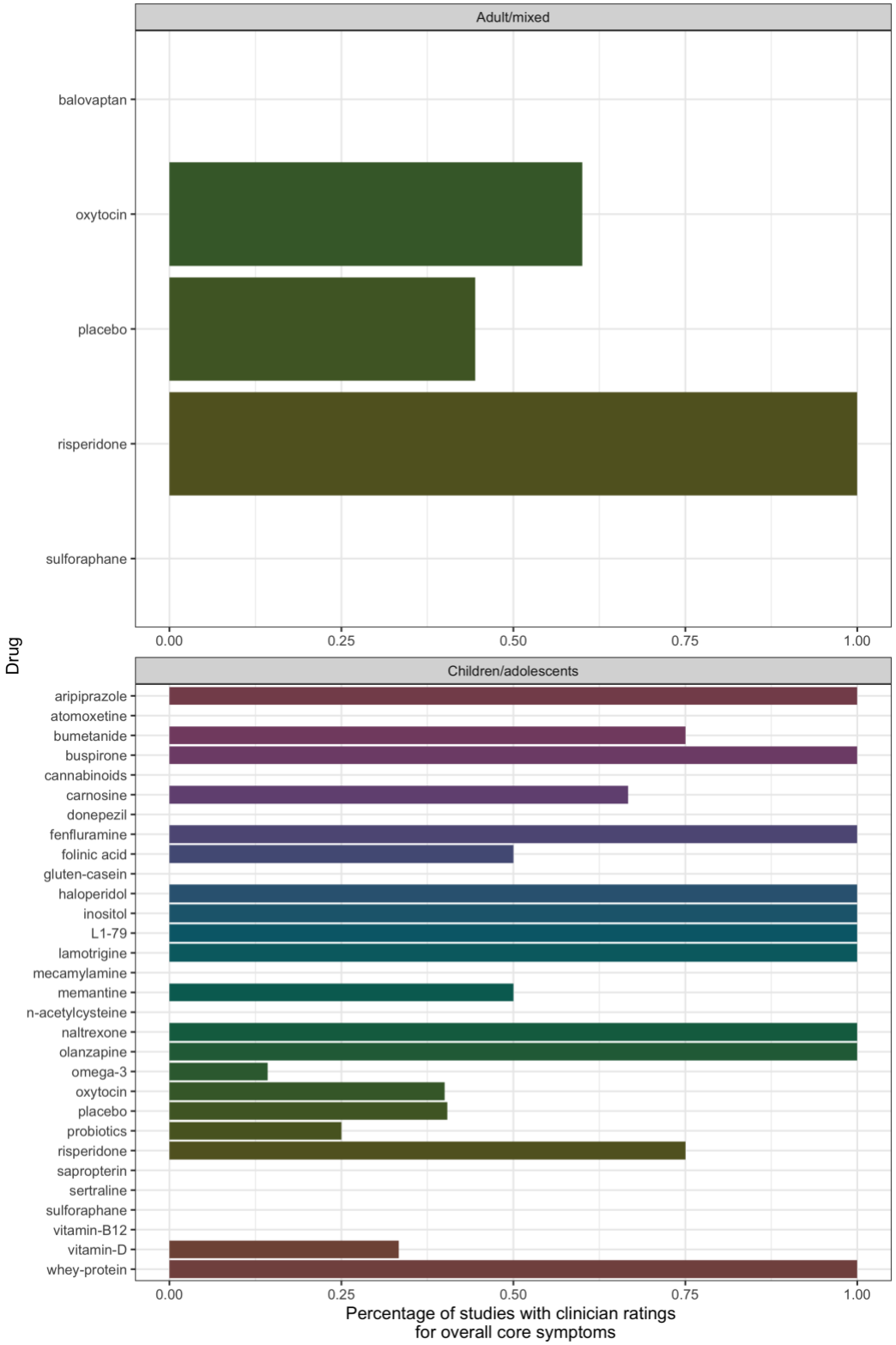
Rater of scales measuring social-communication difficulties



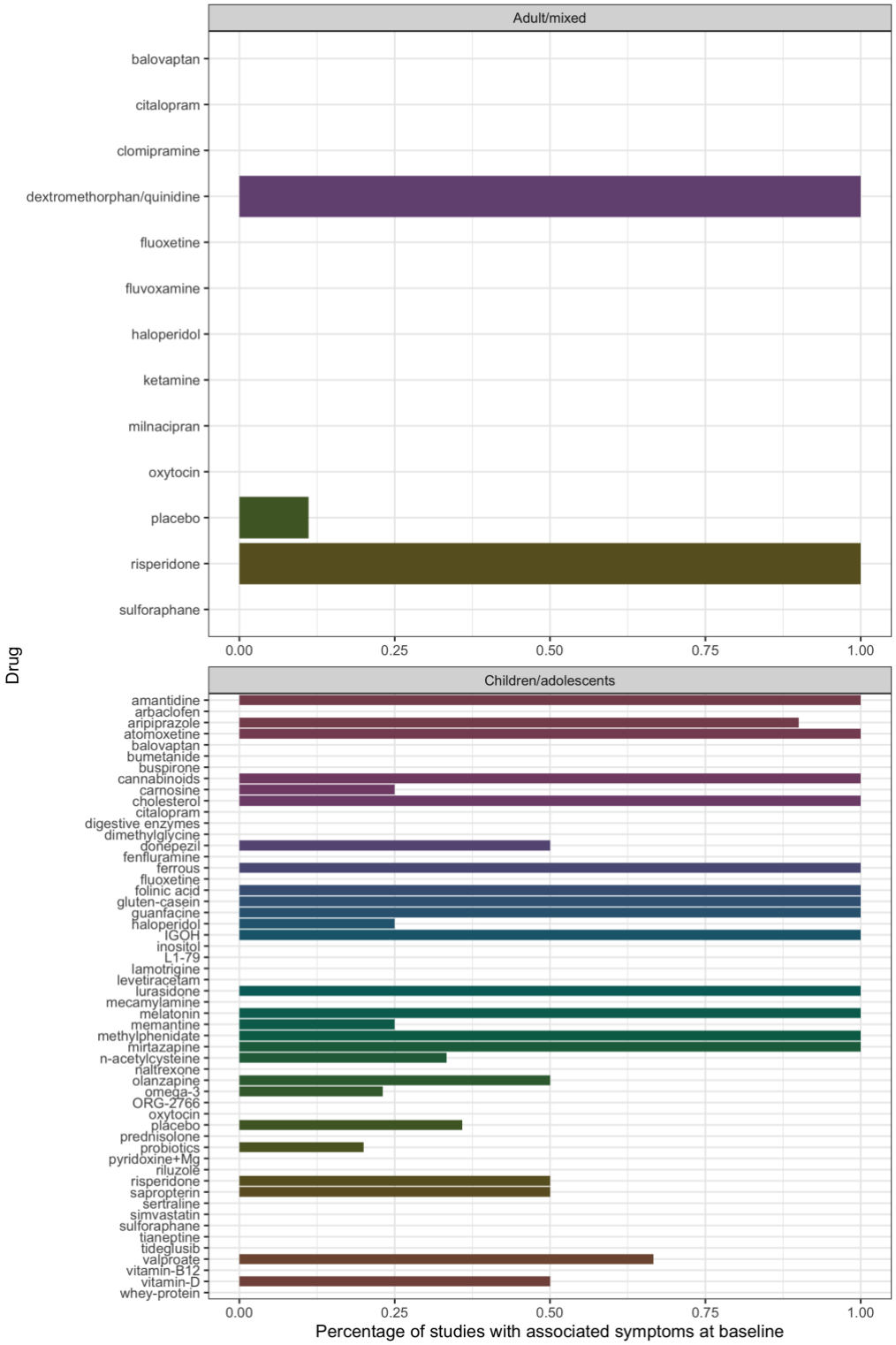
Rater of scales measuring repetitive behaviors and restricted interests



Rater of scales measuring overall core symptoms



6.1.1.6 Presence of associated symptoms as inclusion criteria



Some drugs were evaluated almost only in participants with associated conditions, 15 in children/adolescents-amantadine, atomoxetine, cannabinoids, cholesterol, ferrous sulfate, folinic acid gluten-casein, guanfacine, IGOH, lurasidone, melatonin, methylphenidate, mirtazapine and aripiprazole (in nine out of 10 studies)-and 2 in adults/mixed-dextromethorphan/quinidine and risperidone.

6.1.2 Assessment of baseline imbalance

We found that baseline score imbalance could have inflated effect sizes, when endpoint scores were used in the analysis. For example, Klaiman 2013 found no difference between sapropterin and placebo in the ABC-L/SW in their primary analysis using a mixed-effects regression models [1]. Baseline and endpoint scores of ABC-L/SW were reported, and there was important baseline imbalance (mean baseline score of sapropterin: 9.5 vs placebo: 16.2). When endpoint scores were used in the meta-analysis, sapropterin was found superior to placebo in improving ABC-L/SW with an SMD of 1.34 (95% CI 0.7; 1.99). In contrast when we estimated change scores (from endpoint and baseline means and standard deviations using a pre-post correlation of 0.5), the results were not significant SMD of 0.21 (95% CI -0.37; 0.79), similar to the primary analysis of the trial.

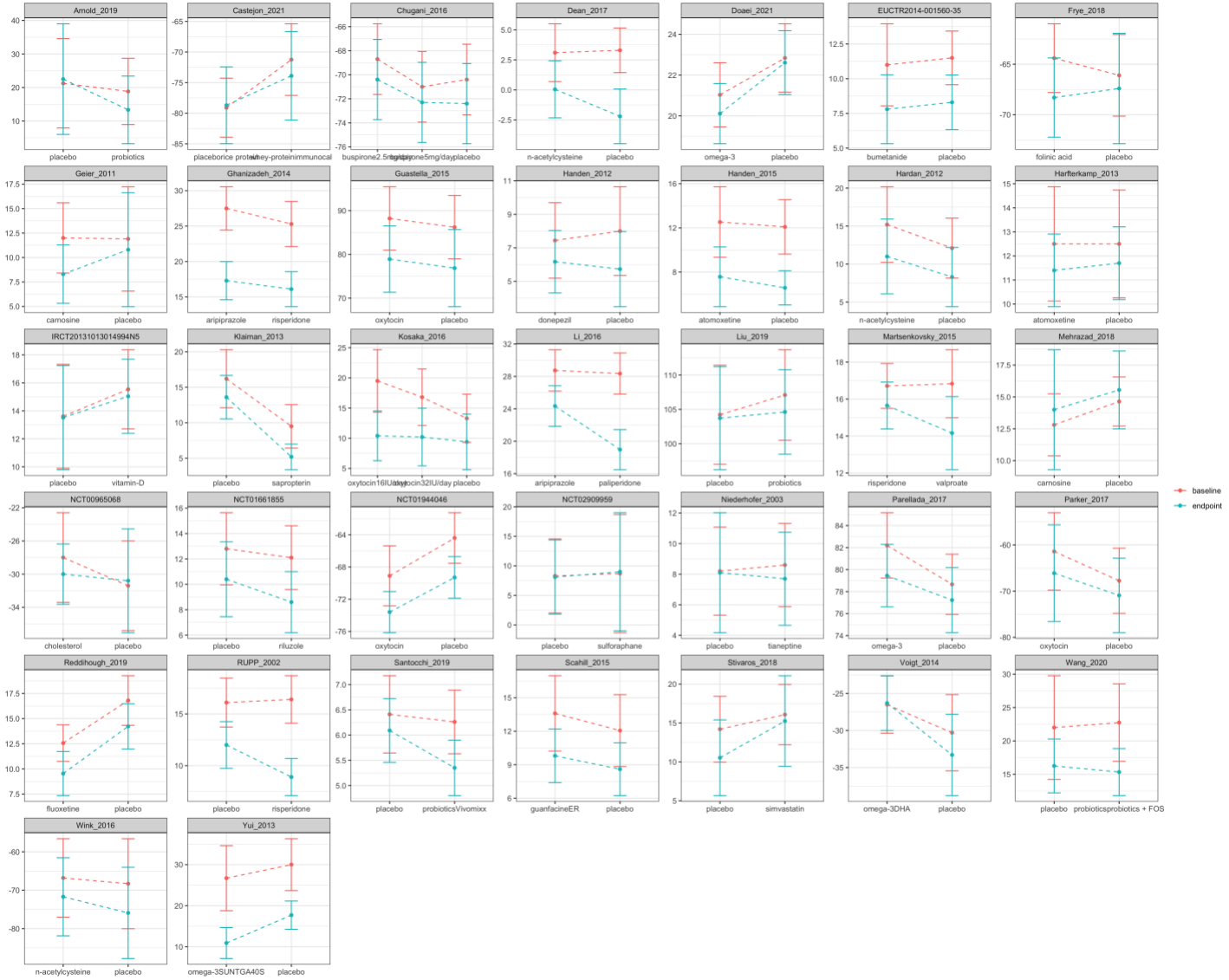
We further investigated this issue by plotting baseline and endpoint mean scores (when both were reported but not change scores) with their 95% confidence intervals (calculated as mean±1.96*(SD/sqrt(N)).

Baseline imbalance can be detected when the slope between interventions is not zero at baseline (slope of red dashed line) and it could have affected effect sizes when the slope at endpoint (slope of blue dashed line) is the same to baseline, but there is no difference in change scores between interventions.

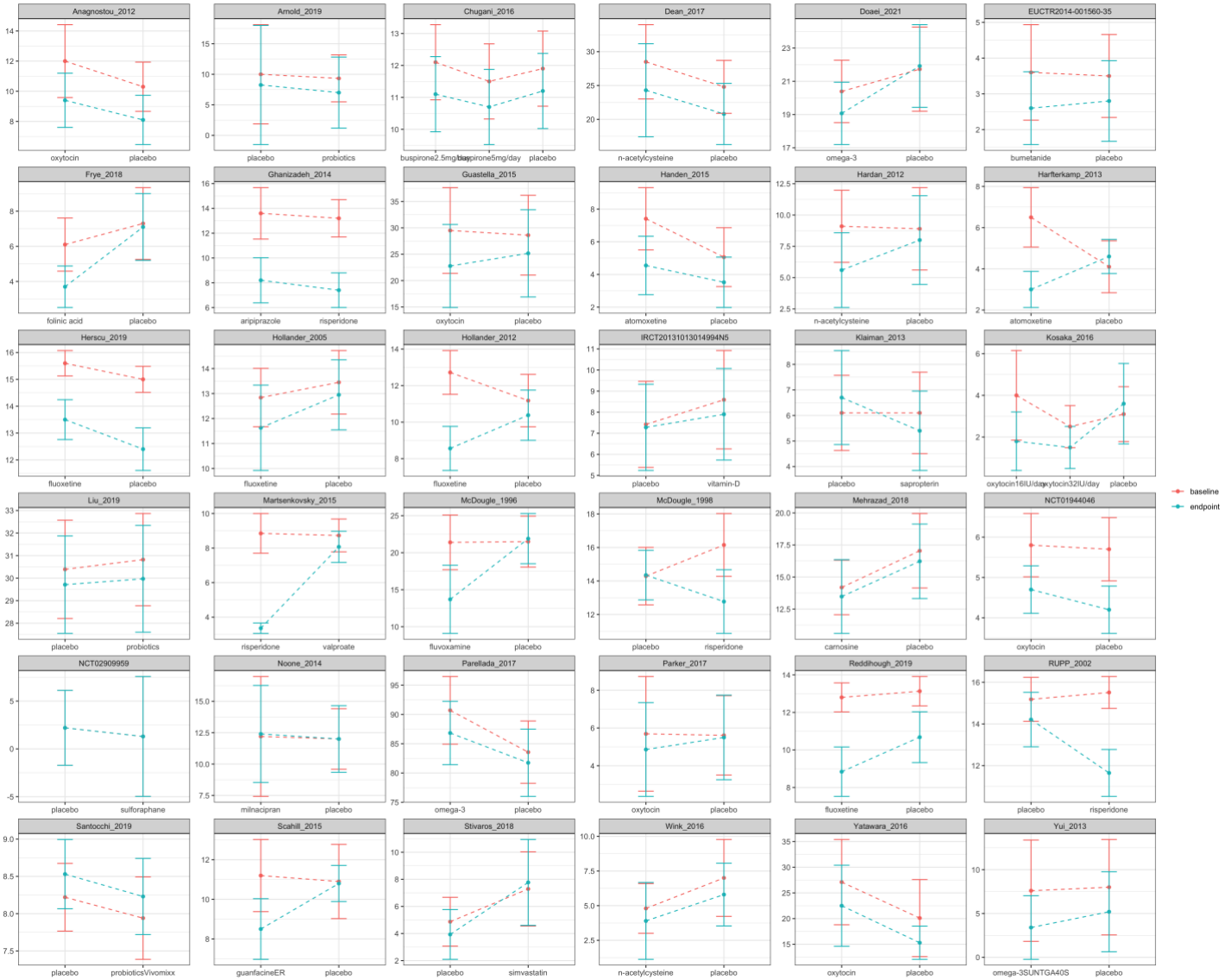
Therefore, we estimated change scores when endpoint and baseline scores were reported.

1. Klaiman C, Huffman L, Masaki L, Elliott GR. Tetrahydrobiopterin as a treatment for autism spectrum disorders: a double-blind, placebo-controlled trial. J Child Adolesc Psychopharmacol. 2013;23(5):320-8. doi: 10.1089/cap.2012.0127.

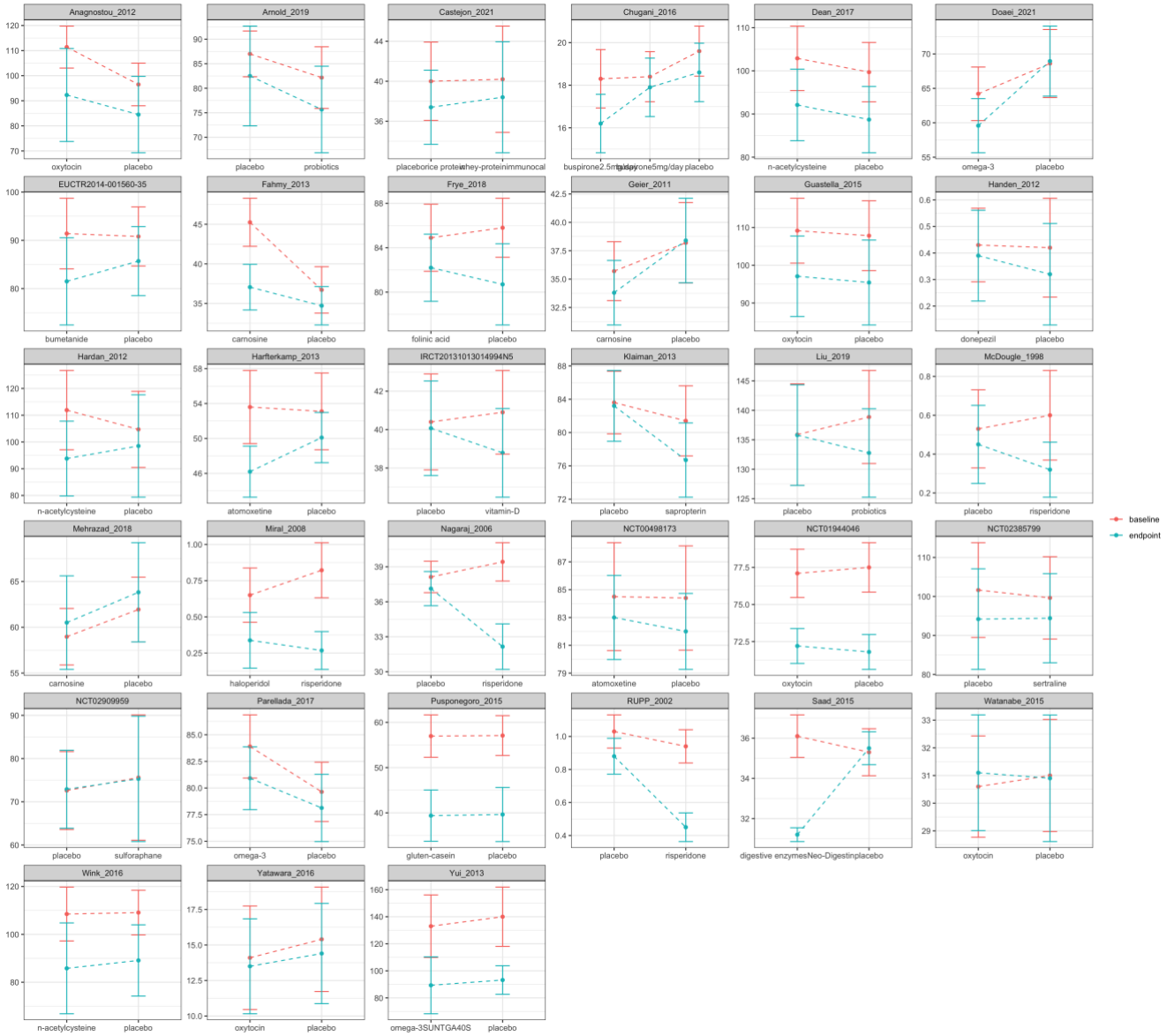
6.1.2.1 Social-communication difficulties



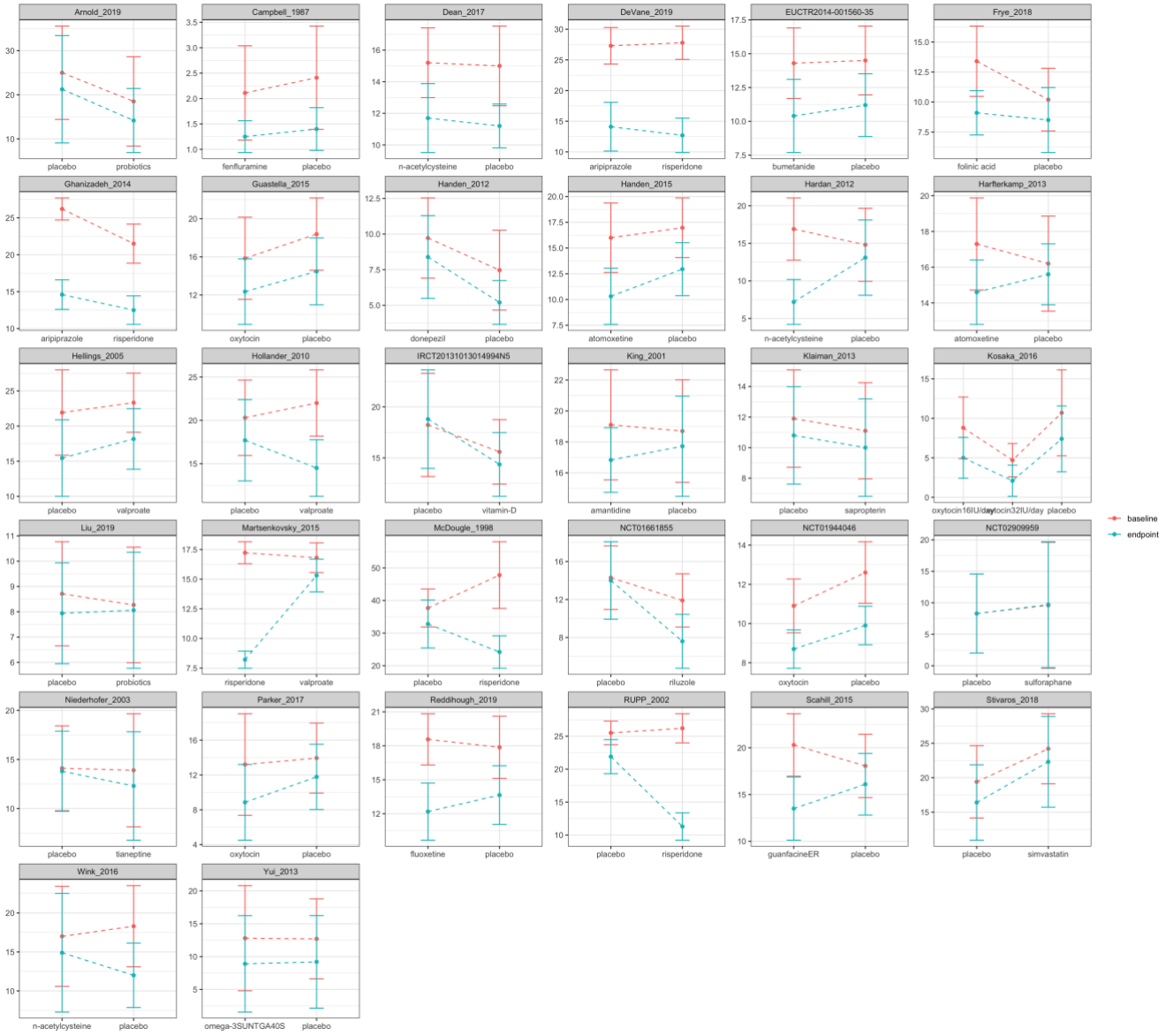
6.1.2.2 Repetitive behaviors and restricted interests



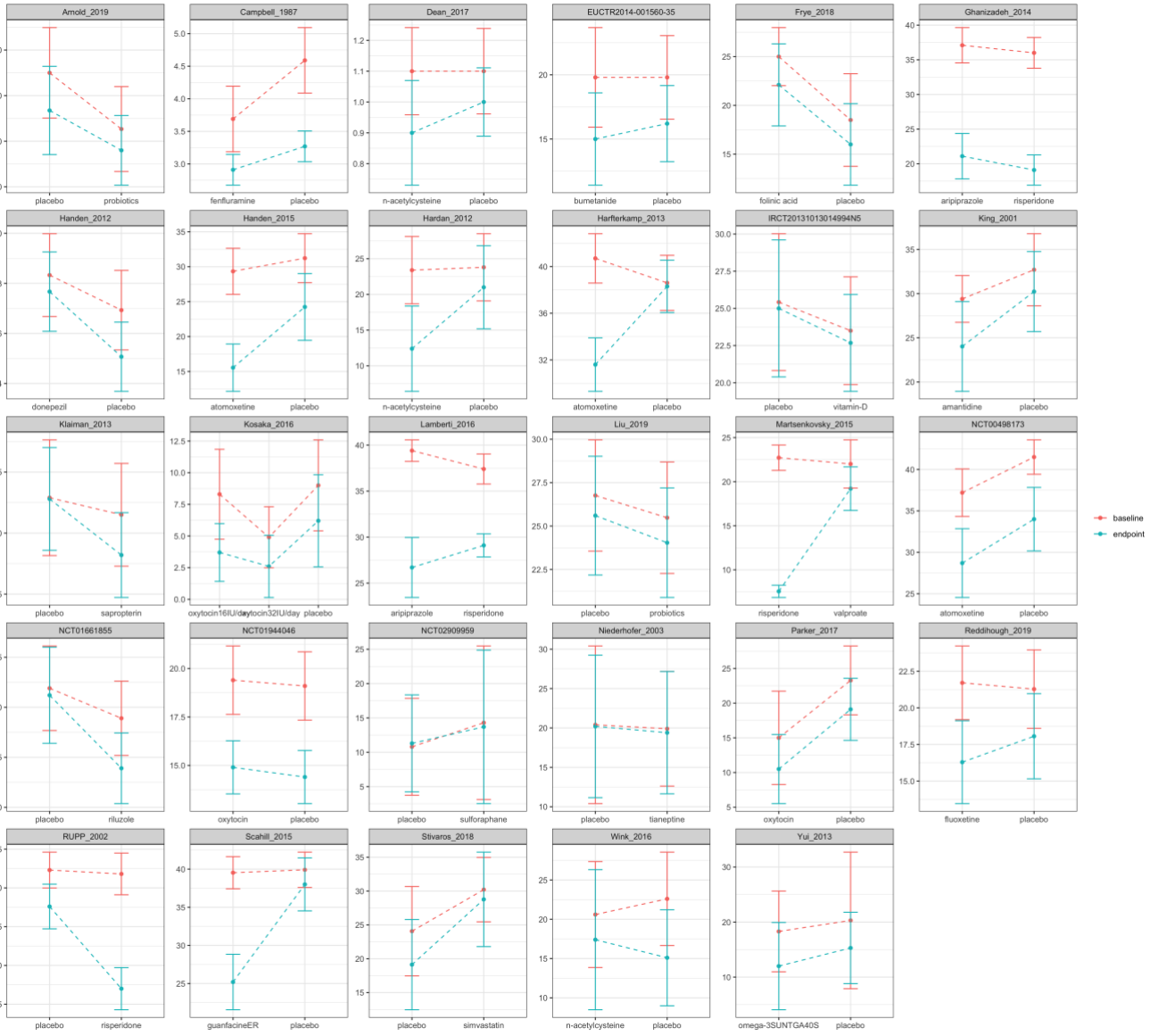
6.1.2.3 Scales measuring overall core symptoms



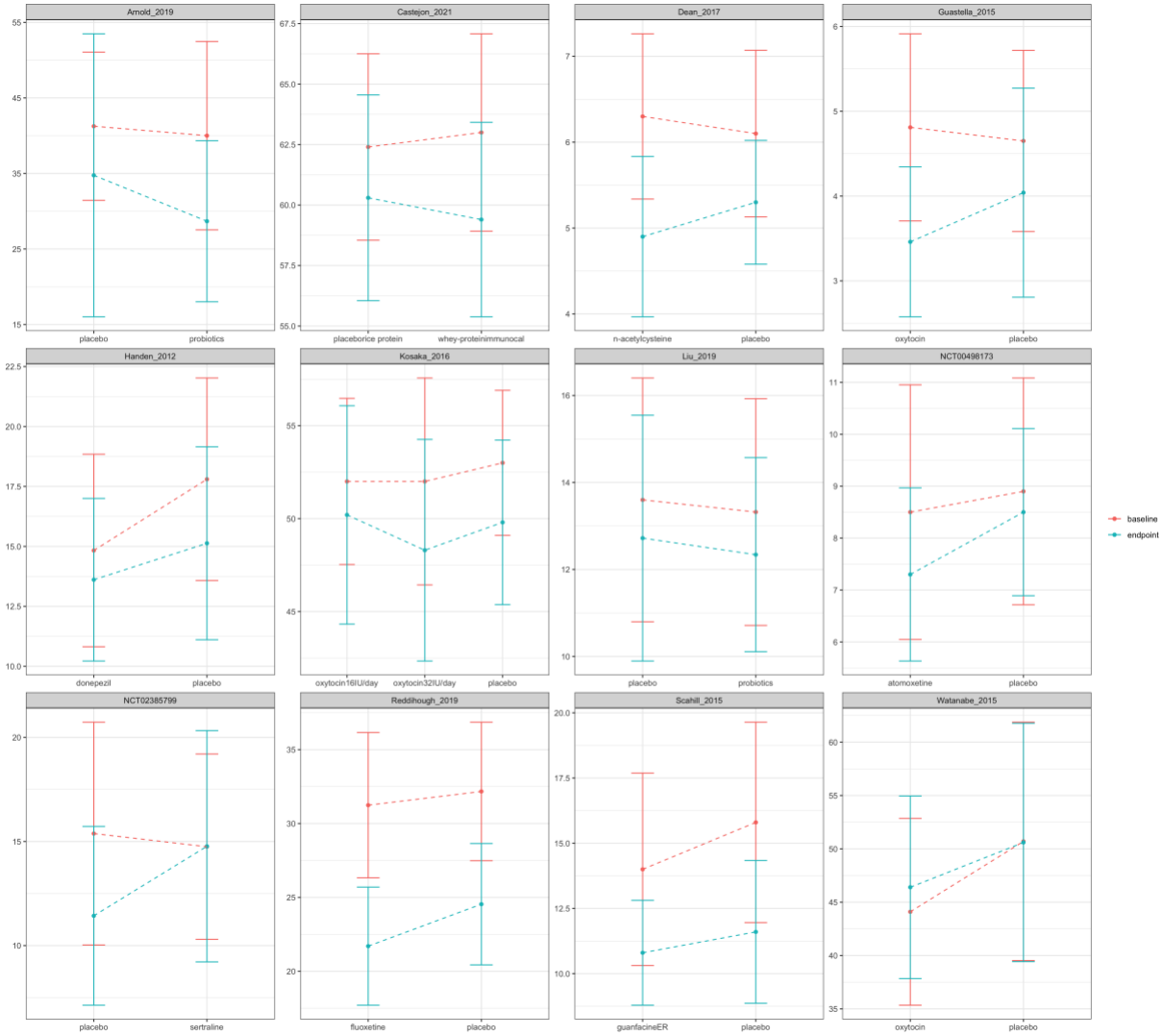
6.1.2.4 Irritability



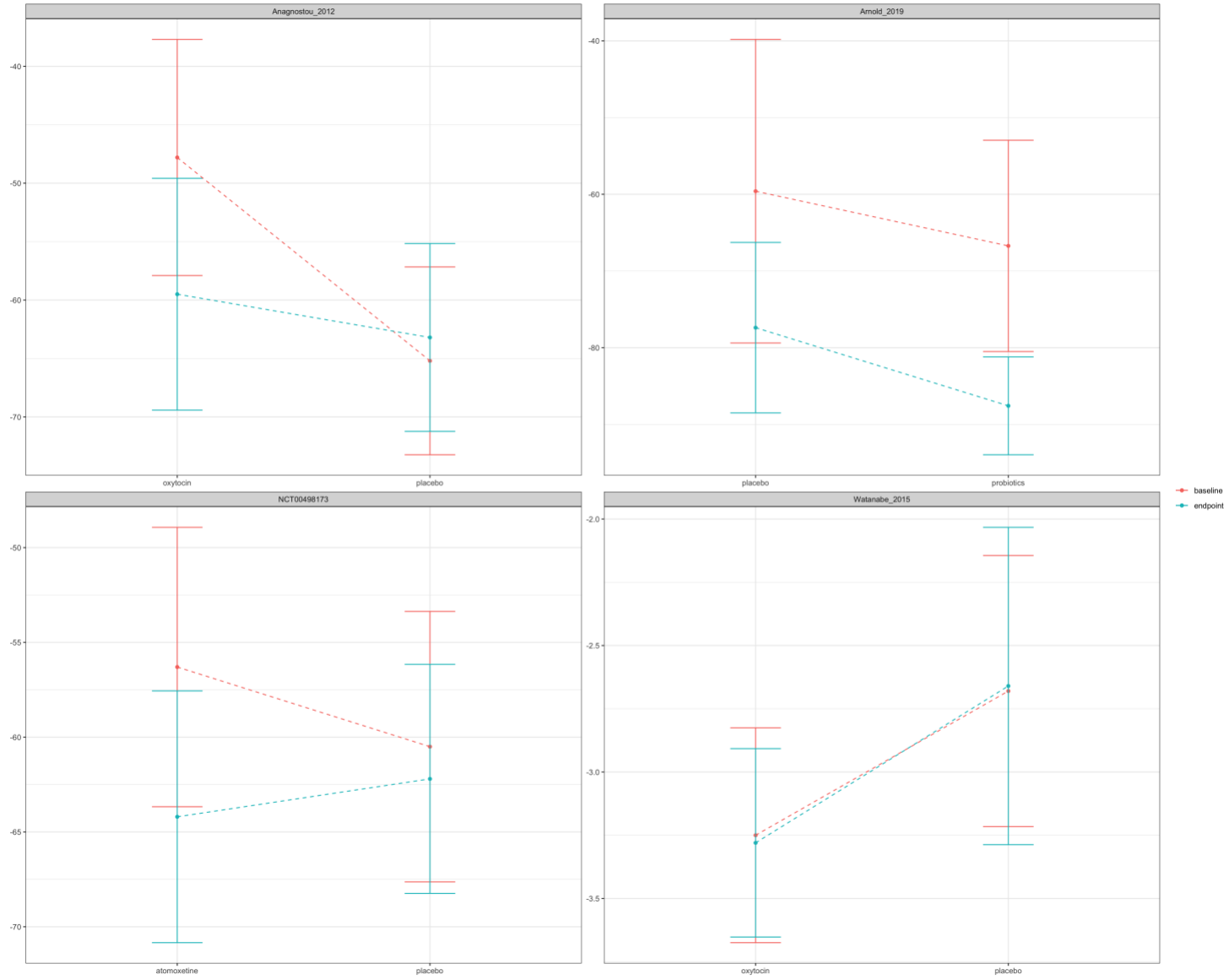
6.1.2.5 ADHD symptoms



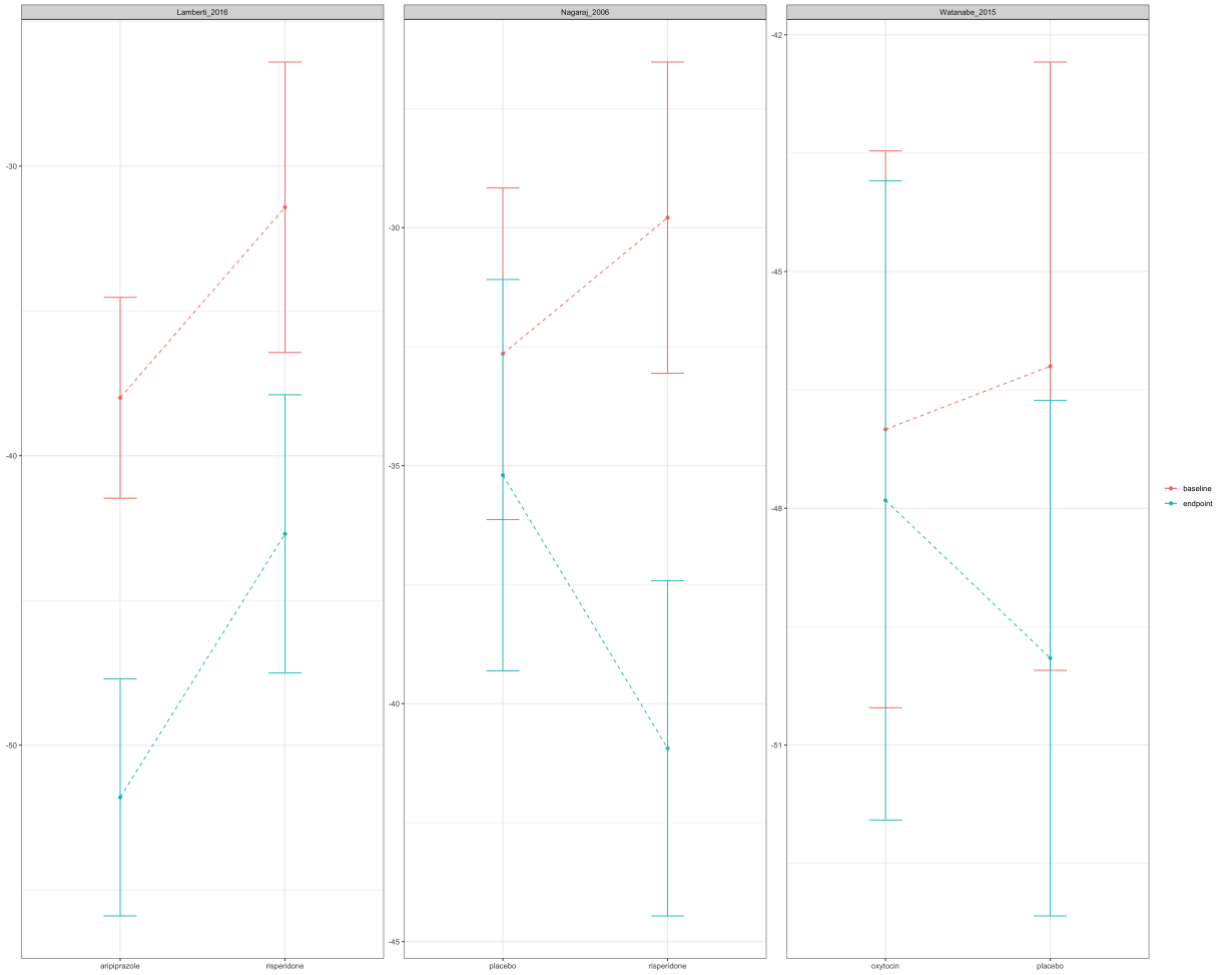
6.1.2.6 Anxiety and depressive symptoms



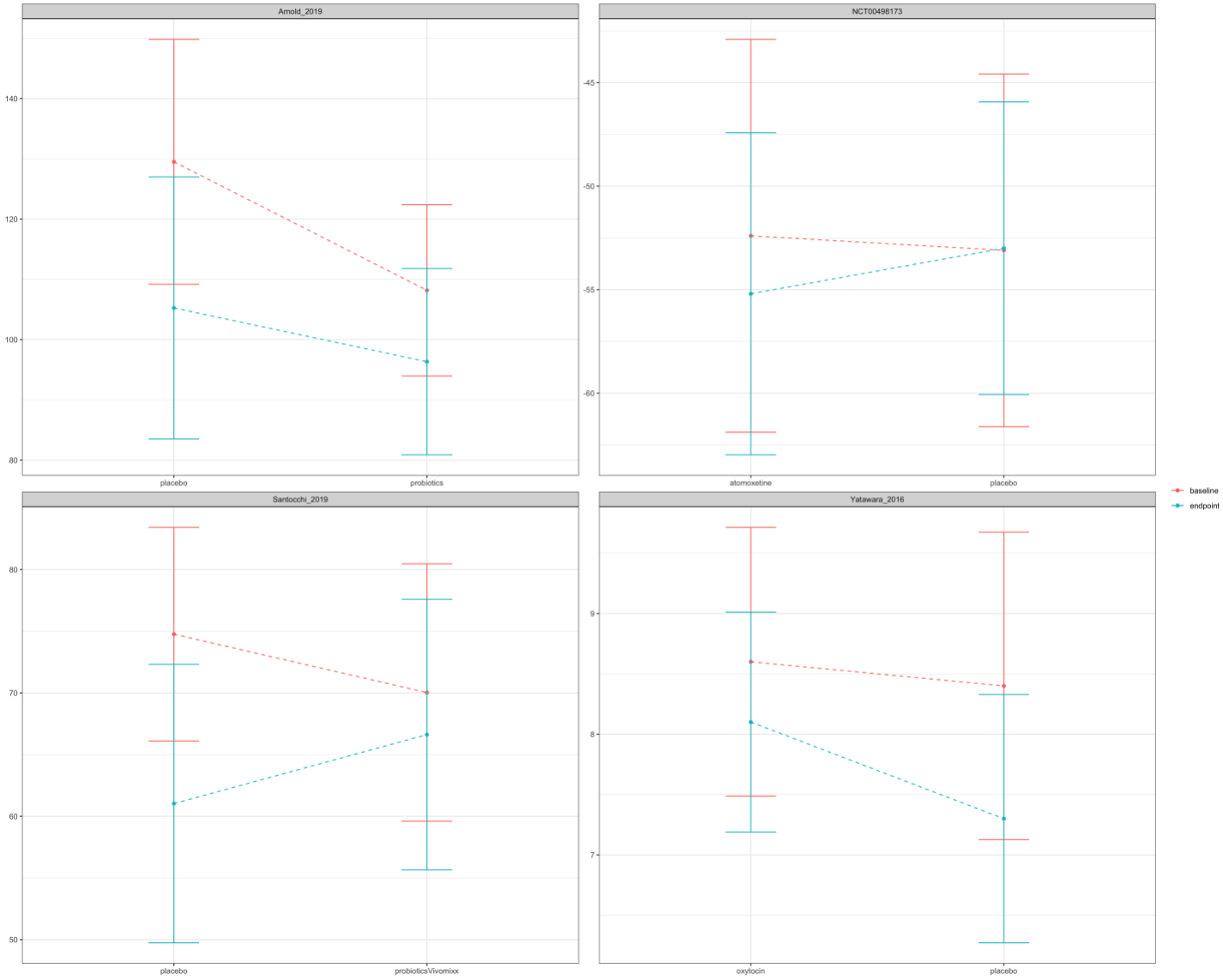
6.1.2.7 Quality of life



6.1.2.8 Global functioning



6.1.2.9 Parental stress



6.2 Network plots

Network plots for all outcomes are presented in Figure-S1. They were mainly star-shaped with placebo as the main node, and a few head-to-head comparisons between other interventions.

6.3 Forest plots of placebo-controlled comparisons for secondary outcomes

Effect sizes of the comparisons between interventions and placebo for the secondary outcomes are presented in Figure-S2.

Interventions are sorted by their P-scores from the best to worst (when a network meta-analysis was conducted) or by their effect sizes from best to worst (when a pairwise meta-analysis was conducted).

6.4 League tables

League tables for each outcome can be found in Table-S1, when a network meta-analysis was conducted. In the lower left corner, effect-sizes based on indirect or mixed evidence are presented. In the upper right corner, effect-sizes based on direct evidence are presented.

Head-to-head comparisons of direct comparisons can also be found in pairwise meta-analysis in Figure-S3.

6.5. Assessment of heterogeneity and incoherence

6.5.1 Table of heterogeneity and incoherence tests

We assessed heterogeneity by comparing the τ^2 of the networks with the empirical distribution of τ^2 of SMDs and ORs. Specifically, the empirical distribution of τ^2 of SMDs for the comparison of pharmacological agents versus placebo on mental health outcomes (such as our outcomes of interest) has a median of 0.049 IQR [0.01, 0.242]. The log-normal empirical distribution of τ^2 of ORs for the comparison of pharmacological agents versus placebo on subjective outcomes has a mean of -2.13 and SD of 1.58 [1], which could correspond to a median of 0.12 IQR [0.04, 0.35]. We considered low heterogeneity when $\tau^2<Q_1$, moderate when $Q_1<\tau^2<Q_2$ and high when $\tau^2>Q_2$. Incoherence was evaluated with a local approach (SIDE approach) and a global approach (design-by-treatment test). We considered the presence of potential evidence of incoherence when the design-by-treatment test was significant (alpha at 0.1) or when there were more than 10% of incoherent loops (alpha at 0.1), since up to 10% of the loops in a network meta-analysis have been found to be incoherent [2].

6.5.1.1 Children/adolescents

Outcomes (effect size)	**Heterogeneity in network meta-analysis**		**Incoherence in network meta-analysis**		
	Between study variance (τ^2) and I^2	**Heterogeneity assessment**	**Percenta0ge of loops showing inconsistency using SIDDE**	**Design-by-treatment test Q (df), p-value**	**Incoherence assessment**
Social-communication difficulties (SMD)	τ^2=0, I^2=0%	Low	0% out of 8 loops	Q=4.747 (df=4), p-value=0.314	No evidence for incoherence
Repetitive behaviors and restricted interests (SMD)	τ^2=0.017, I^2=20%	Low to moderate	0% out of 6 loops	Q=1.329 (df=3), p-value=0.722	No evidence for incoherence
Scales measuring overall core symptoms (SMD)*	τ^2=0.0382, I^2=30%	Moderate	0% out of 6 loops	Q=2.52 (df=3), p-value=0.472	No evidence for incoherence
Irritability (SMD)	*τ^2=0.0394, I^2=33.7%*	*Moderate*	*0% out of 6 loops*	*Q=10.673 (df=3), p-value=0.014*	*There was evidence of incoherence, and pairwise meta-analysis was conducted.*
ADHD symptoms (SMD)	τ^2=0.032, I^2=30.4%	Moderate	0% out of 6 loops	Q=5.124 (df=3), p-value=0.163	No evidence for incoherence
Anxiety and depressive symptoms (SMD)	τ^2=0.041, I^2=25.4%	Moderate to high	No loops	Cannot be evaluated	Cannot be evaluated
Response to treatment (OR)	*τ^2=0.011, I^2=2.6%*	*Low*	*50% out of 10 loops*	*Q=8.732 (df=4), p-value=0.068*	*There was evidence of incoherence, and pairwise meta-analysis was conducted.*
Global functioning (SMD)	τ^2=0.0169, I^2=15.2%	Low to moderate	0% out of 3 loops	Q=2.357 (df=1), p-value=0.125	No evidence for incoherence
Quality of life (SMD)	τ^2= not applicable,	Not applicable	No loops	Cannot be evaluated	Cannot be evaluated

	I^2= not applicable				
Parental stress (SMD)	τ^2=0.0, I^2=0%	Low	No loops	Cannot be evaluated	Cannot be evaluated
Discontinuation due to any reason (OR)	τ^2=0.0061, I^2=1.6%	Low	12.5% out of 8 loops	Q=4.571 (df=4), p-value=0.334	One closed loop was incoherent (omega-3, vitamin-D, placebo). Network meta-analysis was conducted, since up to 10% of the loops are expected to be incoherent.
Discontinuation due to adverse event (OR)	τ^2=0, I^2=0%	Low	0% out of 3 loops	Q=0.232 (df=1), p-value=0.63	No evidence for incoherence
Any adverse event (OR)	τ^2=0., I^2=0%	Low	0% out of 3 loops	Q=0.11 (df=1), p-value=0.74	No evidence for incoherence
Weight gain (OR)	*τ^2=0, I^2=0%*	*Low*	*50% out of 6 loops*	*Q=6.896 (df=2), p-value=0.032*	*There was evidence of incoherence, and pairwise meta-analysis was conducted.*
Sedation (OR)	*τ^2=0.168, I^2=19.3%*	*High*	*75% out of 8 loops*	*Q=7.761 (df=3), p-value=0.051*	*There was evidence of incoherence, and pairwise meta-analysis was conducted.*
Extrapyramidal symptoms (OR)	Not applicable	Not applicable	Cannot be evaluated	Cannot be evaluated	Cannot be evaluated

Italics when network meta-analysis was not conducted. *For overall core symptoms, a small study (Nikvarz et al. 2017) that compared risperidone with memantine (no difference was found SMD=0.0 [-0.71, 0.72]), was excluded from the primary analysis of this outcome, since introduced incoherence and heterogeneity (τ^2=0.054, 25% out of 8 loops were incoherence, and the design-by-treatment test was marginal Q=7.151, df=4, p-value=0.128). The results did not materially change after the inclusion of this study (Figure-S4)

6.5.1.2 Adult and mixed populations

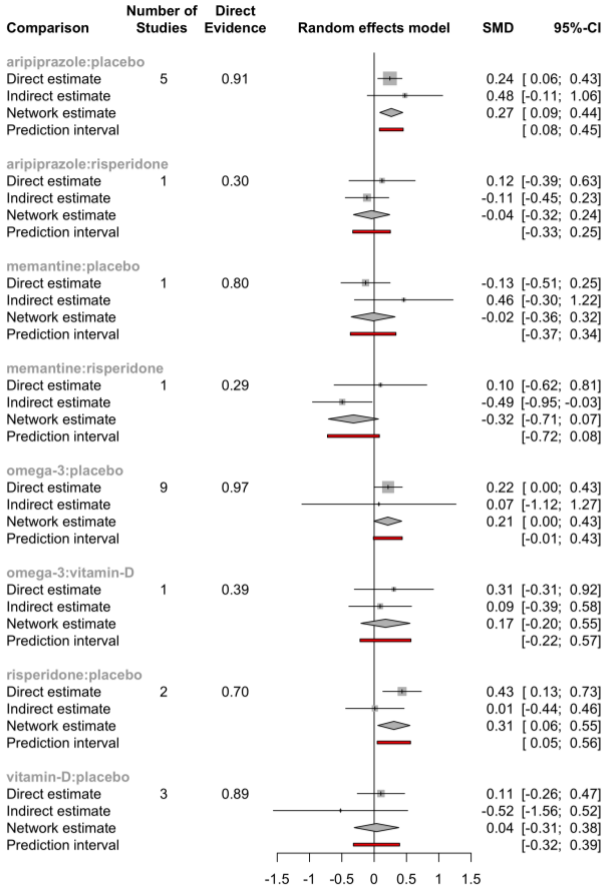
Outcomes	**Heterogeneity in network meta-analysis**		**Incoherence in network meta-analysis**		
	Between study variance (τ^2)	**Heterogeneity assessment**	**Percentage of loops showing inconsistency using SIDDE**	**Design-by-treatment test Q (df,p)**	**Incoherence assessment**
Social-communication difficulties (SMD)	τ^2=0.096, I^2=63 %	High	No loops	Cannot be evaluated	Cannot be evaluated
Repetitive behaviors and restricted interests (SMD)	τ^2=0, I^2=0%	Low	No loops	Cannot be evaluated	Cannot be evaluated
Scales measuring overall core symptoms (SMD)	τ^2=0, I^2=0%	Low	No loops	Cannot be evaluated	Cannot be evaluated
Irritability (SMD)	τ^2=0.0281, I^2=21.6%	Moderate	No loops	Cannot be evaluated	Cannot be evaluated
ADHD symptoms (SMD)	τ^2=0, I^2=0%	Low	No loops	Cannot be evaluated	Cannot be evaluated
Anxiety and depressive symptoms (SMD)	τ^2=0, I^2=0%	Low	No loops	Cannot be evaluated	Cannot be evaluated
Response to treatment (OR)	τ^2=0.257, I^2=42.1%	High	No loops	Cannot be evaluated	Cannot be evaluated

Global functioning (SMD)	τ^2=0, I^2=0%	Low	No loops	Cannot be evaluated	Cannot be evaluated
Quality of life (SMD)	τ^2=0, I^2=0%	Low	No loops	Cannot be evaluated	Cannot be evaluated
Parental stress (SMD)	*Not applicable*	*Not applicable*	*No loops*	*Cannot be evaluated*	*Cannot be evaluated*
Discontinuation due to any reason (OR)	τ^2=0, I^2=0%	Low	No loops	Cannot be evaluated	Cannot be evaluated
Discontinuation due to adverse event (OR)	τ^2=0, I^2=0%	Low	No loops	Cannot be evaluated	Cannot be evaluated
Any adverse event (OR)	τ^2=0.049, I^2=20.8%	Low to moderate	No loops	Cannot be evaluated	Cannot be evaluated
Weight gain (OR)	τ^2=0, I^2=0%	Low	No loops	Cannot be evaluated	Cannot be evaluated
Sedation (OR)	τ^2=0, I^2=0%	Low	No loops	Cannot be evaluated	Cannot be evaluated
Extrapyramidal symptoms (OR)	Not applicable	Not applicable	Cannot be evaluated	Cannot be evaluated	Cannot be evaluated

6.5.2 Forest plots of SIDE

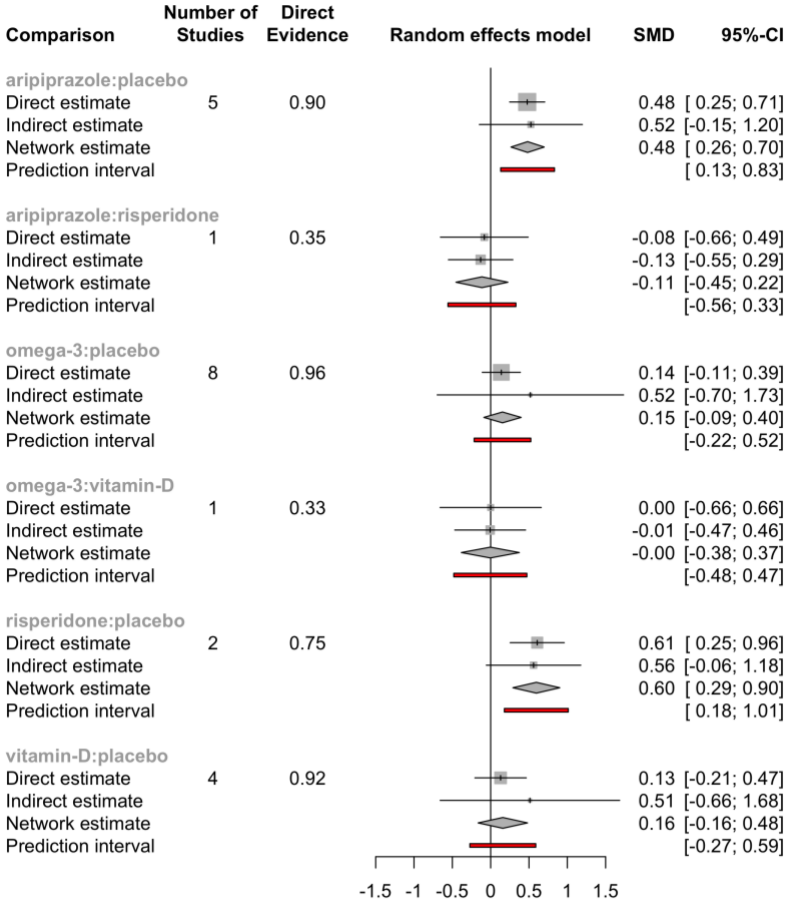
Local incoherence using SIDE could not be tested in studies with no closed loops, i.e., quality of life, caregiver stress, anxiety or depressive symptoms in children/adolescents and all networks in adults.

6.5.2.1 Social-communication difficulties



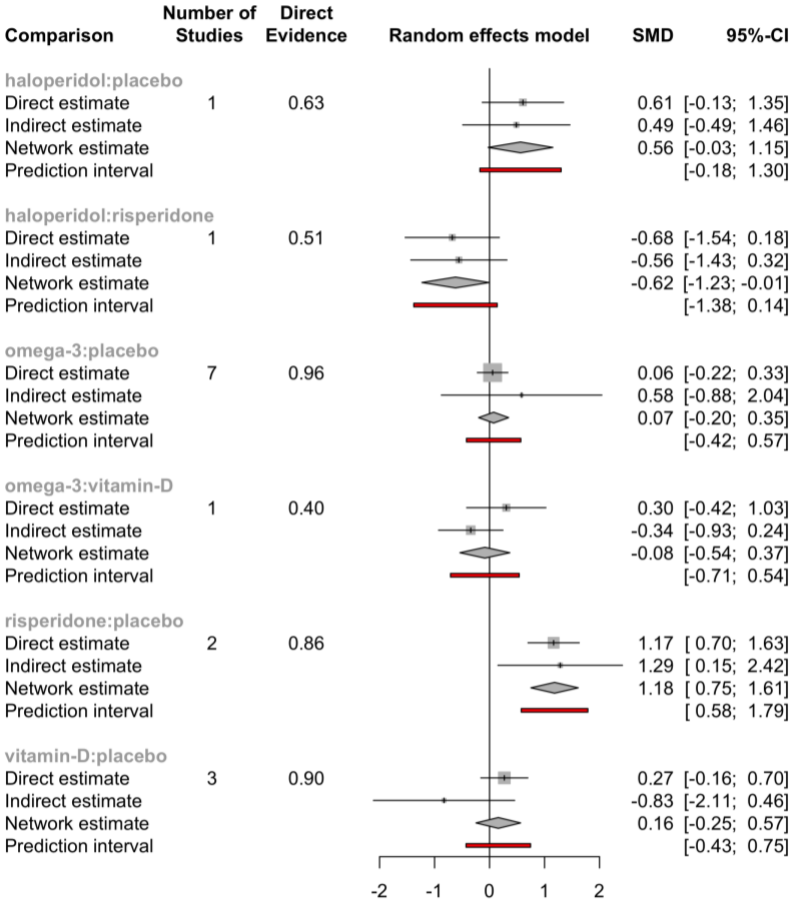
0% of the loops were incoherent.

6.5.2.2 Repetitive behaviors and restricted interests



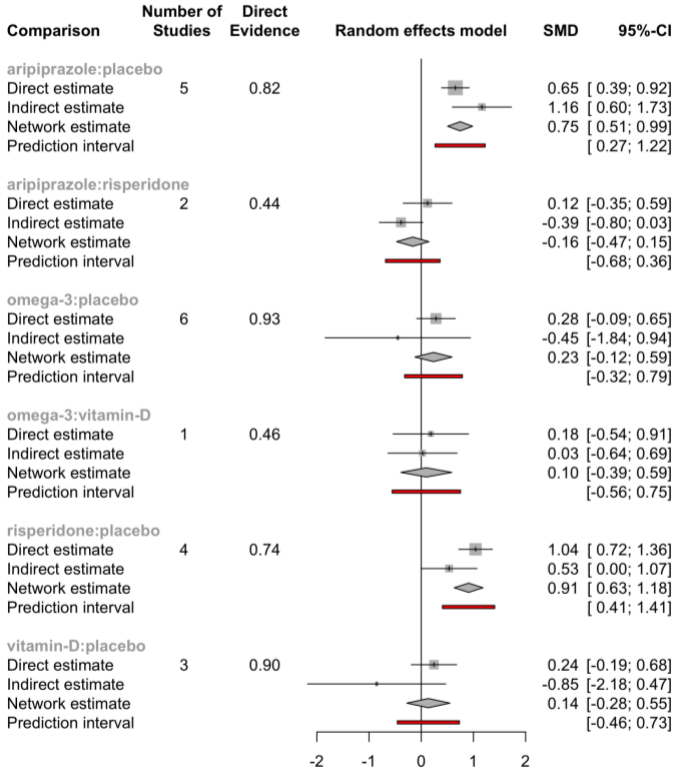
0% of the loops were incoherent.

6.5.2.3 Scales measuring overall core symptoms



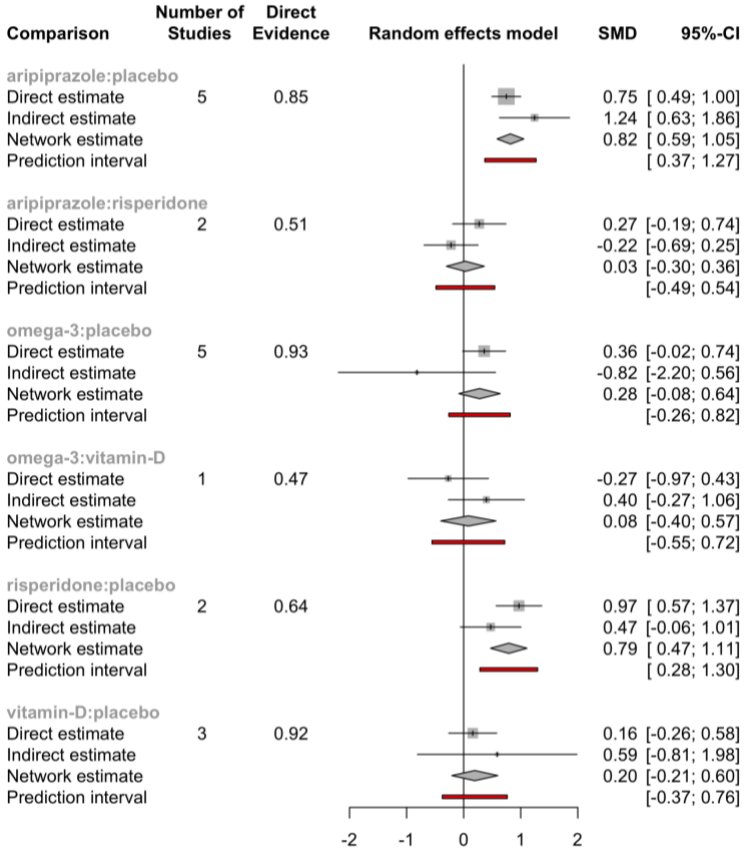
0% of the loops were incoherent. One study was excluded from the primary analysis of this outcome (Nikvarz et al. 2017), that compared risperidone with memantine. This comparison introduced incoherence for the loops between metmantine, risperidone and placebo.

6.5.2.4 Irritability



0% of the loops were incoherence

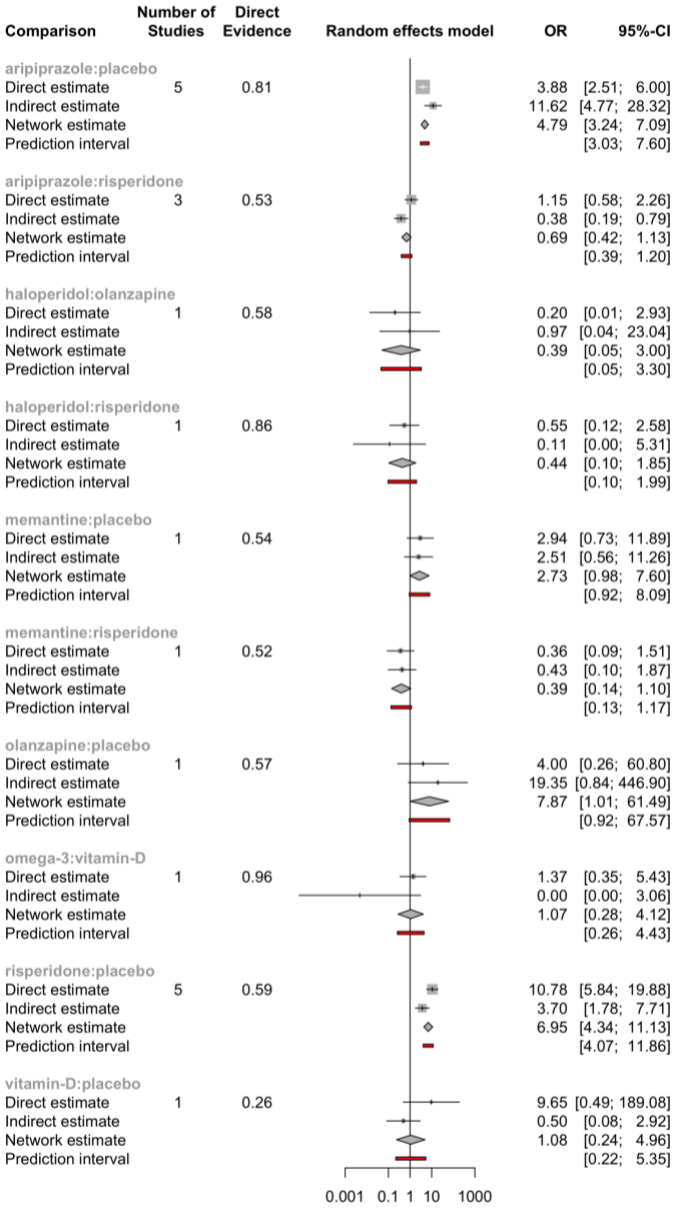
6.5.2.5 ADHD symptoms



0% of the loops were incoherent.

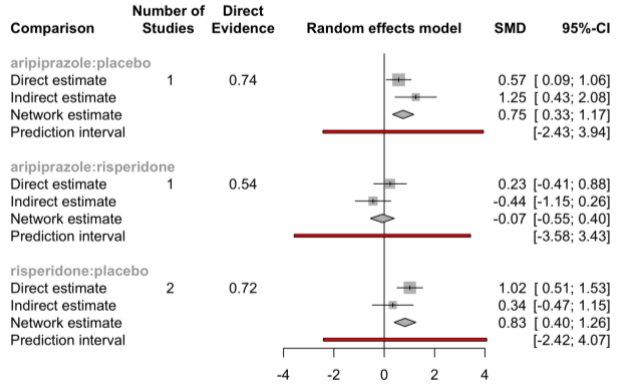
6.5.2.6 Anxiety and depressive symptoms
No closed loop in children/adolescents and adults/mixed popoulations.

6.5.2.7 Response to treatment



50% of the loops were incoherent, i.e., the comparisons of aripiprazole/placebo, aripiprazole/risperidone, omega-3/vitamin-D, risperidone/placebo, vitamin-D/placebo. Therfore, pairwise meta-analysis was conducted.

6.5.2.8 Global functioning

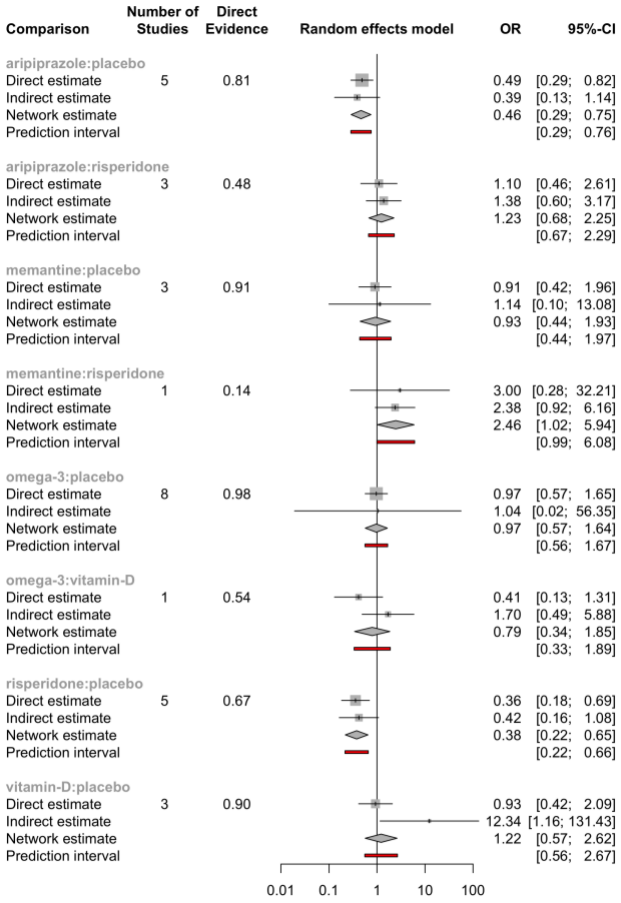


0% of the loops were incoherent.

6.5.2.9 Quality of life
No closed loop in children/adolescents and adults/mixed popoulations.

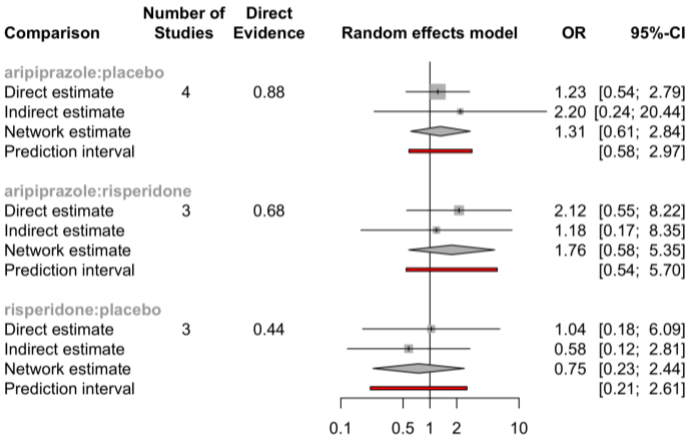
6.5.2.10 Parental stress
No closed loop in children/adolescents and adults/mixed popoulations.

6.5.2.11 Discontinuation due to any reason



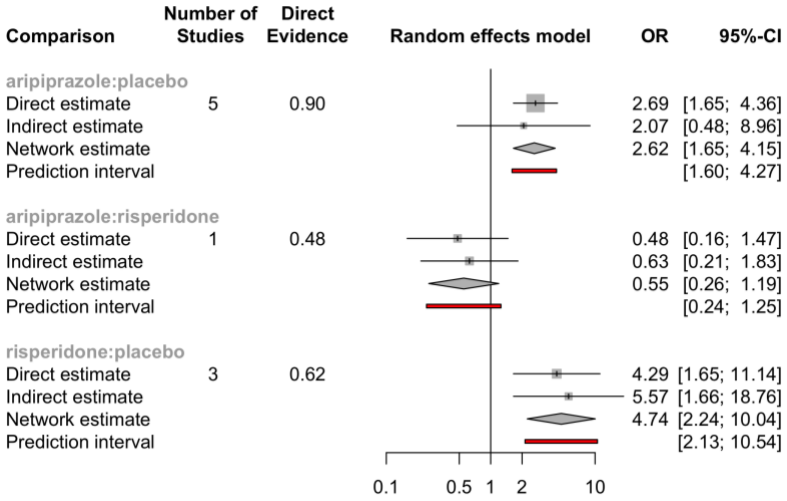
12.5% of the loops were incoherent, i.e., the comparison of vitamin-D and placebo.

6.5.2.12 Discontinuation due to adverse event



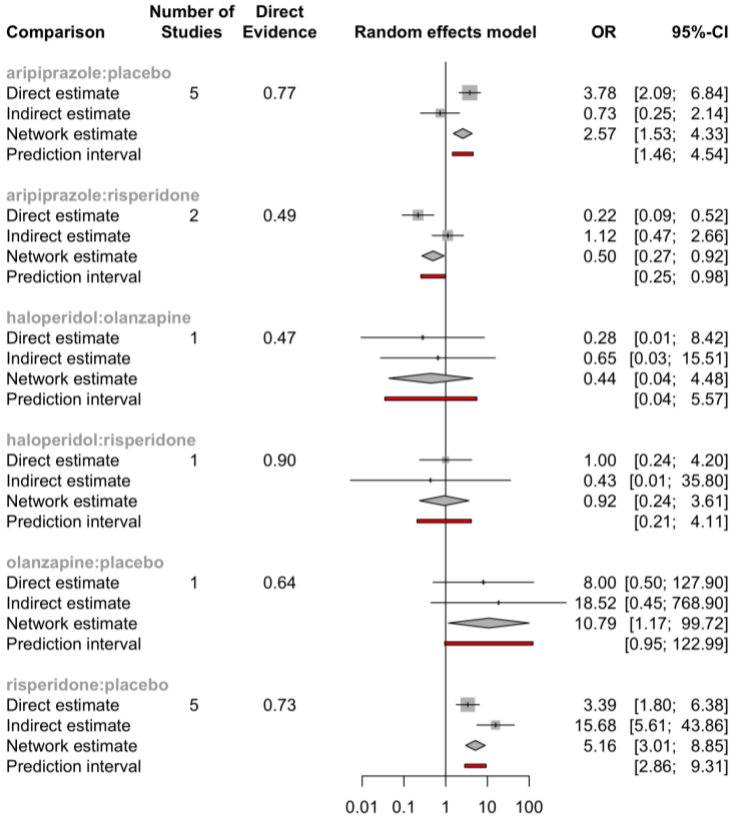
0% of the loops were incoherent.

6.5.2.13 Any adverse event



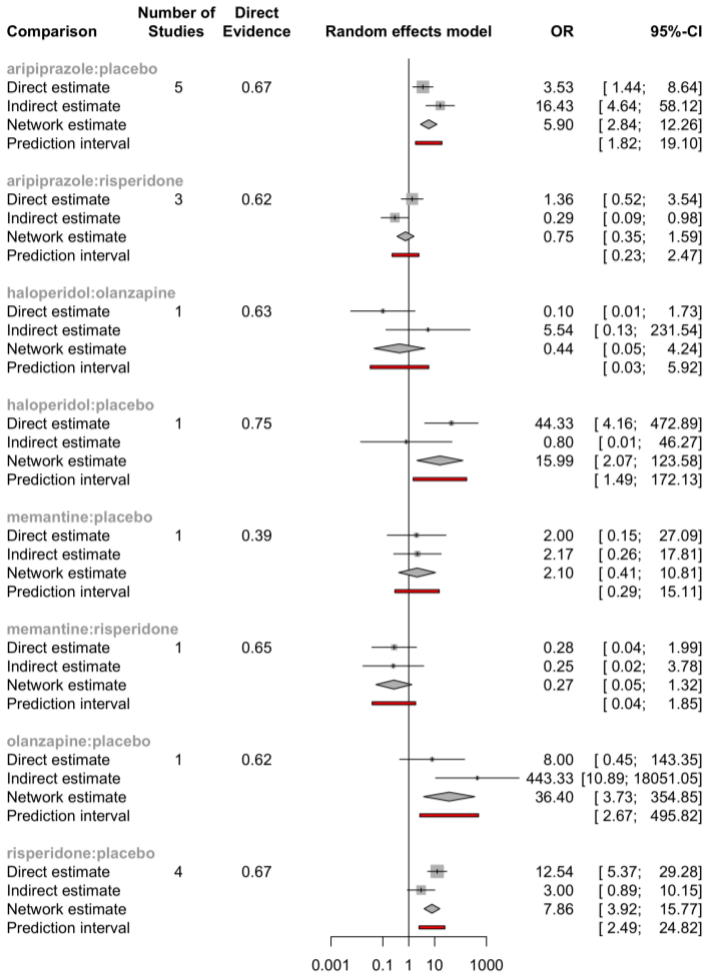
0% of the loops were incoherent.

6.5.2.14 Weight gain



50% of the loops were incoherent, i.e., risperidone/placebo, aripiprazole/placebo, and aripiprazole/risperidone. Therefore, pairwise meta-analysis was conducted.

6.5.2.15 Sedation



75% of the loops were incoherent, i.e., aripiprazole/placebo, aripiprazole/risperidone, haloperidol/olanzapine, haloperidol/placebo, olanzapine/placebo and risperidone/placebo. Therefore, pairwise meta-analysis was conducted.

6.5.2.16 Extrapyramidal symptoms

No closed loop in children/adolescents and adults/mixed popoulations.

6.5.3. References

1. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. International journal of epidemiology. 2012;41(3):818-27. doi: 10.1093/ije/dys041.
2. Veroniki AA, Vasiliadis HS, Higgins JP, Salanti G. Evaluation of inconsistency in networks of interventions. Int J Epidemiol. 2013;42(1):332-45. doi: 10.1093/ije/dys222.

6.6. Sensitivity analysis

Sensitivity analyses for the primary outcomes are presented in Figure-S4. Sensitivity analyses have often smaller statistical power, since fewer studies are usually analyzed. Therefore, we considered the number of studies in the sensitivity analysis, and evaluated changes in the magnitude of the mean effect-sizes, the overlapping of the confidence intervals and whether the sensitivity analysis changed the interpretation of the findings. The results were in general robust across several sensitivity analyses. Some notable differences ($|SMD_{sensitivity} - SMD_{primary}| \geq 0.1$) are discussed below.

Social-communication difficulties

Children/adolescents

	Sensitivity analysis				**Primary analysis**			**Evaluation**	
Drug	**analysis**	**k_{sens}**	**n_{sens}**	**SMD_{sens}**	**$k_{primary}$**	**$n_{primary}$**	**$SMD_{primary}$**	**$SMD_{sensitivity}$-$SMD_{primary}$**	**Comment**
memantine	04. nonimputed SDs	1	15	0.46	2	69	-0.02	0.47	The results of the sensitivity analysis were based on indirect evidence from a single and small study (Nikvarz et al 2017). Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
memantine	12. ABC-L/SW	1	15	0.46	2	69	-0.02	0.47	The results of the sensitivity analysis were based on indirect evidence from a single and small study (Nikvarz et al 2017). Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
carnosine	10. ITT	1	15	0.35	2	36	0.09	0.26	The results of the sensitivity analysis were based on a single study. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
carnosine	16. no associated symptoms	1	15	0.35	2	36	0.09	0.26	The results of the sensitivity analysis were based on a single study. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
carnosine	17. more developed countries	1	15	0.35	2	36	0.09	0.26	The results of the sensitivity analysis were based on a single study. Confidence intervals overlapped. Interpretation of the

									findings of the primary analysis did not change.
omega-3	12. ABC-L/SW	6	79	0.45	10	171	0.21	0.24	SMD was larger when ABC-L/SW was used (0.45 vs. 0.24). Confidence intervals partially overlapped. The results were based on six out of ten studies (46% of the participants). The interpretation of the finding of the primary analysis did not change, i.e., that omega-3 could potentially improve social-communication difficulties with small effect-sizes.
aripiprazole	16. no associated symptoms	1	29	0.41	6	341	0.27	0.14	The results of the sensitivity analysis were based on a single study. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
cholesterol	06. r=0.75	1	8	0.46	1	8	0.33	0.13	The precision of results is higher when a larger pre-post correlation is assumed (e.g., r=0.75). In that case, SMDs are more precise and larger. However, it is unlikely that scales measuring behavioral symptoms have such large correlations. The interpretation of the findings of the primary analysis did not change.
risperidone	17. more developed countries	2	88	0.43	4	133	0.31	0.13	The results were based on two out of the four studies in the primary analysis. Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
risperidone	02. pairwise	2	88	0.43	4	133	0.31	0.13	The results were based on two out of the four studies (placebo-controlled, direct evidence). Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
bumetanide	17. more developed countries	3	115	0.26	4	174	0.14	0.12	Confidence intervals overlapped, and the interpretation of the findings of the primary analysis did not change.
risperidone	18. low ROB (sequence generation and allocation concealment)	2	88	0.43	4	133	0.31	0.13	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
n-acetylcysteine	12. ABC-L/SW	2	27	-0.10	3	75	-0.21	0.11	The results were based on two out of the four available studies, and confidence

									intervals overlapped. The interpretation of the primary analysis did not change.
whey-protein	06. r=0.75	1	19	0.32	1	19	0.21	0.10	The precision of results is higher when a larger pre-post correlation is assumed (e.g., r=0.75). In that case, SMDs are more precise and larger. However, it is unlikely that scales measuring behavioral symptoms have such large correlations. The interpretation of the findings of the primary analysis did not change.
folinic acid	02. pairwise	2	32	0.54	2	32	0.44	0.10	There was heterogeneity in the results of the pairwise meta-analysis. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
probiotics	11. clinician ratings	1	31	0.31	5	92	0.21	0.10	The results of the sensitivity analysis were based on a single study. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
aripiprazole	18. low RoB (sequence generation and allocation concealment)	2	210	0.16	6	341	0.27	-0.11	The results of the senstivitiy analysis were based on two out of the six studies. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
memantine	18. low RoB (sequence generation and allocation concealment)	1	54	-0.13	2	69	-0.02	-0.12	The results of the sensitivity analysis were based on a single study. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
memantine	02. pairwise	1	54	-0.13	2	69	-0.02	-0.12	The results of the sensitivity analysis were based on a single study. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
memantine	17. more developed countries	1	54	-0.13	2	69	-0.02	-0.12	The results of the sensitivity analysis were based on a single study. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
memantine	10. ITT	1	54	-0.13	2	69	-0.02	-0.12	The results of the sensitivity analysis were based on a single study. Confidence intervals overlapped. Interpretation of the

									findings of the primary analysis did not change.
memantine	07. low/moderate RoB	1	54	-0.13	2	69	-0.02	-0.12	The results of the sensitivity analysis were based on a single study. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
memantine	09. blinded trials	1	54	-0.13	2	69	-0.02	-0.12	The results of the sensitivity analysis were based on a single study. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
carnosine	13. DSM/ICD	1	21	-0.03	2	36	0.09	-0.12	The results of the sensitivity analysis were based on a single study. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
carnosine	13. DSM/ICD	1	21	-0.03	2	36	0.09	-0.12	The results of the sensitivity analysis were based on a single study. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
bumetanide	12. ABC-L/SW	1	38	0.00	4	174	0.14	-0.14	The results of the sensitivity analysis are based on a single study. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
simvastatin	06. r=0.75	1	12	-0.45	1	12	-0.30	-0.15	The precision of results is higher when a larger pre-post correlation is assumed (e.g., r=0.75). In that case, SMDs are more precise and larger. However, it is unlikely that scales measuring behavioral symptoms have such large correlations. Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
omega-3	16. no associated symptoms	6	112	0.05	10	171	0.21	-0.16	SMD was smaller when studies focusing on associated symptoms were excluded (0.05 vs 0.21). Confidence intervals partially overlapped. The results were based on 6 out of 10 studies (65% of the participants).
omega-3	11. clinician ratings	3	53	0.03	10	171	0.21	-0.18	SMD was smaller when clinician ratings were used (0.03 vs 0.21). Confidence

									intervals overlapped. The results were based on 3 out of 10 studies (31% of the participants). It should be noted that SMD was larger when ABC-L/SW (a common caregiver-rating) was used (e.g., see sensitivity analysis above).
folinic acid	18. low RoB (sequence generation and allocation concealment)	1	23	0.23	2	32	0.44	-0.21	The results of the sensitivity analysis were based on a single study. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
folinic acid	13. DSM/ICD	1	23	0.23	2	32	0.44	-0.21	The results of the sensitivity analysis were based on a single study. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
folinic acid	13. DSM/ICD	1	23	0.23	2	32	0.44	-0.21	The results of the sensitivity analysis were based on a single study. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
folinic acid	07. low/moderate RoB	1	23	0.23	2	32	0.44	-0.21	The results of the sensitivity analysis were based on a single study. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
folinic acid	12. ABC-L/SW	1	23	0.20	2	32	0.44	-0.24	The results of the sensitivity analysis were based on a single study. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
arbaclofen	12. ABC-L/SW	1	76	-0.11	1	76	0.16	-0.26	SMD was smaller when ABC-L/SW was used (-0.11 vs 0.16). Confidence intervals partially overlapped. They both did not suggest differences with placebo. Therefore, the interpretation of the results of the primary analysis did not change.

Adults

	Sensitivity analysis	**Primary analysis**	**Evaluation**

Drug	analysis	k_{sens}	n_{sens}	SMD_{sens}	$k_{primary}$	$n_{primary}$	$SMD_{primary}$	SMD_{sens}-$SMD_{primary}$	Comment
balovaptan	12. ABC-L/SW	1	111	0.31	2	222	0.06	0.25	The results were based on one of the two studies. Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
oxytocin	10. ITT	3	106	-0.11	4	115	0.01	-0.12	Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.
oxytocin	12. ABC-L/SW	2	55	-0.18	4	115	0.01	-0.18	Confidence intervals overlapped. Interpretation of the findings of the primary analysis did not change.

Repetitive behaviors

Children/adolescents

	Sensitivity analysis				Primary analysis			Evaluation	
Drug	analysis	k_{sens}	n_{sens}	SMD_{sens}	$k_{primary}$	$n_{primary}$	$SMD_{primary}$	SMD_{sens}-$SMD_{primary}$	Comment
lamotrigine	12. ABC-S	1	14	0.63	1	11	-0.04	0.66	SMD was larger when ABC-S was used, yet still not formally statistically significant at two-sided alpha 0.05. Confidence intervals partially overlapped. The results were based on a single study with unclear reporting of ABC-S (Belsito 2001). Mean scores of ABC-S were extracted from Fig.2. of the manuscript and standard deviations were estimated using the reported p=0.10. Mean scores in Fig.2 ranged from about 65 to about 85, yet the maximum score of ABC-S should be 21 (Aman et al 1985). Nevertheless, the interpretation of the findings of the primary analysis did not change.
vitamin-D	11. clinician ratings	2	47	0.46	5	84	0.16	0.30	SMD seemed to be larger when clinician ratings were used (0.46 vs. 0.16), yet confidence intervals overlapped. The results were based

									on two studies from Iran out of five (56% of the participants) that used clinician-ratings of ABC-S and GARS-2-S. Therefore, the interpretation of the results of the primary analysis did not change.
omega-3	11. clinician ratings	2	35	0.37	9	158	0.15	0.22	The results were based on two out of nine studies and confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
folinic acid	06. r=0.75	1	23	0.69	1	23	0.50	0.19	The precision of results is higher when a larger pre-post correlation is assumed (e.g., r=0.75). In that case, SMDs are more precise and larger. However, it is unlikely that scales measuring behavioral symptoms have such large correlations. Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
guanfacine	06. r=0.75	1	30	0.72	1	30	0.55	0.18	The precision of results is higher when a larger pre-post correlation is assumed (e.g., r=0.75). In that case, SMDs are more precise and larger. However, it is unlikely that scales measuring behavioral symptoms have such large correlations. Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
sapropterin	06. r=0.75	1	23	0.46	1	23	0.32	0.14	The precision of results is higher when a larger pre-post correlation is assumed (e.g., r=0.75). In that case, SMDs are more precise and larger. However, it is unlikely that scales measuring behavioral symptoms have such large correlations. Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
atomoxetine	18. low RoB (sequence generation and	2	80	0.64	3	107	0.49	0.15	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.

	allocation concealment)								
memantine	06. r=0.75	1	15	0.61	1	15	0.47	0.14	The precision of results is higher when a larger pre-post correlation is assumed (e.g., r=0.75). In that case, SMDs are more precise and larger. However, it is unlikely that scales measuring behavioral symptoms have such large correlations. Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
risperidone	06. r=0.75	4	133	0.74	4	133	0.60	0.14	The precision of results is higher when a larger pre-post correlation is assumed (e.g., r=0.75). In that case, SMDs are more precise and larger. However, it is unlikely that scales measuring behavioral symptoms have such large correlations. Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
atomoxetine	06. r=0.75	3	107	0.61	3	107	0.49	0.11	The precision of results is higher when a larger pre-post correlation is assumed (e.g., r=0.75). In that case, SMDs are more precise and larger. However, it is unlikely that scales measuring behavioral symptoms have such large correlations. Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
n-acetylcysteine	12. ABC-S	2	27	0.18	3	75	0.08	0.10	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
atomoxetine	05. r=0.25	3	107	0.40	3	107	0.49	-0.10	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
folinic acid	05. r=0.25	1	23	0.40	1	23	0.50	-0.10	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
citalopram	12. ABC-S	1	73	-0.08	1	73	0.03	-0.11	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.

risperidone	16. no associated symptoms	3	84	0.48	4	133	0.60	-0.11	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
memantine	16. no associated symptoms	1	15	0.36	1	15	0.47	-0.11	Confidence intervals overlapped. The results were based on indirect evidence for both the primary and sensitivity analysis based on a single and small study (Nikvarz et al 2017). The interpretation of the findings of the primary analysis did not change.
vitamin-D	18. low RoB (sequence generation and allocation concealment)	3	41	0.04	5	84	0.16	-0.12	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
guanfacine	05. r=0.25	1	30	0.42	1	30	0.55	-0.13	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
simvastatin	06. r=0.75	1	13	-0.44	1	13	-0.30	-0.14	The precision of results is higher when a larger pre-post correlation is assumed (e.g., r=0.75). In that case, SMDs are more precise and larger. However, it is unlikely that scales measuring behavioral symptoms have such large correlations. Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
fluoxetine	07. low/moderate RoB	2	95	-0.07	3	170	0.09	-0.15	The results were based on two out of the three studies (56% of the participants). Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
probiotics	12. ABC-S	2	18	-0.22	4	85	-0.03	-0.19	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
vitamin-D	12. ABC-S	4	59	-0.04	5	84	0.16	-0.20	Confidence intervals generally overlapped. The interpretation of the findings of the primary analysis did not change.
guanfacine	12. ABC-S	1	30	0.29	1	30	0.55	-0.25	SMD was smaller when ABC-S (a common caregiver-rating) was used (0.29 vs. 0.55). Confidence intervals

									partially overlapped. The interpretation of the findings of the primary analysis did not change, i.e., that guanfacine could potentially improve repetitive behaviors. It should be noted that CYBOCS-PDD (a common clinician-rating) was used in the primary analysis.
fluoxetine	12. ABC-S	1	75	-0.18	3	170	0.09	-0.26	The results were based on one out of the three studies (44% of the participants). Confidence intervals generally overlapped. The interpretation of the findings of the primary analysis did not change.
vitamin-D	16. no associated symptoms	2	40	-0.11	5	84	0.16	-0.26	The results were based on two out of the five studies (about 50% of the participants). Confidence intervals generally overlapped. The interpretation of the findings of the primary analysis did not change.
bumetanide	12. ABC-S	1	38	0.08	4	175	0.35	-0.27	The results were based on one out of the four studies (21% of the participants). Confidence intervals generally overlapped. The interpretation of the findings of the primary analysis did not change.
vitamin-D	17. more developed countries	3	37	-0.16	5	84	0.16	-0.32	Confidence intervals generally overlapped. The interpretation of the findings of the primary analysis did not change.

Adults

	Sensitivity analysis				**Primary analysis**			**Evaluation**	
Drug	**analysis**	**k_{sens}**	**n_{sens}**	**SMD_{sens}**	**$k_{primary}$**	**$n_{primary}$**	**$SMD_{primary}$**	**SMD_{sens}-$SMD_{primary}$**	**Comment**
fluoxetine	06. r=0.75	1	21	1.70	1	21	1.20	0.49	The precision of results is higher when a larger pre-post correlation is assumed (e.g., r=0.75). In that case, SMDs are more precise and larger. However, it is unlikely that scales measuring behavioral symptoms have such large correlations. The interpretation of the

									findings of the primary analysis did not change.
fluvoxamine	06. r=0.75	1	15	1.51	1	15	1.04	0.47	The precision of results is higher when a larger pre-post correlation is assumed (e.g., r=0.75). In that case, SMDs are more precise and larger. However, it is unlikely that scales measuring behavioral symptoms have such large correlations. The interpretation of the findings of the primary analysis did not change.
risperidone	06. r=0.75	1	14	1.35	1	14	0.97	0.38	The precision of results is higher when a larger pre-post correlation is assumed (e.g., r=0.75). In that case, SMDs are more precise and larger. However, it is unlikely that scales measuring behavioral symptoms have such large correlations. The interpretation of the findings of the primary analysis did not change.
fluvoxamine	05. r=0.25	1	15	0.88	1	15	1.04	-0.16	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
risperidone	05. r=0.25	1	14	0.78	1	14	0.97	-0.19	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
fluoxetine	05. r=0.25	1	21	0.98	1	21	1.20	-0.22	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.

Overall core symptoms

Children/adolescents

	Sensitivity analysis				**Primary analysis**			**Evaluation**	
Drug	**analysis**	**k_{sens}**	**n_{sens}**	**SMD_{sens}**	**$k_{primary}$**	**$n_{primary}$**	**$SMD_{primary}$**	**SMD_{sens}-$SMD_{primary}$**	**Comment**

folinic acid	11. clinician ratings	1	9	1.11	2	32	0.12	0.99	There was heterogeneity in the primary analysis, which included two small studies on folinic acid. The results of this sensitivity analysis were based on a single and small study that demonstrated a large SMD (NCT02551380). Confidence intervals partially overlapped. The results are inconclusive.
risperidone	06. r=0.75	3	81	1.65	3	81	1.18	0.47	The precision of results is higher when a larger pre-post correlation is assumed (e.g., r=0.75). In that case, SMDs are more precise and larger. However, it is unlikely that scales measuring behavioral symptoms have such large correlations. The interpretation of the findings of the primary analysis did not change.
risperidone	15. no associated symptoms	2	32	1.54	3	81	1.18	0.36	Confidence intervals overlapped. The interpretation of the results of the primary analysis did not change.
risperidone	11. clinician ratings	2	32	1.54	3	81	1.18	0.36	Confidence intervals overlapped. The interpretation of the results of the primary analysis did not change.
omega-3	11. clinician ratings	1	28	0.41	8	151	0.07	0.34	The results are based on one study (19% of the participants). Confidence intervals were generally overlapped. The interpretation of the primary analysis did not change.
memantine	17. including Nikvarz 2017	2	69	0.33	1	54	0.01	0.33	In this sensitivity analysis, a study that introduced incoherence (Nikvarz et al 2017) was included. In the primary analysis, this study was excluded. It compared risperidone and memantine, and found no difference between the two drugs. Confidence intervals partially overlapped. The interpretation of the results of the primary analysis did not change.

carnosine	11. clinician ratings	2	32	0.71	3	53	0.42	0.29	The results were based on two small studies, one of these was from Egypt and demonstrated a large effect-size (SMD=1.06). Confidence intervals partially overlapped. Therefore, the interpretation of the results of the primary analysis did not change.
carnosine	15. no associated symptoms	2	32	0.71	3	53	0.42	0.29	The results were based on the previous analysis. The interpretation of the results of the primary analysis did not change.
probiotics	11. clinician ratings	1	31	0.44	4	85	0.20	0.24	The results were based on one out four studies (36% of the participants). Confidence intervals generally overlapped. The interpretation of the results of the primary analysis did not change.
folinic acid	02. pairwise	32	2	0.35	2	32	0.12	0.23	There was heterogeneity in the primary analysis, which is reflected by the less precise yet a bit larger SMD in the pairwise meta-analysis. The interpretation of the results of the primary analysis did not change.
sapropterin	06. r=0.75	1	23	0.60	1	23	0.41	0.18	The precision of results is higher when a larger pre-post correlation is assumed (e.g., r=0.75). In that case, SMDs are more precise and larger. However, it is unlikely that scales measuring behavioral symptoms have such large correlations. The interpretation of the findings of the primary analysis did not change.
atomoxetine	18. low RoB (sequence generation and allocation concealment)	1	48	0.33	2	73	0.15	0.17	Confidence intervals overlapped. Interpretation of the primary analysis dit not change.
carnosine	06. r=0.75	3	53	0.58	3	53	0.42	0.16	The precision of results is higher when a larger pre-post correlation is assumed (e.g., r=0.75). In that case, SMDs are more precise and larger. However, it is unlikely that scales measuring behavioral symptoms have such large

									correlations. The interpretation of the findings of the primary analysis did not change.
vitamin-D	11. clinician ratings	1	22	0.31	4	59	0.16	0.15	The results were based on one out four studies (37% of the participants). Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
haloperidol	15. no associated symptoms	2	30	0.71	3	36	0.56	0.15	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
olanzapine	11. clinician ratings	1	6	1.34	1	6	1.20	0.15	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
haloperidol	11. clinician ratings	3	36	0.71	3	36	0.56	0.15	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
bumetanide	11. clinician ratings	3	151	0.76	4	189	0.61	0.15	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
omega-3	12. DSM/ICD	7	122	0.19	8	151	0.07	0.12	The results were based on seven out of eight studies (81% of the participants). One study that did not use standardized diagnostic criteria to include participants was excluded (Bent et al 2014). SMD was small but a bit larger than the primary analysis (0.19 vs. 0.07). Confidence intervals generally overlapped. The interpretation of the findings of the primary analysis did not change.
bumetanide	10. ITT	2	124	0.73	4	189	0.61	0.12	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
vitamin-D	15. no associated symptoms	2	40	0.27	4	59	0.16	0.11	Confidence intervals overlapped. The interpretation of the findings

									of the primary analysis did not change.
vitamin-D	07. low/moderate RoB	2	40	0.27	4	59	0.16	0.11	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
vitamin-D	02. pairwise	59	3	0.27	4	59	0.16	0.11	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
omega-3	07. low/moderate RoB	6	128	-0.02	8	151	0.07	-0.10	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
vitamin-D	16. more developed countries	3	37	0.06	4	59	0.16	-0.10	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
bumetanide	16. more developed countries	3	130	0.50	4	189	0.61	-0.11	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.
risperidone	17. including Nikvarz 2017	4	96	1.00	3	81	1.18	-0.18	Confidence intervals overlapped. The interpretation of the results of the primary analysis did not change.
risperidone	05. r=0.25	3	81	0.98	3	81	1.18	-0.20	Confidence intervals overlapped. The interpretation of the results of the primary analysis did not change.
risperidone	16. more developed countries	1	49	0.93	3	81	1.18	-0.25	Confidence intervals overlapped. The interpretation of the results of the primary analysis did not change.
risperidone	04. nonimputed SDs	1	49	0.93	3	81	1.18	-0.25	Confidence intervals overlapped. The interpretation of the results of the primary analysis did not change.
carnosine	12. DSM/ICD	1	21	0.03	3	53	0.42	-0.39	The results were based on one out of the three studies (40% of the participants. Two studies were excluded that did not use standardized diagnostic criteria (Geier 2011 and Fahmy et al.

									2013). The latter was a small study from Egypt that demonstrated a large effect-size (SMD=1.06). In this sensitivity analysis, the SMD was smaller (0.03 vs. 0.42) and confidence intervals partially overlapped. Therefore, the results of the primary analysis are inconclusive.
folinic acid	07. low/moderate RoB	1	23	-0.30	2	32	0.12	-0.42	There was heterogeneity in the primary analysis that was based on two small studies. In this analysis, a study that demonstrated large effect-size (SMD=1.11) and had high risk-of-bias was excluded (NCT02551380). Confidence intervals partially overlapped. The results of the primary analysis were inconclusive.
folinic acid	12. DSM/ICD	1	23	-0.30	2	32	0.12	-0.42	There was heterogeneity in the primary analysis that was based on two small studies. In this analysis, a study that demonstrated large effect-size (SMD=1.11) and did not use standardized diagnostic criteria was excluded (NCT02551380). Confidence intervals partially overlapped. The results of the primary analysis were inconclusive.
folinic acid	18. low RoB (sequence generation and allocation concealment)	1	23	-0.30	2	32	0.12	-0.42	There was heterogeneity in the primary analysis that was based on two small studies. In this analysis, a study that demonstrated large effect-size (SMD=1.11) and did not use standardized diagnostic criteria was excluded (NCT02551380). Confidence intervals partially overlapped. The results of the primary analysis were inconclusive.

Adults

	Sensitivity analysis				Primary analysis			Evaluation	
Drug	**analysis**	**k_{sens}**	**n_{sens}**	**SMD_{sens}**	**$k_{primary}$**	**$n_{primary}$**	**$SMD_{primary}$**	**SMD_{sens}-$SMD_{primary}$**	**Comment**
risperidone	06. r=0.75	1	14	0.66	1	14	0.49	0.18	The precision of results is higher when a larger pre-post correlation is assumed (e.g., r=0.75). In that case, SMDs are more precise and larger. However, it is unlikely that scales measuring behavioral symptoms have such large correlations. The interpretation of the findings of the primary analysis did not change.
risperidone	05. r=0.25	1	14	0.39	1	14	0.49	-0.10	Confidence intervals overlapped. The interpretation of the findings of the primary analysis did not change.

Dichotomous outcomes

In addition, relative risks were used for dichotomous in a sensitivity analysis, which is also presented in Figure-S4. The results did not materially change.

6.7. Effect sizes of individual studies

Effect sizes of individual studies and pairwise meta-analysis are presented in Figure-S3.
SMDs>0 are in favor of the first intervention, meaning more symptom reduction or more improvement in quality of life or global functioning. ORs>1 are in favor of the first intervention in case of response to treatment (higher OR means more patients with a response) or in favor of the second intervention in case of dropouts or adverse events (higher OR means fewer dropouts or patients with adverse events).

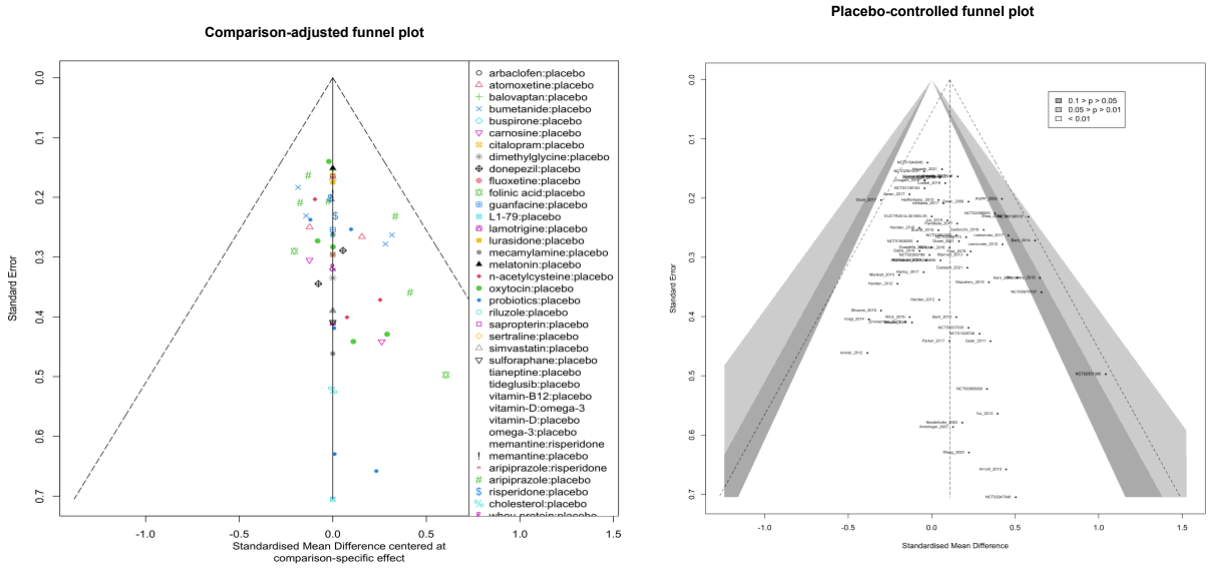
6.8. Assessment of publication bias and small-study effects

When there were more than 10 studies available, we investigated small-study effects with 1) comparison-adjusted funnel plots for the primary network meta-analysis assuming the direction of bias to the more recent interventions of the comparison (i.e. in our study: i) vitamin-D to omega-3, ii) memantine to aripiprazole to olanzapine to risperidone to clomipramine to haloperidol to placebo, iii) any pharmacological or dietary supplement to placebo); 2) contour-enhanced funnel plots for the placebo-controlled comparisons. Linear regression test for funnel plot asymmetry accompanied the visual inspection of the funnel plots.

6.8.1 Social-communication difficulties

	Comparison-adjusted funnel plot (t, df, p-value)	Placebo-controlled funnel plot (t, df, p-value)
Children/adolescents	t=1.79, df=69, p-value=0.078	t=1.778, df=66, p-value=0.080
Adults or mixed	Less than 10 studies were available for this outcome.	Less than 10 studies were available for this outcome.

Funnel plots for children/adolescents:



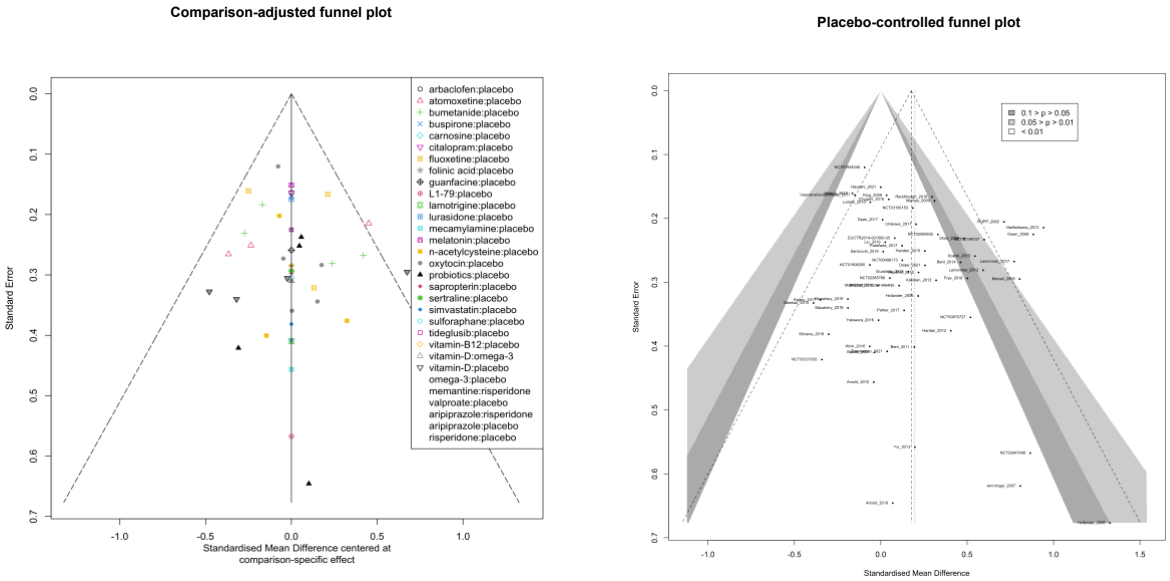
There was asymmetry in the comparison-adjusted and contour-enhanced funnel plot according to visual inspection and statistical tests (p-value=0.078<0.1 and p-value=0.08<0.1, respectively). Asymmetry was mainly due to smaller studies with larger effect sizes comparing aripiprazole, carnosine, folinic acid, n-acetylcysteine omega-3 and probiotics vs. placebo. Therefore, there may be a potential publication bias in studies favoring the experimental intervention in comparison to placebo, which might be more prominent in the above dietary-supplements.

There were less than 10 studies for adults or mixed populations.

6.8.2 Repetitive behaviors and restricted interests

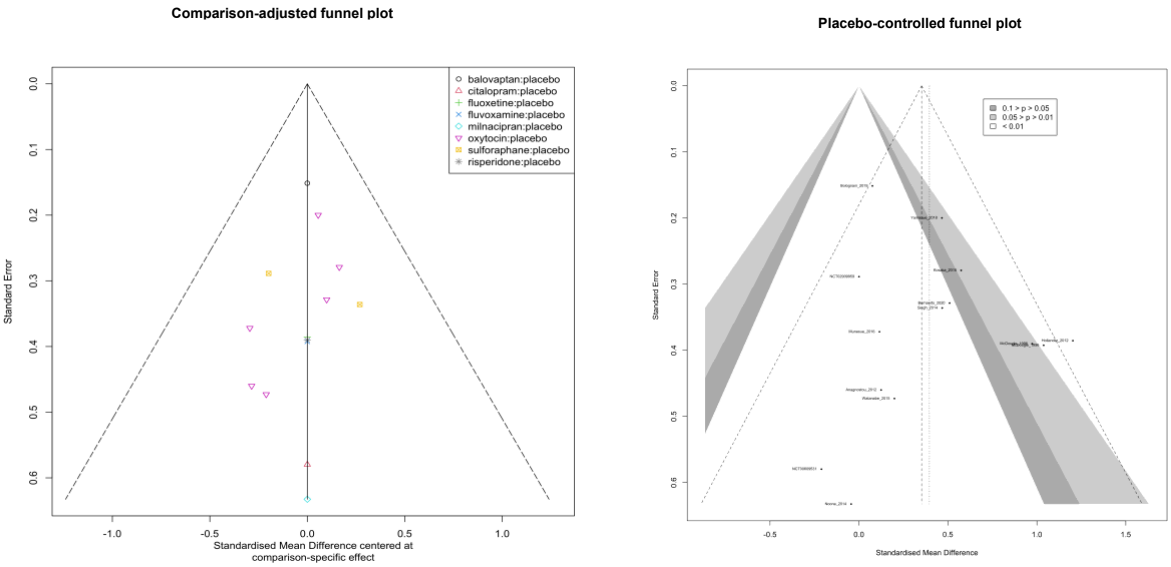
	Comparison-adjusted funnel plot (t, df, p-value)	Placebo-controlled funnel plot (t, df, p-value)
Children/adolescents	t=0.784, df=60, p-value=0.436	t=1.4435, df=57, p-value=0.154
Adults or mixed	t=-0.837, df=12, p-value=0.419	t=0.929, df=12, p-value=0.371

Funnel plots for children/adolescents:



No clear asymmetry was observed in the comparison-adjusted funnel plot, yet asymmetry in the contour-enhanced funnel plot can be observed by visual inspection. This was driven mainly due to three small studies with larger effect sizes (NCT02847048: L1-79 vs. placebo, Amminger 2007: omega-3 vs. placebo and Hollander 2006: valproate vs. placebo). However, statistical tests were not formally significant (at alpha=0.1).

Funnel plots for adults or mixed populations:

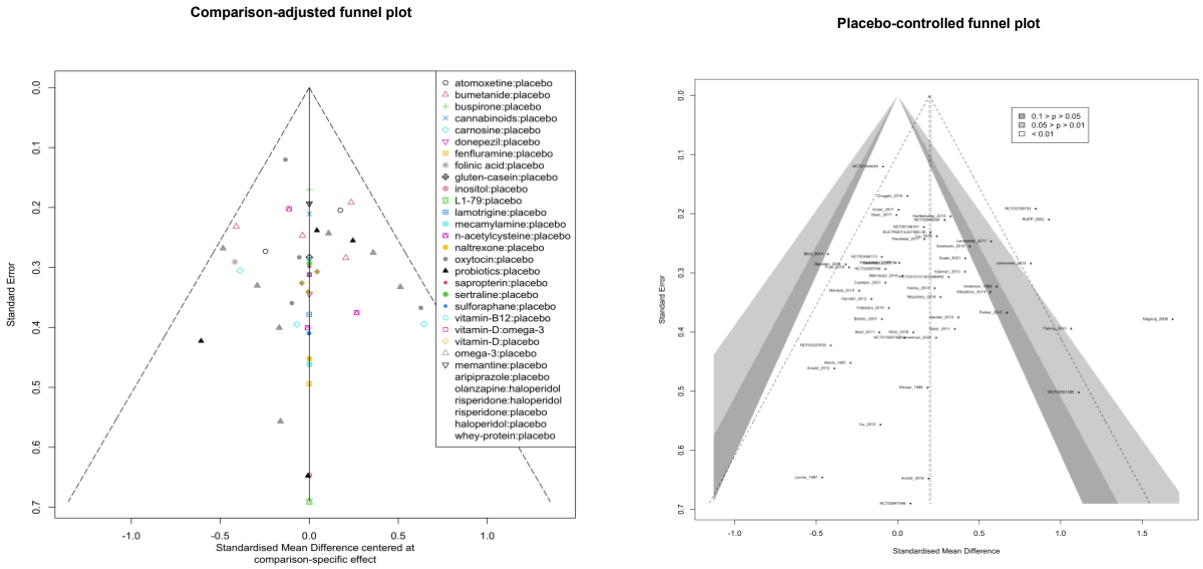


Asymmetry can be visually observed in both comparison-adjusted and contour-enhanced funnel plot, yet statistical tests were not formally significant (at alpha=0.1). The asymmetry was mainly driven by smaller studies that demonstrated smaller effect sizes for the comparison between oxytocin, citalopram and milnacipran vs. placebo.

6.8.3 Scales measuring overall core symptoms

	Comparison-adjusted funnel plot (t, df, p-value)	Placebo-controlled funnel plot (t, df, p-value)
Children/adolescents	t=1.304, df=54, p=0.1977	t=0.277, df=51, p=0.7829
Adults or mixed	Less than 10 studies were available.	Less than 10 studies were available.

Funnel plots for children/adolescents:



No clear asymmetry was observed in contour-enhanced funnel plot, and statistical tests was formally not significant (p>0.1)

There were less than 10 studies for adults or mixed populations.

6.8.4 Available data across studies and comparisons for the primary outcomes

6.8.4.1 Summary table of data per outcome and comparison

Reporting bias per comparison was also investigated by examining the proportion of studies with available data from the total published and unpublished studies. We expected that almost each trial reported usable data on core symptoms, therefore potential reporting bias was suspected when data were available in less than 75% of the total number of completed studies for a comparison (e.g. less than three out four studies). Neverthelss, we took into consideration the sample size of studies with not available data and the potential impact of their results on the meta-analytic estimates, i.e. for the comparison of balovaptan vs. placebo in adults and oxytocin vs. placebo in children/adolescents.

	comparison	n/n	study name	sample size	SMD 95% CI (>0 favors the first intervention of the comparison)			% of studies with data for		
					SCI	RRBI	Overall core symptoms	SCI	RRBI	Overall core symptoms
adults/mixed	agomelatine vs. placebo		Ballester_2015	23	n.i.	n.i.	n.i.	0%	0%	0%
	AZD7325 vs. placebo		NCT01966679	40	unpub.	unpub.	unpub.	0%	0%	0%
	balovaptan vs. placebo	1	Bolognani_2019	223	0.2246 [-0.0729; 0.5221]	0.0754 [-0.2213; 0.3721]	0.0111 [-0.2855; 0.3077]	100%	50% (41% of the participants, but the inclusion of the data of the missing trial may not alter the meta-analytic estimates, since the trial was reported as negative)	50% (41% of the participant, but the inclusion of the data of the missing trial may not alter the meta-analytic estimates, since the trial was reported as negative)
		2	NCT03504917	322	-0.1033 [-0.3745; 0.1678]	n.i.	n.i.			

citalopram vs. placebo		NCT00609531	12	n.i.	-0.2113 [-1.3476; 0.9250]	n.i.	0%	100%	0%
clomipramine vs. desipramine		Gordon_1993	30	crossover	crossover	crossover	0%	0%	0%
clomipramine vs. haloperidol		Remington_2001	37	crossover	crossover	crossover	0%	0%	0%
clomipramine vs. placebo	1	Gordon_1993	30	crossover	crossover	crossover	0%	0%	0%
	2	Remington_2001	37	crossover	crossover	crossover			
desipramine vs. placebo		Gordon_1993	30	crossover	crossover	crossover	0%	0%	0%
dextromethorphan/quinidine vs. placebo		Chez_2017	15	crossover	crossover	crossover	0%	0%	0%
fluoxetine vs. placebo		Hollander_2012	37	n.i.	1.2024 [0.4469; 1.9579]	n.i.	0%	100%	0%
fluvoxamine vs. placebo		McDougle_1996	30	n.i.	1.0382 [0.2691; 1.8074]	n.i.	0%	100%	0%
haloperidol vs. placebo		Remington_2001	37	crossover	crossover	crossover	0%	0%	0%
ketamine vs. placebo		Wink_2020	21	crossover	crossover	crossover	0%	0%	0%
milnacipran vs. placebo		Noone_2014	10	n.i.	-0.0441 [-1.2840; 1.1957]	n.i.	0%	100%	0%
oxytocin vs. placebo	1	Anagnostou_2012	19	n.i.	0.1242 [-0.7774; 1.0259]	0.2896 [-0.6169; 1.1960]	50%	75%	63%
	2	Bernaerts_2020	40	n.i.	0.5093 [-0.1347; 1.1534]	-0.0584 [-0.7529; 0.6361]			

	3	EUCTR2010-018740-NL	78 (antisocial or ASD)	unpub.	unpub.	unpub.			
	4	Kosaka_2016	60	0.3726 [-0.1685; 0.9138]	0.5742 [0.0270; 1.1214]	n.i.			
	5	Munesue_2016	29	-0.8267 [-1.5902; -0.0633]	0.1150 [-0.6140; 0.8440]	-0.0459 [-0.7743; 0.6826]			
	6	NCT01788072	70	unpub.	unpub.	unpub.			
	7	Watanabe_2015	20	0.7312 [-0.2314; 1.6939]	0.1991 [-0.7277; 1.1260]	-0.1801 [-1.1064; 0.7462]			
	8	Yamasue_2018	106	-0.1134 [-0.4999; 0.2732]	0.4660 [0.0743; 0.8577]	0.0243 [-0.3620; 0.4106]			
propanolol vs. placebo		NCT02871349	69	unpub.	unpub.	unpub.	0%	0%	0%
risperidone vs. placebo	1	Hellings_2006	40	crossover	crossover	crossover	0%	50%	50%
	2	McDougle_1998	31	n.i.	0.9735 [0.2091; 1.7379]	0.4886 [-0.2409; 1.2180]			
sulforaphane vs. placebo	1	NCT02909959	48	-0.1033 [-0.3745; 0.1678]	0.0000 [-0.5658; 0.5658]	0.0196 [-0.5463; 0.5854]	100%	100%	100%
	2	Singh_2014	44	0.6194 [-0.0459; 1.2846]	0.4678 [-0.1909; 1.1264]	0.8555 [0.2046; 1.5064]			
acamprosate vs. placebo	1	NCT01813318	36	unpub.	unpub.	unpub.	0%	0%	0%

amantidine vs. placebo		King_2001	39	n.i.	n.i.	n.i.	0%	0%	0%
arbaclofen vs. placebo		VeenstraVanderWeele_2017	150	0.1559 [-0.1647; 0.4765]	-0.15 [-0.47; 0.15]	n.i.	100%	100%	0%
aripiprazole vs. risperidone	1	DeVane_2019	61	n.i.	n.i.	n.i.	33%	33%	0%
	2	Ghanizadeh_2014	59	0.1231 [-0.3879; 0.6340]	-0.0830 [-0.5936; 0.4276]	n.i.			
	3	Lamberti_2016	44	n.i.	n.i.	n.i.			
aripiprazole vs. placebo	1	Ichikawa_2017	92	0.0696 [-0.3393; 0.4786]	0.2047 [-0.2052; 0.6146]	n.i.	71%	71%	14%
	2	Marcus_2009	218	0.1131 [-0.2062; 0.4323]	0.3114 [-0.0266; 0.6494]	n.i.			
	3	NCT00198107	81	0.5789 [0.1253; 1.0326]	0.5985 [0.1413; 1.0556]	0.1600 [-0.2763; 0.5963]			
	4	NCT00468130	15	unpub.	unpub.	unpub.			
	5	NCT00870727	33	0.6568 [-0.0464; 1.3601]	0.5193 [-0.1763; 1.2150]	n.i.			
	6	NCT03487770	111	unpub.	unpub.	unpub.			
	7	Owen_2009	98	0.2206 [-0.1831; 0.6242]	0.8831 [0.4419; 1.3243]E	n.i.			
atomoxetine vs. placebo	1	Arnold_2006	16	crossover	crossover	crossover	60%	60%	40%
	2	Handen_2015	128	-0.0737 [-0.5638; 0.4165]	0.2552 [-0.2369; 0.7474]	n.i.			
	3	Harfterkamp_2013	97	0.0413 [-0.3568; 0.4393]	0.9425 [0.5220; 1.3629]	0.3237 [-0.0771; 0.7244]			
	4	Martsenkovska 2015	80	n.i.	n.i.	n.i.			
	5	NCT00498173	60	0.2062 [-0.3153; 0.7276]	0.1246 [-0.3958; 0.6451]	-0.0972 [-0.6324; 0.4380]			

atomoxetine vs. risperidone	1	Martsenkovska 2015	80	n.i.	n.i.	n.i.	0%	0%	0%
balovaptan vs. placebo	1	NCT02901431	308	-0.0451 [-0.3486; 0.2584]	n.i.	n.i.	100%	0%	0%
bumetanide vs. placebo	1	EUCTR2014-001560-35	92	0.0000 [-0.4527; 0.4527]	0.0807 [-0.3722; 0.5336]	0.2009 [-0.2529; 0.6548]	67%	67%	67%
	2	Lemonnier_2012	60	0.4240 [-0.1210; 0.9690]	0.5920 [0.0409; 1.1431]	0.8171 [0.2602; 1.3740]			
	3	Lemonnier_2017	88	0.4591 [-0.0565; 0.9746]	0.7720 [0.2475; 1.2964]	0.5733 [0.0899; 1.0566]			
	4	NCT03156153	120	-0.0428 [-0.4022; 0.3166]	0.1849 [-0.1753; 0.5450]	0.8468 [0.4711; 1.2224]			
	5	NCT03715153	211	unpub.	unpub.	unpub.			
	6	NCT03715166	211	unpub.	unpub.	unpub.			
buspirone vs. placebo	1	Chugani_2016	166	-0.0433 [-0.3768; 0.2901]	0.0461 [-0.2874; 0.3795]	0.0600 [-0.2735; 0.3935]	50%	50%	50%
	2	NCT00166621	20	unpub.	unpub.	unpub.			
cannabinoids vs. placebo		NCT02956226	150	n.i.	n.i.	0.2882 [-0.1246; 0.7009]	0%	0%	100%
carnosine vs. placebo	1	Fahmy_2013	30	n.i.	n.i.	1.0644 [0.2911; 1.8377]	50%	25%	75%
	2	Geier_2011	30	0.3523 [-0.5131; 1.2176]	n.i.	0.3505 [-0.4238; 1.1248]			
	3	Ghodsi_2018	44	n.i.	n.i.	n.i.			
	4	Mehrazad_2018	50	-0.0340 [-0.6320; 0.5640]	-0.0165 [-0.6145; 0.5814]	0.0306 [-0.5674; 0.6285]			
cholesterol vs. placebo	1	NCT00965068	15	0.3312 [-0.6925; 1.3549]	n.i.	n.i.	100%	0%	0%

citalopram vs. placebo		King_2009	149	0.0516 [-0.2696; 0.3729]	0.0334 [-0.2878; 0.3547]	n.i.	100%	100%	0%
D-cycloserine vs. placebo		NCT00198120	80	unpub.	unpub.	unpub.	0%	0%	0%
digestive enzymes vs. placebo	1	Munasinghe_2010	43	crossover	crossover	crossover	0%	0%	0%
	2	NCT00881452	182	unpub.	unpub.	unpub.			
	3	NCT02410902	335	unpub.	unpub.	unpub.			
dimethylglycine vs. placebo	1	Bolman_1999	10	crossover	crossover	crossover	50%	0%	0%
	2	Kern_2001	37	0.5125 [-0.1439; 1.1689]	n.i.	n.i.			
valproate vs. placebo	1	Hollander_2006	13	n.i.	1.3261 [-0.0005; 2.6528]	n.i.	0%	33%	0%
	2	Hollander_2010	27	n.i.	n.i.	n.i.			
	3	Hellings_2005	30	n.i.	n.i.	n.i.			
donepezil vs. placebo	1	Handen_2012	34	-0.2048 [-0.8802; 0.4706]	n.i.	-0.1618 [-0.8365; 0.5129]	100%	0%	50%
	2	Gabis_2019	60	-0.0731 [-0.6396; 0.4934]	n.i.	n.i.			
fenfluramine vs. placebo	1	August_1987	10	crossover	crossover	crossover	0%	0%	11%
	2	Barthelemy_1989	13	crossover	crossover	crossover			
	3	Campbell_1987	28	n.i.	n.i.	n.i.			
	4	Ekman_1989	20	crossover	crossover	0.1835 [-0.7849; 1.1520]			
	5	Leventhal_1993	15	crossover	crossover	crossover			
	6	Realmuto_1986	14	crossover	crossover	crossover			
	7	Sherman_1989	15	crossover	crossover	crossover			
	8	Stern_1990	20	crossover	crossover	crossover			

	9	Duker_1991	11	crossover	crossover	crossover			
ferrous vs. placebo		Reynold_2019	20	n.i.	n.i.	n.i.	0%	0%	0%
fluoxetine vs. placebo	1	Herscu_2019	158	n.i.	-0.1646 [-0.4800; 0.1509]	n.i.	25%	75%	0%
	2	Hollander_2005	44	n.i.	0.2165 [-0.4134; 0.8465]	n.i.			
	3	NCT00183339	18	n.i.	n.i.	n.i.			
	4	Reddihough_2019	146	0.0478 [-0.2768; 0.3724]	0.2969 [-0.0294; 0.6233]	n.i.			
fluvoxamine vs. placebo	1	McDougle_2000	34	unpub.	unpub.	unpub.	0%	0%	0%
	2	NCT00655174	108	unpub.	unpub.	unpub.			
	3	Sugie_2005	18	crossover	crossover	crossover			
fluvoxamine vs. setraline	1	NCT00655174	108	unpub.	unpub.	unpub.	0%	0%	0%
folinic acid vs. placebo	1	Frye_2018	48	0.2328 [-0.3356; 0.8011]	0.5007 [-0.0752; 1.0765]	-0.2984 [-0.8681; 0.2713]	66%	33%	66%
	2	NCT00672360	13	unpub.	unpub.	unpub.			
	3	NCT02551380	19	1.0426 [0.0681; 2.0171]	n.i.	1.1106 [0.1266; 2.0946]			
galantamine vs. placebo	1	NCT00252603	20	unpub.	unpub.	unpub.	0%	0%	0%
	2	Niederhofer_2002a	20	crossover	crossover	crossover			
gluten-casein vs. placebo		Pusponegoro_2015	74	n.i.	n.i.	0.0094 [-0.5454; 0.5642]	0%	0%	100%
guanfacine vs. placebo		Scahill_2015	62	0.0401 [-0.4580; 0.5383]	0.5450 [0.0371; 1.0529]	n.i.	100%	100%	0%

haloperidol vs. olanzapine		Malone_2001	12	n.i.	n.i.	-0.6316 [-1.8045; 0.5412]	0%	0%	100%
haloperidol vs. risperidone		Miral_2008	30	n.i.	n.i.	-0.6779 [-1.4449; 0.0891]	0%	0%	100%
haloperidol vs. placebo	1	Anderson_1989	45	crossover	crossover	0.6072 [-0.0264; 1.2408]	0%	0%	33%
	2	Campbell_1982	41	crossover	crossover	crossover			
	3	Cohen_1980	10	crossover	crossover	crossover			
IGOH vs. placebo		Handen_2009	125	n.i.	n.i.	n.i.	0%	0%	0%
inositol vs. placebo		Levine_1997	10	n.i.	n.i.	-0.4632 [-1.7299; 0.8035]	0%	0%	100%
L1-79 vs. placebo		NCT02947048	39	0.5036 [-0.8783; 1.8855]	0.8651 [-0.2470; 1.9772]	0.0783 [-1.2749; 1.4315]	100%	100%	100%
lamotrigine vs. placebo		Belsito_2001	37	-0.1181 [-0.9219; 0.6857]	-0.0364 [-0.8394; 0.7666]	-0.0968 [-0.8381; 0.6445]	100%	100%	100%
levetiracetam vs. placebo		Wasserman_2006	20	n.i.	n.i.	n.i.	0%	0%	0%
levodopa vs. placebo		Sugiyama_1998	20	crossover	crossover	crossover	0%	0%	0%
lofexidine vs. placebo		Niederhofer_2002b	12	crossover	crossover	crossover	0%	0%	0%
lurasidone vs. placebo		Loebel_2016	150	0.0812 [-0.2613; 0.4237]	-0.0609 [-0.4033; 0.2815]	n.i.	100%	100%	0%
mecamylamine vs. placebo		Arnold_2012	20	-0.3854 [-1.2899; 0.5191]	-0.0411 [-0.9358; 0.8536]	-0.3889 [-1.2935; 0.5158]	100%	100%	100%
melatonin vs. placebo	1	Cortesi_2012	160	n.i.	n.i.	n.i.	17%	17%	0%
	2	Gringras_2017	125	n.i.	n.i.	n.i.			

	3	Hayashi_2021	196	0.0619 [-0.2344; 0.3582]	0.0000 [-0.2962; 0.2962]	n.i.			
	4	NCT01993251	26	unpub.	unpub.	unpub.			
	5	Tordjman_2013	32	unpub.	unpub.	unpub.			
	6	Wright_2011	20	crossover	crossover	crossover			
melatonin+donepezil vs. placebo		NCT02487082	12	unpub.	unpub.	unpub.	0%	0%	0%
memantine vs. risperidone		Nikvarz_2017	34	0.09 [-0.62; 0.81]	-0.11 [-0.83; 0.61]	0.00 [-0.71; 0.72]	100%	100%	100%
memantine vs. placebo	1	Aman_2017	121	-0.1329 [-0.5123; 0.2465]	n.i.	0.0053 [-0.3736; 0.3843]	25%	0%	25%
	2	Hage_2016	50	unpub.	unpub.	unpub.			
	3	NCT01372449	23	n.i.	n.i.	n.i.			
	4	NCT01972074	43	n.i.	n.i.	n.i.			
methylphenidate vs. placebo	1	Ghuman_2009	12	crossover	crossover	crossover	0%	0%	0%
	2	Handen_2000	13	crossover	crossover	crossover			
	3	Pearson_2013	24	crossover	crossover	crossover			
	4	Quintana_1995	10	crossover	crossover	crossover			
	5	RUPP_2005	72	crossover	crossover	crossover			
mirtazapine vs. placebo		NCT01302964	30	n.i.	n.i.	n.i.	0%	0%	0%
multivitamin vs. placebo		NCT00572741	39	unpub.	unpub.	unpub.	0%	0%	0%
n-acetylcysteine vs. placebo	1	Dean_2017	102	-0.3035 [-0.7019; 0.0949]	0.0104 [-0.3856; 0.4065]	-0.0073 [-0.4034; 0.3888]	100%	100%	100%
	2	Hardan_2012	33	0.0452 [-0.6833; 0.7736]	0.4055 [-0.3314; 1.1425]	0.3724 [-0.3632; 1.1080]			

	3	Wink_2016	31	-0.1320 [-0.9176; 0.6536]	-0.0645 [-0.8494; 0.7204]	0.0963 [-0.6889; 0.8814]			
naltrexone vs. placebo	1	Akkok_1995	20	n.i.	n.i.	-0.2890 [-1.1756; 0.5976]	0%	0%	17%
	2	Bouvard_1995	10	crossover	crossover	crossover			
	3	Campbell_1993	45	n.i.	n.i.	n.i.			
	4	Kolmen_1997	11	crossover	crossover	crossover			
	5	Scifo_1991	12	crossover	crossover	crossover			
	6	Willemsen_1996	23	crossover	crossover	crossover			
olanzapine vs. placebo	1	Hollander_2006b	11	n.i.	n.i.	n.i.	0%	0%	0%
	2	Malone_2010	32	unpub.	unpub.	unpub.			
	3	NCT00057408	78	unpub.	unpub.	unpub.			
omega-3 vs vitamin-D		Mazahery_2019	117	0.3053 [-0.3062; 0.9168]	0.0000 [-0.6076; 0.6076]	0.3046 [-0.3068; 0.9161]	100%	100%	100%
omega-3 vs. placebo	1	Amminger_2007	13	0.1281 [-1.0212; 1.2775]	0.8074 [-0.4060; 2.0209]	n.i.	60%	57%	50%
	2	Bent_2011	27	0.1474 [-0.6385; 0.9332]	0.1938 [-0.5930; 0.9806]	-0.1130 [-0.8984; 0.6723]			
	3	Bent_2014	57	0.6187 [0.0863; 1.1512]	0.4612 [-0.0654; 0.9879]	-0.4284 [-0.9540; 0.0973]			
	4	Doaei_2021	54	0.1630 [-0.3718; 0.6977]	0.2559 [-0.2803; 0.7920]	0.4150 [-0.1250; 0.9549]			
	5	ISRCTN2023387	50	unpub.	unpub.	unpub.			
	6	Mankad_2015	38	-0.1954 [-0.8418; 0.4510]	-0.3896 [-1.0411; 0.2618]	-0.2366 [-0.8838; 0.4106]			
	7	Mazahery_2019	117	0.6478 [-0.0081; 1.3036]	-0.1908 [-0.8304; 0.4488]	0.5678 [-0.0840; 1.2195]			

	8	NCT00467818	17	n.i.	n.i.	n.i.			
	9	NCT01260961	132	unpub.	unpub.	unpub.			
	10	NCT02222285	56	unpub.	unpub.	unpub.			
	11	NCT03550209	72	n.i.	n.i.	n.i.			
	12	Parellada_2017	77	0.1524 [-0.3239; 0.6287]	0.1229 [-0.3532; 0.5989]	0.1642 [-0.3122; 0.6406]			
	13	Voigt_2014	48	-0.3763 [-1.1691; 0.4165]	n.i.	n.i.			
	14	Yui_2013	13	0.3942 [-0.7112; 1.4997]	0.1972 [-0.8970; 1.2914]	-0.1057 [-1.1973; 0.9858]			
ORG-2766 vs. placebo	1	Buietlaar_1990	14	crossover	crossover	crossover	0%	0%	0%
	2	Buitelaar_1992	20	crossover	crossover	crossover			
oxytocin vs. placebo	1	Guastella_2015	50	-0.0030 [-0.5578; 0.5518]	0.1591 [-0.3967; 0.7148]	-0.0126 [-0.5674; 0.5422]	71% (85.3% of the participants are included in the analysis, based also on a large well-powered clinical trial)	71% (88% of the participants are included in the analysis, based also on a large well-powered clinical trial)	71% (81% of the participants are included in the analysis, based also on a large well-powered clinical trial)
	2	NCT01308749	25	0.2866 [-0.5544; 1.1275]	n.i.	0.0414 [-0.7616; 0.8445]			
	3	NCT01908205	60	-0.0848 [-0.6199; 0.4504]	-0.0638 [-0.5989; 0.4712]	n.i.			
	4	NCT01944046	290	-0.0249 [-0.2994; 0.2495]	-0.0940 [-0.3296; 0.1417]	-0.0895 [-0.3251; 0.1462]			
	5	Parker_2017	35	0.1058 [-0.7592; 0.9708]	0.1350 [-0.5393; 0.8093]	0.6701 [-0.0500; 1.3902]			
	6	UMIN000009075	40	unpub.	unpub.	unpub.			

	7	Yatawara_2016	39	n.i.	-0.0133 [-0.7177; 0.6911]	-0.0545 [-0.7591; 0.6501]			
prednisolone vs. placebo		Vasconcelos_2014	40	n.i.	n.i.	n.i.	0%	0%	0%
probiotics vs. placebo	1	Arnold_2019	13	0.4459 [-0.8440; 1.7357]	0.0691 [-1.1967; 1.3348]	0.1896 [-1.0800; 1.4593]	83% (77% of the participants)	67%	67%
	2	Liu_2019	80	0.0932 [-0.3723; 0.5587]	0.0252 [-0.4401; 0.4904]	0.2399 [-0.2271; 0.7070]			
	3	NCT03337035	35	0.2215 [-0.5361; 0.9791]	-0.3493 [-1.1109; 0.4123]	-0.4134 [-1.1776; 0.3509]			
	4	NCT03369431	69	unpub.	unpub.	unpub.			
	5	Santocchi_2019	85	0.3106 [-0.1865; 0.8076]	0.0139 [-0.4800; 0.5078]	0.4418 [-0.0585; 0.9422]			
	6	Wang_2020	26	0.2228 [-1.0112; 1.4568]	n.i.	n.i.			
riluzole vs. placebo		NCT01661855	58	0.1471 [-0.3684; 0.6625]	n.i.	n.i.	100%	0%	0%
risperidone vs. placebo	1	Kent_2013	96	n.i.	n.i.	n.i.	29%	29%	29%
	2	Martsenkovska 2015	80	n.i.	n.i.	n.i.			
	3	Nagaraj_2006	40	n.i.	n.i.	1.6871 [0.9453; 2.4288]			
	4	NCT01171937	41	unpub.	unpub.	unpub.			
	5	NCT01624675	39	n.i.	n.i.	n.i.			
	6	RUPP_2002	101	0.4208 [0.0261; 0.8155]	0.7128 [0.3099; 1.1157]	0.9286 [0.5171; 1.3401]			
	7	Shea_2004	80	0.4477 [-0.0049; 0.9003]	0.4823 [0.0288; 0.9358]	n.i.			

sapropterin vs. placebo	1	Danfors_2005	12	crossover	crossover	crossover	50%	50%	50%
	2	Klaiman_2013	61	0.2123 [-0.3674; 0.7921]	0.3202 [-0.2618; 0.9022]	0.4127 [-0.1720; 0.9973]			
secretin vs. placebo		Ratliff_2005	15	crossover	crossover	crossover	0%	0%	0%
sertraline vs. placebo		NCT00655174	108	unpub.	unpub.	unpub.	50%	50%	50%
		NCT02385799	58	-0.0131 [-0.5933; 0.5670]	0.0523 [-0.5228; 0.6275]	-0.0758 [-0.6510; 0.4995]			
simvastatin vs. placebo		Stivaros_2018	30	-0.3039 [-1.0680; 0.4603]	-0.3022 [-1.0498; 0.4454]	n.i.	100%	100%	0%
sulforaphane vs. placebo	1	NCT02879110	110	unpub.	unpub.	unpub.	50%	50%	50%
	2	Zimmerman_2021	57	-0.1588 [-0.9605; 0.6428]	0.0369 [-0.7634; 0.8371]	0.2359 [-0.5675; 1.0394]			
tianeptine vs. placebo		Niederhofer_2003	13	0.1834 [-0.9517; 1.3186]	n.i.	n.i.	100%	0%	0%
tideglusib vs. placebo		NCT02586935	83	0.3786 [-0.0638; 0.8209]	0.3305 [-0.1109; 0.7719]	n.i.	100%	100%	0%
venlafaxine vs. placebo		Niederhofer_2004	14	crossover	crossover	crossover	0%	0%	0%
vitamin-B12 vs. placebo	1	Bertoglio_2010	30	crossover	crossover	crossover	50%	50%	50%
	2	Hendren_2016	57	0.1072 [-0.4494; 0.6638]	0.2184 [-0.3396; 0.7763]	-0.3196 [-0.8795; 0.2404]			
vitamin-B6 vs. placebo	1	Martineuaeu_1985	60	crossover	crossover	crossover	0%	0%	0%
	2	NCT01230359	40	unpub.	unpub.	unpub.			

	3	Findling_1997	12	crossover	crossover	crossover			
vitamin-D vs. placebo	1	IRCT20131013014994N5	52	0.0524 [-0.5457; 0.6505]	0.1058 [-0.4926; 0.7042]	0.27 [−0.1; 0.64]	60%	80%	60%
	2	Kerley_2017	42	-0.0484 [-0.6852; 0.5885]	-0.3491 [-0.9912; 0.2931]	0.2271 [-0.4120; 0.8661]			
	3	Mazahery_2019	117	0.3421 [-0.3284; 1.0125]	-0.1903 [-0.8570; 0.4764]	0.2629 [-0.4053; 0.9312]			
	4	Moradi_2018	100	n.i.	0.8038 [0.2257; 1.3820]	n.i.			
	5	NCT02550912	42	unpub.	unpub.	unpub.			
whey-protein vs. placebo		Castejon_2021	81	0.2132 [-0.4093; 0.8357]	n.i.	-0.0744 [-0.6952; 0.5464]	100%	0%	100%

6.9. Grading the confidence in evidence with CINeMA

6.9.1 General

We evaluated confidence in the evidence of network meta-analytic estimates of placebo-controlled comparisons using Confidence In Network Meta-Analysis (CINeMA) framework [1] and the online tool (https://cinema.ispm.unibe.ch/)

6.9.1.1 Domains of CINeMA

i. Within-study bias

Within-study bias was assessed using the Cochrane's Risk-of-bias tool [2] and an overall judgment of risk of bias was assigned to each study, i.e., 'low, 'moderate' and 'high' risk [3] (see eAppendix-5.2). The contribution of each study to each effect size was estimated in CINeMA and a contribution matrix was constructed. Within-study bias for each comparison was classified into 'no concerns', 'some concerns' and 'major concerns' based on the average overall risk of bias according to the contribution matrix.

ii. Reporting bias

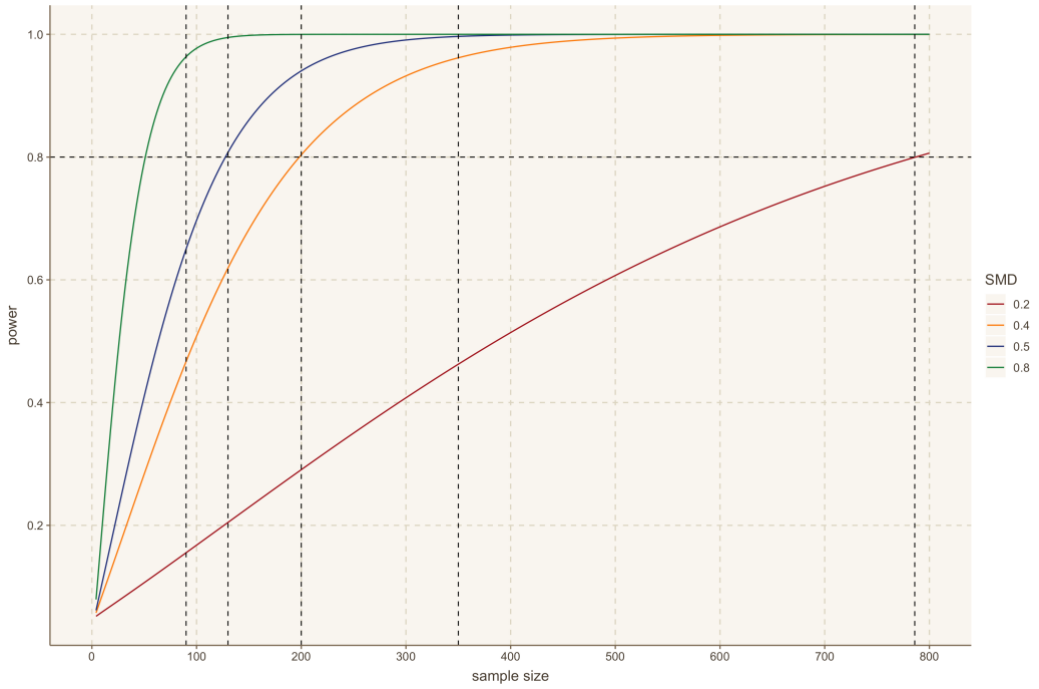
Our search was comprehensive and funnel plot analysis suggested small-study effects for social-communication dififculties in children/adolescnets, yet funnel plots for other outcomes were inconclusive (see eAppendix-6.8.1, 6.8.2, 6.8.3). In addition, there was no single comparison with at least 10 studies in order to perform a funnel plot analysis for a specific comparison. Therefore, we further assessed reporting bias for a comparison by examining the percentage of studies with sufficient data. A comparison was judged with 'suspected' reporting bias when less than 75% of available studies report sufficient data for this outcome, otherwise reporting bias was 'unsuspected". Neverthelss, we also took into consideration the sample size of missing studies and the potential impact of their results (in case they were impartially reported) on the meta-analytic estimates, i.e., for the comparison of balovaptan vs. placebo in adults and oxytocin vs. placebo in children/adolescents. See eAppendix-6.8 for the decision on reporting bias for each comparison.

iii. Indirectness

We assigned 'moderate' levels of indirectness to studies focused on a specific subgroup of patients by utilizing inclusion/exclusion criteria for an associated condition (e.g. irritability, ADHD symptoms, sleep disorders, intolerance or non-response to previous psychopharmacological treatments), a genetic syndrome (e.g. NF1), intellectual disability or high-functioning participants (see study characteristics in eAppendix-5.1.2). The rest of the studies were rated with 'low' levels of indirectness. There was no apparent reason to of indirectness due to interventions or outcomes. A comparison was judged with 'no concerns' or 'some concerns' due to indirectness based on the average indirectness of the contributions of each study to the comparison.

iv. Imprecision

Since the majority of the interventions were examined in one or two trials (usually with a small sample size), the available evidence was often based on a small number of participants. We set the optimal information size (OIS) at 200 participants, since an assumed trial with equal randomization would have been powered (80%) to detect a small to medium effect size of SMD=0.4 (see figure below) with an alpha of 0.05. Nevertheless, larger sample sizes are required to detect smaller effect sizes, i.e. 350 participants are required for SMD=0.3 and 786 for SMD=0.2, while smaller sample sizes are required for larger effect sizes, i.e., 90 participants treated with an intervention for SMD=0.6 and 130 for SMD=0.5. Given that small-to-medium effect sizes might be expected for the core symptoms of ASD, we set the threshold of sufficient evidence at 200 participants.



SMD: standardized mean difference, power: statistical power to detect an effect size at alpha 0.05

We set as clinically meaningful threshold of SMD the range between -0.21 and 0.21 (area of equivalence), since effect sizes within this range are often considered trivial. Imprecision was evaluated based on the relation between the sample size (number of participants received the medication in the network meta-analysis and number of participants received placebo in the studies of the direct comparison) and the OIS [4], and between the 95% confidence intervals of the effect size and the clinically meaningful threshold according to the rules described in CINeMA documentation [1].

Imprecision of a comparison could be classified as 'no concerns', 'some concerns' and 'major concerns': 1) "no concerns" when the OIS was met, and the 95%CI were within the area of equivalence or did not cross the effect line, 2) "some concerns" when the OIS was not met and/or the 95%CI crossed the null effect line but did not cross beyond the area of equivalence, 3) "major concerns" when the 95%CI crossed beyond the area of equivalence to both sides around the null effect line (irrespective if the OIS was met or not).

v. Heterogeneity

Heterogeneity was evaluated based on the relation of both the 95% confidence intervals and the 95% prediction intervals with the clinically meaningful threshold defined above in the domain of imprecision. The rules described in CINeMA documentation were used [1]. Since our sample was mainly consisted of a few small studies per comparison, we further assessed heterogeneity by examining the τ^2 of the pairwise comparisons, when there were more than two studies for the comparison. Similar to the assessment of heterogeneity in eAppendix-6.7, we compared τ^2 with its empirical distribution, and the magnitude of heterogeneity was classified as low, moderate or high levels. In comparisons with at least two studies, when the assessment according to prediction intervals and τ^2 did not agree, we used the assessment based on τ^2. Accordingly, comparisons could be classified according to heterogeneity evaluation as 'no concerns', 'some concerns', 'major concerns.

vi. Incoherence

Incoherence was evaluated using a design-by-treatment test (for comparisons with only direct or indirect evidence) and the SIDE approach (when both direct and indirect evidence was available) according to CINeMA documentation [1]. Comparisons could be classified according to

incoherence evaluation as ‘no concerns’, ‘some concerns’, ‘major concerns’. When there was only indirect evidence, incoherence was classified as ‘some concerns’. In case there were no closed loops and incoherence could not be evaluated, we rated incoherence as “no concerns” in contrast to CINeMA documentation, since we evaluated evidence on placebo-controlled comparisons, for which there was direct evidence.

6.9.1.2 Summarizing judgments across the domains

Judgments for each domain were summarized in an overall judgment on the confidence in the NMA estimate. The confidence was classified as ‘very low’, ‘low’, ‘moderate’ and ‘high’, and starting from ‘high’, it could be downgraded by one level for ‘some concerns’ (or ‘suspected bias’) and two levels for ‘major concerns’ in a domain. We jointly examined the domains imprecision and heterogeneity, as well as incoherence, since they are interconnected [5]. Therefore, the confidence could have been downgraded by up to 1) two levels for within-study bias, 2) one level for reporting bias, 3) one level for indirectness, 4) two levels for the common domain of imprecision-heterogeneity/incoherence. The latter was rated as below:

Judgment of the joint domain of heterogeneity, imprecision and incoherence	Number of subdomains with ‘major concerns’	Number of subdomains with ‘some concerns’	Number of subdomains with ‘no concerns’
‘major concerns’	2	1	0
‘major concerns’	2	0	1
‘major concerns’	1	1	1
‘major concerns’	1	2	0
‘some concerns’	1	0	2
‘some concerns’	0	3	0
‘some concerns’	0	2	1
‘some concerns’	0	1	2
‘no concerns’	0	0	3

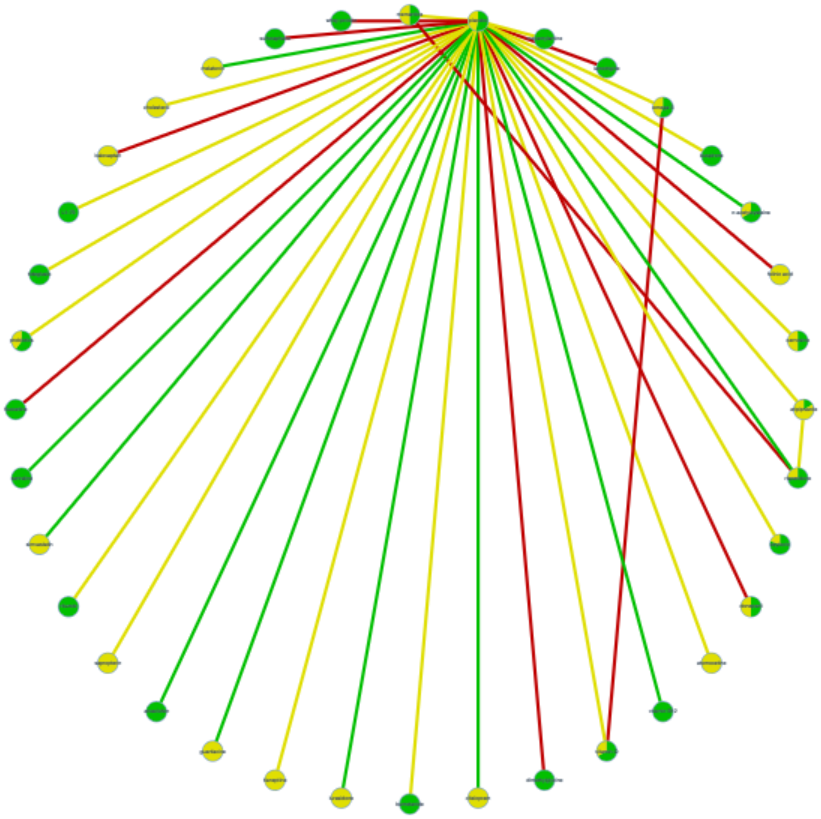
6.9.2 CINeMA for each primary outcome

In the network plots below, the color of the edge represents the average overall risk of bias and the color of the node the distribution of indirectness. Low risk of bias or low levels of indirectness is represented with green color, unclear risk of bias or moderate levels of indirectness with yellow and high risk of bias with red.

6.9.2.1 Social-communication difficulties

6.9.2.1.1 Children/adolescents

a. Network plot



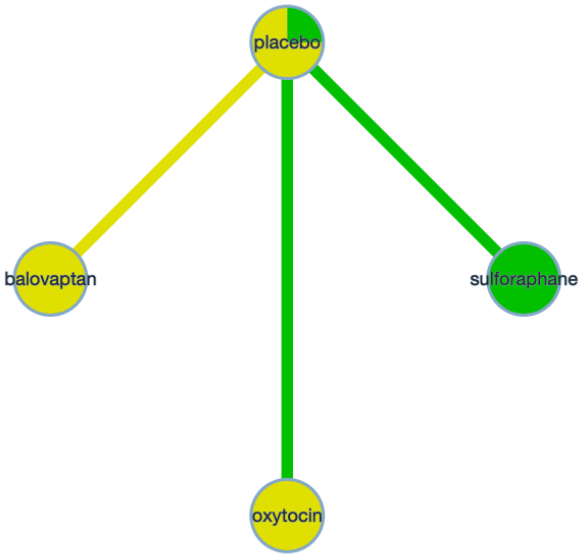
b. Confidence in evidence

Drug	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence
arbaclofen	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
aripiprazole	No concerns	Suspected	Some concerns	No concerns	No concerns	No concerns	Low
atomoxetine	Some concerns	Suspected	Some concerns	Major concerns	No concerns	No concerns	Very Low
balovaptan	Major concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Very Low
bumetanide	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
buspirone	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very Low
carnosine	Some concerns	Suspected	Some concerns	Major concerns	No concerns	No concerns	Very Low
cholesterol	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Very Low
citalopram	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
dimethylglycine	Major concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Very Low
donepezil	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very Low

fluoxetine	Major concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very Low
folinic acid	Some concerns	Suspected	Some concerns	Some concerns	Major concerns	No concerns	Very Low
guanfacine	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
L1-79	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
lamotrigine	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very Low
lurasidone	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
mecamylamine	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
melatonin	No concerns	Suspected	Some concerns	Major concerns	No concerns	No concerns	Very Low
memantine	Some concerns	Suspected	Some concerns	Major concerns	No concerns	No concerns	Very Low
n-acetylcysteine	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
omega-3	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Very Low
oxytocin	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
probiotics	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Low
riluzole	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
risperidone	No concerns	Suspected	Some concerns	No concerns	No concerns	No concerns	Low
sapropterin	Some concerns	Suspected	Some concerns	Major concerns	No concerns	No concerns	Very Low
sertraline	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
simvastatin	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
sulforaphane	Major concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very Low
tianeptine	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Very Low
tideglusib	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Low
vitamin-B12	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
vitamin-D	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very Low
whey-protein	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very Low

6.9.2.1.2 Adults or mixed

a. Network plot



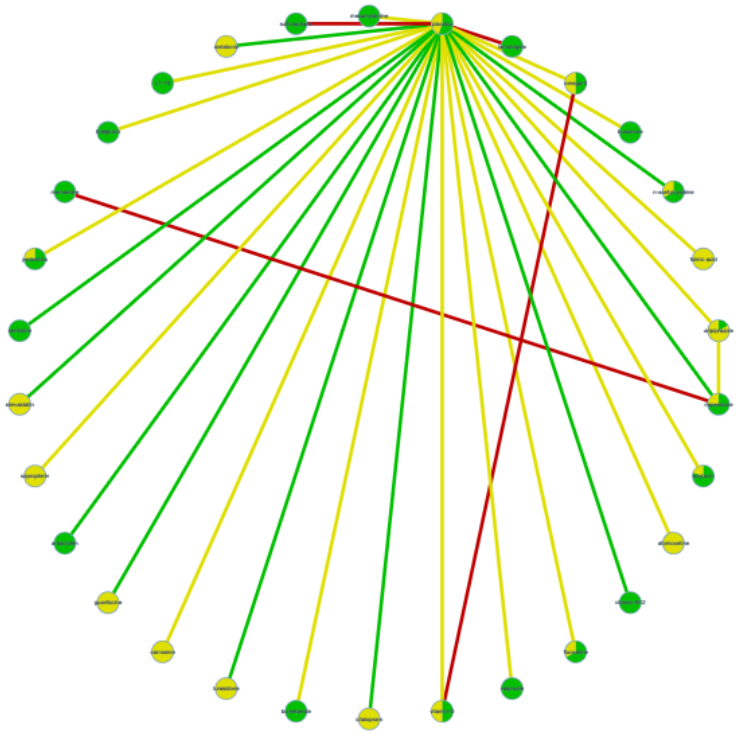
b. Confidence in evidence

Drug	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence
balovaptan	Some concerns	Undetected	Some concerns	Major concerns	Some concerns	No concerns	Very Low
oxytocin	No concerns	Suspected	Some concerns	Major concerns	Major concerns	No concerns	Very Low
sulforaphane	No concerns	Undetected	No concerns	Major concerns	Major concerns	No concerns	Low

6.9.2.2 Repetitive behaviors and restricted interests

6.9.2.2.1 Children/adolescents

a. Network plot



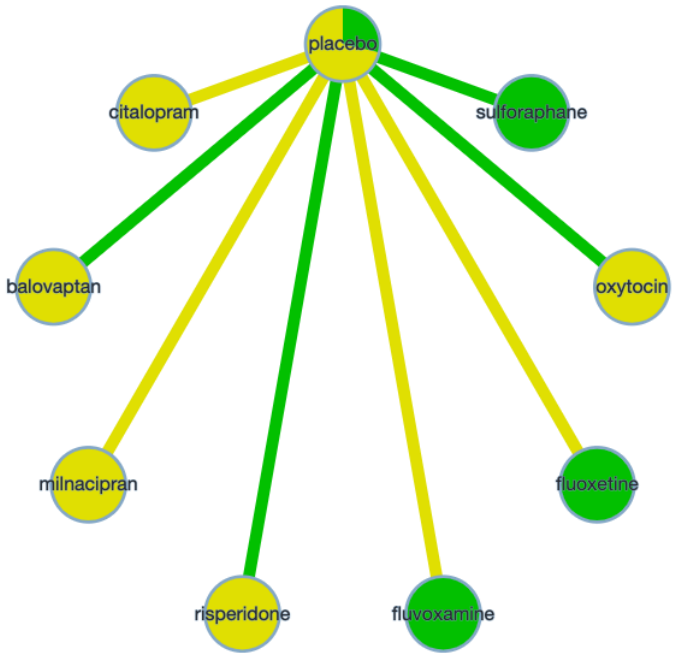
b. Confidence in evidence

Drug	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence
arbaclofen	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
aripiprazole	Some concerns	Suspected	Some concerns	No concerns	Some concerns	No concerns	Very Low
atomoxetine	Some concerns	Suspected	Some concerns	No concerns	Major concerns	No concerns	Very Low
bumetanide	No concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
buspirone	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very Low
carnosine	Some concerns	Suspected	Some concerns	Major concerns	No concerns	No concerns	Very Low
citalopram	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
fluoxetine	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
folinic acid	Some concerns	Suspected	Some concerns	Some concerns	No concerns	No concerns	Very Low
guanfacine	No concerns	Undetected	Some concerns	Some concerns	No concerns	No concerns	Low
L1-79	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
lamotrigine	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very Low
lurasidone	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low

mecamylamine	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
melatonin	No concerns	Suspected	Some concerns	Major concerns	No concerns	No concerns	Very Low
memantine	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very Low
n-acetylcysteine	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
omega-3	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Very Low
oxytocin	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
probiotics	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very Low
risperidone	No concerns	Suspected	Some concerns	No concerns	No concerns	No concerns	Low
sapropterin	Some concerns	Suspected	Some concerns	Major concerns	No concerns	No concerns	Very Low
sertraline	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
simvastatin	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
sulforaphane	Major concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very Low
tideglusib	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
valproate	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Very Low
vitamin-B12	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
vitamin-D	Some concerns	Undetected	No concerns	Some concerns	Major concerns	No concerns	Very Low

6.9.2.2.2 Adults or mixed

a. Network plot



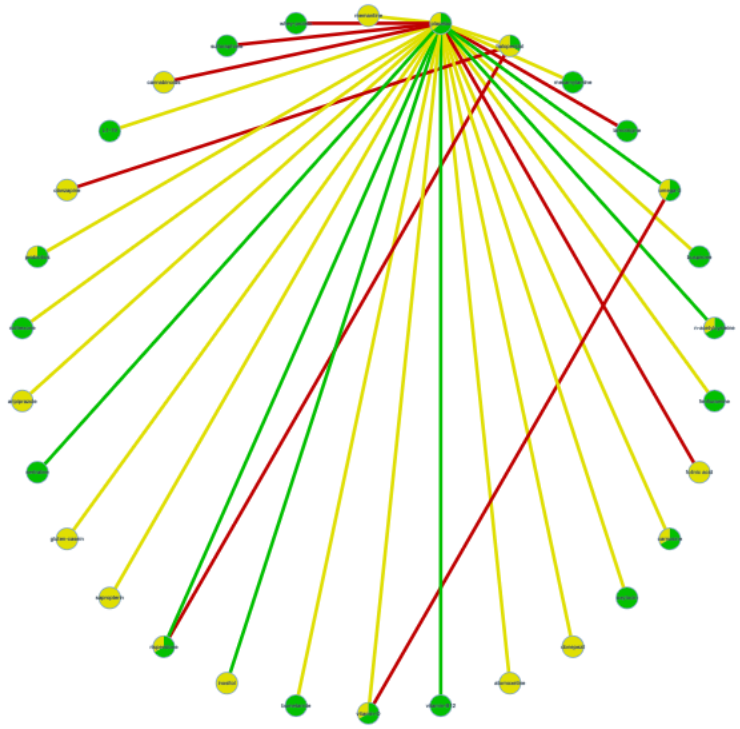
b. Confidence in evidence

Drug	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence
balovaptan	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
citalopram	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Very Low
fluoxetine	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Low
fluvoxamine	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Low
milnacipran	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Very Low
oxytocin	No concerns	Undetected	Some concerns	No concerns	No concerns	No concerns	Moderate
risperidone	No concerns	Suspected	Some concerns	Some concerns	Some concerns	No concerns	Very Low
sulforaphane	No concerns	Undetected	No concerns	Major concerns	Some concerns	No concerns	Low

6.9.2.3 Overall core symptoms

6.9.2.3.1 Children/adolescents

a. Network plot



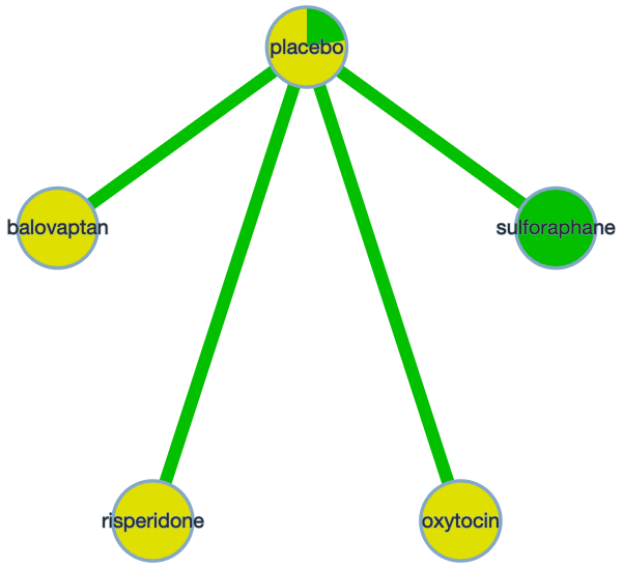
b. Confidence in evidence

Drug	Within-Study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence
L1-79	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
aripiprazole	Some concerns	Suspected	Some concerns	Major concerns	No concerns	No concerns	Very Low

atomoxetine	Some concerns	Suspected	Some concerns	Major concerns	Some concerns	No concerns	Very Low
bumetanide	No concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
buspirone	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very Low
cannabinoids	Major concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Very Low
carnosine	Some concerns	Undetected	No concerns	Some concerns	Major concerns	No concerns	Very Low
donepezil	Some concerns	Suspected	Some concerns	Major concerns	No concerns	No concerns	Very Low
fenfluramine	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very Low
folinic acid	Some concerns	Suspected	Some concerns	Major concerns	Major concerns	No concerns	Very Low
gluten-casein	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Very Low
haloperidol	Some concerns	Suspected	Some concerns	Some concerns	No concerns	No concerns	Very Low
inositol	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
lamotrigine	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very Low
mecamylamine	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
memantine	Some concerns	Suspected	Some concerns	Major concerns	No concerns	No concerns	Very Low
n-acetylcysteine	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
naltrexone	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very Low
omega-3	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Very Low
oxytocin	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
probiotics	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Very Low
risperidone	No concerns	Suspected	Some concerns	Some concerns	Major concerns	No concerns	Very Low
sapropterin	Some concerns	Suspected	Some concerns	Major concerns	No concerns	No concerns	Very Low
sertraline	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
sulforaphane	Major concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very Low
vitamin-B12	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
vitamin-D	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very Low
whey-protein	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very Low
olanzapine	Some concerns	Suspected	Some concerns	Some concerns	Some concerns	Some concerns	Very Low

6.9.2.3.2 Adults or mixed

a. Network plot



b. Confidence in evidence

Drug	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence
balovaptan	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
oxytocin	No concerns	Suspected	Some concerns	Major concerns	No concerns	No concerns	Very Low
risperidone	No concerns	Suspected	Some concerns	Major concerns	No concerns	No concerns	Very Low
sulforaphane	No concerns	Undetected	No concerns	Some concerns	Major concerns	No concerns	Low

6.9.3 References

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