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<td>Complete List of Authors:</td>
<td>Lopes, Luis; Universidade da Sorocaba, de Oliveira, Jardel; Secretaria Municipal de Saúde, Médico de Família e Comunidade, Especialista em Saúde da Família, Geriatria e Gerontologia Bergamaschi, Cristiane; Universidade de Sorocaba, Pharmaceutical Science Fulone, Izabela; Universidade de Sorocaba, Pharmaceutical Science Lima, Elisangela; Federal University of Rio de Janeiro Pharmacy School Abe, Flávia; University of Sorocaba Mazzei, Lauren; Universidade da Sorocaba Lopes, Luciane; Universidade de Sorocaba, Pharmaceutical Science</td>
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Use of second-generation antipsychotics in Autism Spectrum Disorder: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction: Atypical antipsychotics have been studied to treat Autism Spectrum Disorder (ASD). However, little is known whether these drugs are effective in real life. This study aims to assess the efficacy and safety of second-generation antipsychotics in ASD in randomized controlled trials (RCT) and observational studies.

Methods and Analysis: This Systematic Review will include RCT and prospective cohorts evaluating second-generation antipsychotics in people five years and older diagnosed with ASD. Searches will be conducted in Medline, Embase, Cochrane Library, Epistemonikos, Lilacs, CINAHL, PsycINFO, trial registries, and gray literature databases without restriction on publication status, year of publication, and language. The primary outcomes will be symptoms of aggressive behavior, quality of life for the individual or their careers, and discontinuation or dropouts/withdrawals of antipsychotics due to adverse events. The secondary outcomes are adverse events and adherence to pharmacotherapy. Selection, data extraction, and quality assessment will be performed by pairs of reviewers, independently. The Risk of Bias 2 (RoB 2) and Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tools will be used to assess the risk of bias in the included studies. If appropriate, a meta-analysis will be conducted to synthesize the results. The overall quality of the evidence for each outcome will be determined by the Recommendation, Assessment, Development, and Evaluation (GRADE) approach.

Ethics and dissemination: This study will systematically summarize the existing evidence evaluating the use of second-generation antipsychotics for treating ASD, in controlled and uncontrolled studies. The results of this review will be disseminated through peer-reviewed publications and conference presentations.

Protocol Registration: PROSPERO – CRD42022353795

Keywords: Autism Spectrum Disorder. Antipsychotic Agents. Real-World Evidence. Systematic Review.
STRENGTHS AND LIMITATIONS OF THIS STUDY

- This systematic review, in addition to evaluating the efficacy and safety of second-generation antipsychotics in ASD, will examine the performance of these interventions in RCT and uncontrolled (observational studies) settings;
- The search will be performed with the help of a specialized librarian experienced in medical literature searching;
- This study will consider the key stakeholders (e.g., policymakers, opinion leader, health care professionals, community representatives of patients, etc.) to overcome barriers to implementing the evidence summarized;
- Our systematic review proposal may have limitations inherent to the methodological quality of the included studies, especially non-randomized studies, which will be discussed.
INTRODUCTION

Autism Spectrum Disorder (ASD) was restructured and categorized by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), involving clinical conditions such as childhood autism, Kanner’s autism, high functioning autism, atypical autism, pervasive developmental disorder not otherwise specified, childhood disintegrative disorder, and Asperger’s [1].

Estimates of the prevalence of ASD vary. About 52 million people live with ASD worldwide [2]. Studies indicate approximately 1% to 2% of children in the US and other developed countries [3,4,2,5]. A systematic review of prevalence studies of ASD identified an overall estimate of the prevalence of 7.1 per 10,000 for autism and 20 per 10,000 for all ASD [6]. Another systematic review found that the average worldwide prevalence of ASD was 17 per 100,000, with a range of 2.8 to 94 per 100,000 across all age groups [7]. Hispanic and African-American children are underdiagnosed compared to non-Hispanic white children [6]. People with higher socioeconomic status and better access to health care are diagnosed earlier [7].

ASD is considered a brain-based neurodevelopmental disorder that lasts for life [8]. The three characteristic manifestations of ASD are impaired social interaction, impaired communication, and restricted repetitive and stereotyped patterns of behavior [9]. Challenging behavior has a great impact on the quality of life of individuals with ASD, family members, and the people they live with [10,11]. It is a situation that encompasses irritability, aggression, and self-harm [12]. These symptoms are the main causes of psychiatric hospitalization, and the use of antipsychotics is recommended in the absence of effectiveness of behavioral interventions [13,14,15].

Despite the claims of curative interventions, there is no specific treatment for autism and therapies target the symptoms of the disease. Pharmacological interventions have been used as adjuncts to behavioral treatments in both children and adults and may reduce specific autistic symptoms and behaviors such as self-injury and aggression [15]. There is evidence of widespread prescribing of psychotropic drugs to people with ASD [16]. Antipsychotic drugs generally tranquilize and relieve psychotic symptoms without impairing
consciousness [15]. Second-generation antipsychotics tend to cause fewer unwanted motor adverse effects than typical ones [17].

Typical (first-generation) and atypical (second-generation) antipsychotics have been evaluated for the treatment of behavioral symptoms in individuals with ASD. It is well established in the literature that first-generation antipsychotics are not recommended for treating symptoms in ASD due to their adverse effects. First-generation antipsychotics have been associated with drug-induced movement disorders [15]. Haloperidol, for example, has been evaluated for the treatment of ASD in several trials and has been associated with improvements in withdrawal and stereotypies [18] and positive effects on learning. However, it has also been related to extrapyramidal side effects such as acute dystonic reactions, withdrawal dyskinesias, and tardive dyskinesia in this population [19].

However, short-term randomized controlled trials (RCTs) have suggested the efficacy of second-generation antipsychotics to ameliorate some challenging symptoms of ASD in children and adolescents [20]. A systematic review investigated the use of risperidone for ASD and demonstrated the efficacy of this drug in treating symptoms of aggression, irritability, and repetitive behavior. Notable adverse events, including weight gain, increased appetite, and sedation, were described [21].

In addition, evidence from two RCTs suggests that aripiprazole can be effective as a short-term medication for some behavioral aspects of ASD in children/adolescents [22–24]. The participants presented less irritability and hyperactivity and fewer stereotypies such as repetitive and purposeless actions. However, weight gain, sedation, drooling, and tremors occurrence must also be considered [25]. Another systematic review [17] found that antipsychotics (aripiprazole, clozapine, haloperidol, levosulpiride, lurasidone, olanzapine, risperidone, trifluoperazine) for children and adolescents with ASD were more efficacious than placebo in reducing stereotypies, hyperactivity, irritability and obsessions, compulsions, and increasing social communication and global functioning.

Systematic reviews published evaluating the use of antipsychotics presented important methodological limitations. An overview of systematic...
reviews on aripiprazole and risperidone found 16 systematic reviews of critically low methodological quality [26]. Published Cochrane systematic reviews have only evaluated the pediatric population and have not included all second-generation antipsychotics [21,25].

This systematic review will evaluate the performance of second-generation antipsychotics in the treatment of ASD in controlled environments or not.

METHODS AND ANALYSIS

Study design, protocol, and registration

This systematic review (SR) will be performed according to the recommendations of the Cochrane Handbook for Intervention Reviews [27]. This protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [28] (Supplementary Material 1), and registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under registration nº. CRD42022353795

Patient and public involvement

We will involve users in classifying outcomes’ importance and interpretation of evidence [29]. Before conducting this review, we will identify such stakeholders through personal and professional networks and will consider their engagement and interest in the research issue.

We plan to hold stakeholder meetings: (i) to present the protocol and its research activities; (ii) to classify the relevance of the outcomes, and (iii) to review preliminary results after a meta-analysis has been carried out.

Eligibility criteria

The research question was structured using the Population, Intervention, Comparison, and Outcomes (PICO) structure.

Types of participants
Participants five years and older diagnosed with ASD using a standardized diagnostic instrument or established diagnostic criteria that include the following International Statistical Classification of Diseases and Related Health Problems (ICD-10): Infantile autism (F84.0); Atypical autism (F84.1); Other childhood disintegrative disorder (F84.3); Asperger’s Syndrome (F84.5); and Other pervasive developmental disorders (F84.8).

Studies involving other mental disorders will be included as long as the results are separate and at least 80% of the population has a diagnosis of ASD.

Type of interventions

Second-generation antipsychotics (amisulpride, aripiprazole, asenapine, brexiprazole, cariprazine, clozapine, iloperidone, lumateperone, lurasidone, olanzapine, paliperidone, pimavanserine, quetiapine, risperidone, sulpiride, ziprasidone), without restriction as to dose, route of administration, frequency or duration of treatment.

Types of comparators

1. Second-generation antipsychotics other than intervention;
2. Placebo.

Types of outcome measures

We will include studies regardless of the scales used to measure outcomes.

Primary outcomes

1. Symptoms of the aggressive behavior (agitation; irritability; and self-aggression), measured using validated scales reported by the patient, physician or parents;
2. Quality of life for the individual or their caregivers;
3. Discontinuation or dropouts/withdrawals of antipsychotics due to adverse events.

Secondary outcomes
1. Adverse events of interest according to the Guideline on the clinical development of medicinal products for the treatment of ASD [30]:
   - Central Nervous System adverse events;
   - Endocrinological adverse events;
   - Other adverse events, for example, somnolence, insomnia, headache, rash and constipation.

2. Adherence to pharmacotherapy measured by validated scales, or reported by the patient, physician and parents.

Types of studies

We will include RCTs and pragmatic trials irrespective status of publication (online clinical trials results, summaries of unpublished clinical trials, abstracts, reports from pharmaceutical companies, since that they contain sufficient data for analysis), year of publication and language. In addition, prospective cohort studies will be included.

The RCTs will be included because they are the best study designs for evaluating the effectiveness of health interventions and cohorts will be considered especially for safety outcomes as they generally have a longer follow-up. We will not impose any limitation regarding the length of follow-up.

Search methods for identification of studies

The search strategy will use DeCS/MeSH descriptors and synonyms, being adapted according to each database searched (Supplementary Material 2). The searches will be conducted by an experienced librarian and will be reviewed by another professional librarian, according to the Peer Review of Electronic Search Strategies (PRESS) [31].

Electronic searches

A structured search for eligible primary studies will be conducted in the main electronic databases: MEDLINE via PubMed, Embase via Elsevier, Cochrane Central Register of Controlled Trials (Central), Epistemonikos, Latin American and Caribbean Health Sciences Literature (Lilacs) via Virtual Health
Searching other resources

1. Grey literature

We will adapt a specific structured search strategy for the grey literature, including: ProQuest Dissertations and Theses (<https://about.proquest.com/en/products-services/pqdtglobal/>), Portal Capes (<https://catalogodeteses.capes.gov.br/catalogo-teses/#!/>), and Open Grey (<https://opengrey.eu/>).

2. Trial registries:

- Clinical Trials: <www.ClinicalTrials.gov>
- International Clinical Trials Platform: <www.who.int/ictrp>
- Registry Platform Current Controlled Trials: <www.isrctn.com>
- EU Clinical Trials Register: <www.clinicaltrialsregister.eu>
- Brazilian Registry of Clinical Trials: <www.ensaiosclinicos.gov.br>

3. Hand searches

Appropriate journals and conference proceedings (Supplementary Material 3) relating to second-generation antipsychotic treatment for ASD will be hand searches and incorporated.

4. Personal communication

Pharmaceutical companies and experts in the fields will be asked if they knew of any studies that met the inclusion criteria of this review.

5. Reference checking

Reference lists of the included studies, previous systematic reviews, systematic scoping reviews, and narrative reviews of ASD will be checked for published reports and citations of unpublished research.

6. Automatic alerts
We set automatic alerts in each database to receive notifications of published new studies. We monitored the medical literature and kept the review as current as possible.

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved through an electronic database search to a reference management database <https://www.covidence.org/> and remove duplicates. Pairs of reviewers will independently screen titles and abstracts for inclusion. We will retrieve the full text of potentially relevant references, and pairs of reviewer’s authors will independently assess the full-text articles for inclusion. We will record reasons for exclusion from studies following the full-text review. Any disagreements will be resolved through discussion or, if required, by consulting a third review author.

For the two selection stages, the reviewers will carry out a pilot exercise for consensus on the eligibility criteria.

Data extraction and management

A pre-piloted and standardized form will be used to extract data from the included studies. The reviewers will be calibrated by extracting at least three articles, in pairs and independently, and, afterward, they will carry out a consensus. This process will take place until the standardization of the extracted data. The overlap of two articles in all teams of reviewers will be adopted to assess the reliability between reviewers in extracting data in the different teams.

After this stage, two reviewers will extract the data independently, and any discrepancies will be identified and resolved with a third author, when necessary.

The data collected will be a) bibliometric information (year of study publication, authors, title); b) characteristics of studies (funding, follow-up time, design: randomized or non-randomized, scales used; clinical setting: hospitals, specialty clinics, primary care, research centers; countries, country, registered number, number of sites, duration of the study, the timing of outcome measurement: weeks or months, numbers of participants in each arm); c) characteristics of patients (inclusion and exclusion criteria, age, antipsychotics:
naive vs experienced, psychiatric comorbidities, other treatments, drug regimen, 
route and frequency of medication administration and adverse events). We will 
extract data comprehensively to cover all relevant outcomes and methods 
reported across studies.

Where key data are missing from the study reports, we will attempt to 
contact the authors to obtain such information. Where multiple reports of the 
same trial are published, we will extract data from those we deem to be most 
complete.

Assessment of methodological quality of individual studies

The quality of RCTs will be assessed using Cochrane’s Risk of Bias (RoB) 
tool version 2.0 for randomized trials on bias arising from the randomization 
process, deviations from intended intervention, missing outcome data, 
measurement of the outcome, and selection of the reported result [32].

The quality of observational studies will be assessed using Risk of Bias In 
Non-randomized Studies of Interventions (ROBINS-I) tool on bias arising from 
the confounding, selection bias, information bias and reporting bias [33].

Two reviewers will assess the risk of bias. Reviewers will resolve 
disagreements through discussion, and a third person will judge unresolved 
disagreements.

Statistical analysis

Measures of treatment effect

We will use the standardized mean difference (SMD) to summarise 
continuous outcomes and the odds ratio (OR) to summarise binary outcomes. 
We will use results based on the intention-to-treat analysis (ITT) whenever 
available.

Missing data

We will employ standard techniques to back-calculate the necessary 
statistics from reported confidence intervals, standard errors, z, t or P values. We 
will use approximate Bayesian computation models to derive the necessary
information for meta-analysis when reported data are more complex [34] (e.g., median and interquartile range, continuous variables divided into mutually exclusive groups based on cutoffs). We will extract data from figures if data are reported graphically.

**Pair-wise meta-analysis**

We will use fully Bayesian random-effects models. Throughout our analyses, we will use only random-effects models. The choice of a random-effects model is based on the anticipated clinical and methodological heterogeneity across studies [35].

We will use the binomial likelihood for binary outcomes and model the log odds ratio. If results in primary studies are available as odds ratios (95% confidence interval), we will model binary outcomes using the normal likelihood. We will use the normal likelihood and the identity link for continuous outcomes. As suggested, statistical heterogeneity will be interpreted based on the between-study variance ($\tau^2$) [36,37].

**Network meta-analysis**

We will use the generalized linear model framework (the "NICE" model) described previously [38]. If feasible, we will use the arm-based approach. The model preserves randomization, assumes consistency and allows for multi-arm trials. However, if necessary, we will employ an adapted model that uses arm-level and comparison-level data. For binary outcomes, we will use the binomial likelihood. We will use the normal likelihood and the identity link for continuous outcomes [39].

To evaluate the plausibility of the transitivity assumption, we will investigate the distribution of presumed effect modifiers across treatment comparisons. The list of potential effect modifiers will be defined by listing all covariates investigated at the baseline. This list will be evaluated by a multidisciplinary panel of practicing psychiatrists and clinical pharmacologists, who will rank the importance of each covariate regarding the treatment effect.
Transitivity will be judged based on the five most relevant potential effect modifiers.

We will compare the fit of the consistency model to the fit of a random-effects model that relaxes the consistency assumption ("inconsistency model"). Models will be compared via the posterior mean of the residual deviance and the deviance information criterion (DIC), with lower DIC values indicating a better model fit [39]. If appropriate, we will fit the node split model and compare direct, indirect, and network estimates for all treatments [40, 38]

We will present summary treatment effect estimates and between-trial variance derived from the median and 95% credibility intervals (Crls) from the 2.5th and 97.5th percentile of the posterior distribution. Treatment rankings (with 95% Crl) and the probability that each treatment is the best will be calculated from the posterior distributions.

Meta-regression models

If pertinent, we will examine the association between the magnitude of treatment effects and study-level characteristics, via random-effects Bayesian meta-regression models. We will not employ average patient-level characteristics to avoid ecological fallacy [41].

Priors

We will assume non-informative, but biologically plausible priors for treatment effects for all models and between-study variances. However, in sensitivity analyses, we will also use informative priors for the between-study variances [41,42].

Funnel plot asymmetry and small-study bias in pair-wise meta-analysis

Whenever feasible (i.e., ten or more estimates), we will investigate funnel plot asymmetry using graphical and statistical approaches. For pair-wise meta-analyses, we will employ contour-enhanced plots and generate Doi plots [43]. We will calculate the LFK [44] index and conduct Egger's linear regression test or Peter's test.
Funnel plot asymmetry and small-study bias in network meta-analysis

For network meta-analysis, we will create a comparison-adjusted funnel plot, as suggested by Chaimani et al. We will also use the recently proposed Risk of Bias due to Missing Evidence in Network meta-analysis (ROB-MEN) approach [45].

Implementation

All Bayesian models will be implemented in MultiBUGS 2.0 (Cambridge, UK), and estimates will be obtained via Markov chain Monte Carlo methods [46]. Models will be fitted with three chains (166667 simulations each), totaling 500,000 iterations. The burn-in period will be 100,000 simulations. Convergence will be checked graphically by running three chains and using the Gelman-Rubin statistic, $R$. We will check autocorrelation and density of the posterior estimates graphically in Stata 16 (College Station, TX, USA).

Subgroup analysis and investigation of heterogeneity

If appropriate, we will perform subgroup analyses or meta-regression to investigate differences among two or more subgroups according to each of the following characteristics of participants, which might have an effect on the outcomes: type of clinical conditions: Infantile autism (F84.0); Atypical autism (F84.1); Other childhood disintegrative disorder (F84.3); Asperger's Syndrome (F84.5); and Other pervasive developmental disorders (F84.8); participants' mean age; types of scales used to measure outcomes; duration of follow-up; sex; dose of antipsychotics; presence of comorbidities.

If additional analyses cannot be conducted by RevMan 5, we will perform analyses in Stata Statistical Software (Stata 2015).

Sensitivity analysis

We will perform sensitivity analyses of outcomes to assess the robustness of the findings. If feasible, we will restrict the analysis of outcomes to studies of low risk of bias, impute missing data considering worst-case scenario, and effects of fixed-effect or random-effects methods [47].
Summary of findings and assessment of the certainty of the evidence

After the results have been grouped, two reviewers will independently assess the overall certainty of the evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [48]. The main results of the review will be presented in outcome tables (Summary of Findings - SoF), as recommended by The Cochrane Collaboration [49]. This table will be built with the aid of the GRADEpro software program [48].

ETHICS AND DISSEMINATION

Since it is a literature-based study, ethical approval is not required. The results will be shared through publication in scientific journals of high impact, peer reviewed and also published in national and international conferences.

DISCUSSION

The results of this systematic review could highlight Engagement findings in decision-making considering the use of antipsychotics in treating ASD in different age groups.

The analysis of evidence from observational studies can improve the understanding of the use of antipsychotics in the treatment of ASD and support more assertive decisions about the actual performance of these interventions.

Our future results may impact public policy for ASD patients, healthcare professionals, and managers by providing evidence that can highlight challenges and areas for improvement, with a special look at pharmacological interventions in ASD.

In addition to being to date, the only systematic review with a robust proposal for controlled and uncontrolled evidence analyses. However, there are potential limitations. Primary studies may bring limitations to this review considering the confounders present in observational studies; meta-analyses
may be hampered by a lack of standardization in the measurement of efficacy outcomes and diagnostic criteria for ASD.

The methodological rigor and data analysis plan proposed in this review will provide transparency to the evidence found and may demonstrate the degree of confidence in the estimates found. For the refinement of the construction of the final protocol of this systematic review, we are proposing the involvement of stakeholders such as patient representatives, managers, and health professionals who work in the treatment of ASD.

**AUTHOR CONTRIBUTIONS**

LPNL is the principal investigator and wrote the protocol and the final version. JCdO, IF, CCB, ECL, FCA, and LGM reviewed and edited the manuscript. LCL is the review guarantor, advised on background, helped to write the protocol, and revised the manuscript.

**ACKNOWLEDGEMENTS**

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COMPETING INTERESTS

None to declare.

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REFERENCES


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42. Rhodes KM, Turner RM, Higgins JPT. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. J Clin Epidemiol [Internet]. 2015 Jan 1 [cited 2022 Sep 23];68(1):52. Available from: /pmc/articles/PMC4270451/


# SUPPLEMENTARY MATERIAL 1 - Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist: recommended items to address in a systematic review protocol*

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<td>Contact</td>
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<td>Study records:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data management</td>
<td>11a</td>
<td>Describe the mechanism(s) that will be used to manage records and data throughout the review</td>
<td>11-12</td>
</tr>
<tr>
<td>Selection process</td>
<td>11b</td>
<td>State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)</td>
<td>11-12</td>
</tr>
<tr>
<td>Data collection process</td>
<td>11c</td>
<td>Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators</td>
<td>11-12</td>
</tr>
<tr>
<td>Data items</td>
<td>12</td>
<td>List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications</td>
<td>11-12</td>
</tr>
<tr>
<td>Outcomes and prioritization</td>
<td>13</td>
<td>List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale</td>
<td>8-9</td>
</tr>
<tr>
<td>Risk of bias in individual studies</td>
<td>14</td>
<td>Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis</td>
<td>12</td>
</tr>
<tr>
<td>Data synthesis</td>
<td>15a</td>
<td>Describe criteria under which study data will be quantitatively synthesised</td>
<td>12-16</td>
</tr>
<tr>
<td></td>
<td>15b</td>
<td>If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as ( I^2 ), Kendall’s ( \tau ))</td>
<td>12-16</td>
</tr>
<tr>
<td></td>
<td>15c</td>
<td>Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)</td>
<td>12-16</td>
</tr>
<tr>
<td></td>
<td>15d</td>
<td>If quantitative synthesis is not appropriate, describe the type of summary planned</td>
<td>N/A</td>
</tr>
<tr>
<td>Meta-bias(es)</td>
<td>16</td>
<td>Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)</td>
<td>15-16</td>
</tr>
<tr>
<td>Confidence in cumulative evidence</td>
<td>17</td>
<td>Describe how the strength of the body of evidence will be assessed (such as GRADE)</td>
<td>16</td>
</tr>
</tbody>
</table>

*It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

SUPPLEMENTARY MATERIAL 2 – Search strategies

Database Portal da BVS e Lilacs <April, 2022> Results: 548 (Portal da BVS) e 16 (Lilacs). Search Strategy

1. "Transtorno Autístico" or "Autistic Disorder"
2. "Autismo" or "Autism"
3. "Autismo Infantil" or "Child Autism"
4. "Transtorno do Espectro Autista" or "Autism Spectrum Disorder" or "Transtorno do Espectro do Autismo"
5. or/1-4
6. Antipsicóticos
7. "Agente Antipsicótico" or "Antipsychotic Agents"
8. "Agente Neuroléptico" or "Medicamento Neuroléptico" or "Medicamento Antipsicótico"
9. "Agentes Antipsicóticos"
10. "Droga Antipsicótica" or "Drogas Antipsicóticas"
11. "Fármaco Antipsicótico"
12. "Droga Neuroléptica" or "Fármaco Neuroléptico"
13. "Efeito Antipsicótico"
14. "Tranquilizante Maior"
15. “Risperidona” or “Risperidone”
16. Aripiprazol or aripiprazole
17. Clozapina or clozapine
18. Lurasidona or lurasidone
19. Quetiapina or quetiapine
20. Olanzapina or olanzapine
21. Ziprasidona or ziprasidone
22. Paliperidona or paliperidone
23. Brexiprazol or brexiprazole
24. Asenapina or asenapine
25. Cariprazina or cariprazine
26. Iloperidona or iloperidone
27. Lumateperona or lumateperone
28. Pimavanserina or pimavanserine
29. or/6-28
30. 5 AND 29

Database MEDLINE <April, 2022> Results: 1303. Search Strategy

1. “Autistic Disorder” or “(Disorder, Autistic)” or “(Disorders, Autistic)”
2. “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early”
3. “Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum” or “Autistic Disorder” or “Autism Spectrum Disorder” or “Disorder, Autistic” OR “Disorders, Autistic”
4. “Child Development Disorders, Pervasive”
5. “Asperger Syndrome”
6. “Kanner's Syndrome” or “Kanner Syndrome” or “Kanners Syndrome”
7. “Autism, Infantile” or “Infantile Autism” or Autism or “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early” or “Autism Spectrum Disorders”
8. “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum”
9. “Pervasive Child Development Disorders” or “Pervasive Development Disorders”
10. “Syndrome, Asperger” or “Asperger's Disease” or “Asperger's Diseases” or “Aspergers Disease” or “Disease, Asperger's” OR “Diseases, Asperger’s” or “Asperger Disease” or “Asperger Diseases” or “Disease, Asperger” or “Diseases, Asperger” or “Asperger Disorder” or “Asperger Disorders” or “Disorder, Asperger” or “Disorders, Asperger” or “Asperger's Disorder” or “Aspergers Disorder” or “Disorder, Asperger's” or “Disorders, Asperger” or “Asperger’s Disorder” or “Aspergers Disorder” or “Disorder, Asperger’s” or “Disorders, Asperger” or “Asperger's Syndrome” or “Aspergers Syndrome” or “Syndrome, Asperger’s”
11. or/1-10
12. “Tranquilizing Agents, Major” or “Major Tranquilizing Agents” or “Major Tranquilizer” or “Tranquilizer, Major”
13. “Antipsychotic Drug” or “Drug, Antipsychotic” or “Antipsychotic Agent” OR “Agent, Antipsychotic”
14. “Antipsychotic Medication” or “Medication, Antipsychotic”
15. “Neuroleptic Agent” or “Agent, Neuroleptic” or “Neuroleptic Drug” or “Drug, Neuroleptic” or Neuroleptic or Antipsychotic
16. “Antipsychotic Drugs” or Antipsychotics or “Major Tranquilizers” or “Neuroleptic Agents” or “Neuroleptic Drugs” or Neuroleptics or “Tranquilizing Agents, Major” or “Major Tranquilizing Agents”
17. “Antipsychotic Effect” or “Effect, Antipsychotic” or “Antipsychotic Effects” or “Antipsychotic Agents”
18. “Dopamine Antagonists” or “Antagonists, Dopamine” or “Antagonists, Dopamine Receptor” or “Antagonists, Dopaminergic” or “Dopamine Blockers” or “Blockers, Dopamine” or “Dopamine Receptor Antagonists” or “Receptor Antagonists, Dopamine” or “Dopamine Blocker” or “Blocker, Dopamine” or “Dopamine Receptor Antagonist” or “Antagonist, Dopamine” or “Receptor Antagonist, Dopamine” or “Dopaminergic Antagonists” or “Antagonist, Dopaminergic” or “Dopaminergic Antagonists” or “Dopamine Antagonist” or “Antagonist, Dopamine”
19. aripiprazole
20. clozapine
21. lurasidone
22. quetiapine
23. olanzapine
24. risperidone
25. ziprasidone
26. paliperidone
27. brexiprazole
28. asenapine
29. cariprazine
30. iloperidone
31. Lumateperone
32. pimavanserine
33. or/12-32
34. 11 AND 33

Database EMBASE <April, 2022> Results: 2683. Search strategy

1. 'autistic disorder'/exp or 'autistic disorder' or 'autism spectrum disorder'/exp or 'autism spectrum disorder'
2. 'child development disorders, pervasive'/exp or 'child development disorders, pervasive'
3. 'asperger syndrome'/exp or 'asperger syndrome' or 'disorder, autistic' or 'disorders, autistic'
4. 'syndrome, asperger' or 'aspergers diseases' or 'aspergers disease' or 'disease, aspergers' or 'diseases, aspergers' or 'asperger disease' or 'disease, asperger' or 'diseases, asperger' or 'asperger disorder'/exp or 'asperger disorder' or 'disorder, aspergers' or 'aspergers disorder'/exp or 'disorder, aspergers' or 'aspergers syndrome'/exp or 'syndrome, aspergers'
5. 'kanner syndrome'/exp or 'kanner syndrome' or 'kanners syndrome'
6. 'autism, infantile'/exp or 'autism, infantile' or 'infantile autism'/exp or 'infantile autism' OR 'autism'/exp
7. 'autism, early infantile'/exp or 'autism, early infantile' or 'early infantile autism'/exp OR 'early infantile autism' or 'infantile autism, early' or 'autism spectrum disorders'/exp or 'autism spectrum disorders' or 'autistic spectrum disorder'/exp or 'autistic spectrum disorder' or 'autistic spectrum disorders' or 'disorder, autistic spectrum'
8. 'pervasive child development disorders'/exp or 'pervasive child development disorders' or 'pervasive development disorders'
9. or/1-8
10. ‘tranquillizing agents, major’ or ‘major tranquillizing agents’ or ‘major tranquilizer’ or ‘tranquilizer, major’

11. ‘antipsychotic drug’ or ‘drug, antipsychotic’ or ‘antipsychotic agent’ or ‘agent, antipsychotic’ or ‘antipsychotic medication’ or ‘medication, antipsychotic’

12. ‘neuroleptic agent’ or ‘agent, neuroleptic’ or ‘neuroleptic drug’ or ‘drug, neuroleptic’ or neuroleptic

13. antipsychotic or ‘antipsychotic drugs’ or antipsychotics or ‘major tranquilizers’

14. ‘neuroleptic agents’ or ‘neuroleptic drugs’ or neuroleptics

15. ‘tranquilizing agents, major’ or ‘major tranquilizing agents’

16. ‘antipsychotic effect’ or ‘effect, antipsychotic’ or ‘antipsychotic effects’ or ‘antipsychotic agents’

17. ‘dopamine antagonists’ or ‘antagonists, dopamine’ or ‘antagonists, dopamine receptor’ or ‘antagonists, dopaminergic’ or ‘dopamine blockers’ or ‘blockers, dopamine’ or ‘dopamine receptor antagonists’ or ‘receptor antagonists, dopamine’ or ‘dopamine blocker’ or ‘blocker, dopamine’ or ‘dopamine receptor antagonist’ or ‘antagonist, dopaminergic’ or ‘antagonist, dopaminergic antagonist’ or ‘antagonist, dopamine antagonist’ or ‘antagonist, dopamine’

18. aripiprazole

19. clozapine

20. lurasidone

21. quetiapine

22. paliperidone

23. olanzapine

24. ziprasidone

25. brexiprazole

26. asenapine

27. cariprazine

28. iloperidone

29. Lumateperone

30. pimavanserin

31. or/10-31

32. 9 AND 32

Database CINAHL <April, 2022> Results: 1800. Search strategy

1. “Autistic Disorder” or “(Disorder, Autistic)” or “(Disorders, Autistic)”

2. “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early”
3. “Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autism Spectrum” or “Autistic Disorder” or “Autism Spectrum Disorder” or “Disorder, Autistic” OR “Disorders, Autistic”
4. “Child Development Disorders, Pervasive”
5. “Asperger Syndrome”
6. “Kanner's Syndrome” or “Kanner Syndrome” or “Kanners Syndrome”
7. “Autism, Infantile” or “Infantile Autism” or Autism or “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early” or “Autism Spectrum Disorders”
8. “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum”
9. “Pervasive Child Development Disorders” or “Pervasive Development Disorders”
10. “Syndrome, Asperger” or “Asperger's Disease” or “Asperger's Diseases” or “Aspergers Disease” or “Disease, Asperger's” OR “Diseases, Asperger's” or “Asperger Disease” or “Asperger Diseases” or “Disease, Asperger” or “Diseases, Asperger” or “Asperger Disorder” or “Asperger Disorders” or “Disorder, Asperger” or “Disorders, Asperger” or “Asperger's Disorder” or “Disorder, Asperger's” or “Aspergers Syndrome” or “Syndrome, Aspergers”
11. or/1-10
12. “Tranquilizing Agents, Major” or “Major Tranquilizing Agents” or “Major Tranquilizer” or “Tranquilizer, Major”
13. “Antipsychotic Drug” or “Drug, Antipsychotic” or “Antipsychotic Agent” OR “Agent, Antipsychotic”
14. “Antipsychotic Medication” or “Medication, Antipsychotic”
15. “Neuroleptic Agent” or “Agent, Neuroleptic” or “Neuroleptic Drug” or “Drug, Neuroleptic” or Neuroleptic or Antipsychotic
16. “Antipsychotic Drugs” or Antipsychotics or “Major Tranquilizers” or “Neuroleptic Agents” or “Neuroleptic Drugs” or Neuroleptics or “Tranquilizing Agents, Major” or “Major Tranquilizing Agents”
17. “Antipsychotic Effect” or “Effect, Antipsychotic” or “Antipsychotic Effects” or “Antipsychotic Agents”
18. “Dopamine Antagonists” or “Antagonists, Dopamine” or “Antagonists, Dopamine Receptor” or “Antagonists, Dopaminergic” or “Dopamine Blockers” or “Blockers, Dopamine” or “Dopamine Receptor Antagonists” or “Receptor Antagonists, Dopamine” or “Dopamine Blocker” or “Blocker, Dopamine” or “Dopamine Receptor Antagonist” or “Antagonist, Dopamine Receptor” or “Receptor Antagonist, Dopamine” or “Dopaminergic Antagonist” or “Antagonist, Dopaminergic” or “Dopaminergic Antagonists” or “Dopamine Antagonist” or “Antagonist, Dopamine”
19. aripiprazole
20. clozapine
21. lurasidone
22. quetiapine  
23. olanzapine  
24. risperidone  
25. ziprasidone  
26. paliperidone  
27. brexiprazole  
28. asenapine  
29. cariprazine  
30. iloperidone  
31. Lumateperone  
32. pimavanserine  
33. or/12-32  
34. 11 AND 33

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Database PSYCINFO <April, 2022> Results: 1898. search strategy

1. “Autistic Disorder” or “(Disorder, Autistic)” or “(Disorders, Autistic)”  
2. “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early”  
3. “Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Autistic Spectrum Disorder” or “Autism Spectrum Disorders” or “Disorder, Autism, Early Infantile” or “Infantile Autism, Early” or “Autism Spectrum Disorders”  
4. “Child Development Disorders, Pervasive”  
5. “Asperger Syndrome”  
6. “Kanner’s Syndrome” or “Kanner Syndrome” or “Kanners Syndrome”  
7. “Autism, Infantile” or “Infantile Autism” or Autism or “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early” or “Autism Spectrum Disorders”  
8. “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum”  
9. “Pervasive Child Development Disorders” or “Pervasive Development Disorders”  
10. “Syndrome, Asperger” or “Asperger’s Disease” or “Asperger’s Diseases” or “Asperger’s Disease” or “Disease, Asperger’s” OR “Diseases, Asperger’s” OR “Asperger Disease” or “Asperger’s Disease” or “Disease, Asperger’s” or “Diseases, Asperger’s” or “Asperger Disorder” or “Asperger Diseases” or “Disorder, Asperger” or “Disorders, Asperger” or “Disorder, Asperger’s” or “Asperger’s Disorder” or “Aspergers Disorder” or “Disorder, Asperger’s” or “Asperger’s Syndrome” or “Aspergers Syndrome” or “Syndrome, Asperger’s”  
11. or/1-10  
12. “Tranquilizing Agents, Major” or “Major Tranquilizing Agents” or “Major Tranquilizer” or “Tranquilizer, Major”
13. “Antipsychotic Drug” or “Drug, Antipsychotic” or “Antipsychotic Agent” OR “Agent, Antipsychotic”
14. “Antipsychotic Medication” or “Medication, Antipsychotic”
15. “Neuroleptic Agent” or “Agent, Neuroleptic” or “Neuroleptic Drug” or “Drug, Neuroleptic” or Neuroleptic or Antipsychotic
16. “Antipsychotic Drugs” or Antipsychotics or “Major Tranquilizers” or “Neuroleptic Agents” or “Neuroleptic Drugs” or Neuroleptics or “Tranquilizing Agents, Major” or “Major Tranquilizing Agents”
17. “Antipsychotic Effect” or “Effect, Antipsychotic” or “Antipsychotic Effects” or “Antipsychotic Agents”
18. “Dopamine Antagonists” or “Antagonists, Dopamine” or “Antagonists, Dopamine Receptor” or “Antagonists, Dopaminergic” or “Dopamine Blockers” or “Blockers, Dopamine” or “Dopamine Receptor Antagonists” or “Receptor Antagonists, Dopamine” or “Dopamine Blocker” or “Blocker, Dopamine” or “Dopamine Receptor Antagonist” or “Antagonist, Dopamine” or “Dopaminergic Antagonist” or “Antagonist, Dopaminergic” or “Dopaminergic Antagonists” or “Dopamine Antagonist” or “Antagonist, Dopamine”
19. aripiprazole
20. clozapine
21. lurasidone
22. quetiapine
23. olanzapine
24. risperidone
25. ziprasidone
26. paliperidone
27. brexiprazole
28. asenapine
29. cariprazine
30. iloperidone
31. Lumateperone
32. pimavanserine
33. or/12-32
34. 11 AND 33

Database Cochrane <April, 2022> Results: 459. Search strategy

1. Autism or “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early”
2. “Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum” or “Autistic Disorder” or “Autism Spectrum Disorder”
3. or/1-2
4. aripiprazole
5. clozapine
6. lurasidone
7. quetiapine
8. olanzapine
9. risperidone
10. ziprasidone
11. paliperidone
12. brexiprazole
13. asenapine
14. cariprazine
15. iloperidone
16. Lumateperone
17. pimavanserine
18. “Antipsychotic Drug” or “Drug, Antipsychotic”
19. “Antipsychotic Agent” or “Agent, Antipsychotic”
20. “Antipsychotic Medication” OR “Medication, Antipsychotic”
21. or/4-20
22. 3 AND 21

Database EPISTEMONIKOS <April, 2022> Results: 800. Estratégia de busca

1. Autism or “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early”
2. “Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum” or “Autistic Disorder” or “Autism Spectrum Disorder”
3. or/1-2
4. Risperidone
5. aripiprazole
6. clozapine
7. lurasidone
8. quetiapine
9. olanzapine
10. risperidone
11. ziprasidone
12. paliperidone
13. brexiprazole
14. asenapine
15. cariprazine
16. iloperidone
17. Lumateperone
18. pimavanserine
19. “Antipsychotic Drug” or “Drug, Antipsychotic”
20. “Antipsychotic Agent” or “Agent, Antipsychotic”
21. “Antipsychotic Medication” OR “Medication, Antipsychotic”
22. or/4-21
23. 3 AND 22

*******************************************************************************

CLINICAL TRIALS <April, 2022> Results: 192. Search strategy

*****************************************************************************

1. Autism
2. Antipsychotic
3. 1 AND 2

*******************************************************************************

WHO International Clinical Trials Registry Platform <April, 2022> Results: 126. Search strategy

*******************************************************************************

1. Autism
2. Antipsychotic
3. 1 AND 2

*******************************************************************************

EU Clinical Trials Register <April, 2022> Results: 100. Search strategy

*******************************************************************************

1. Autism
2. Antipsychotic
3. 1 AND 2

*******************************************************************************

Portal CAPES (Teses e Dissertações) <April, 2022>. Results: 619. Search strategy

*****************************************************************************

1. Autismo
2. Antipsicótico
3. 1 AND 2
4. Filtro: Ciências da Saúde

*******************************************************************************

ProQuest <April, 2022>. Results: 80. Search strategy
1. Autism
2. Antipsychotic
3. 1 AND 2

*******************************************************************************
SUPPLEMENTARY MATERIAL 3 - Journals and Conference

- International Congress on Psychopharmacology;
- Annual Meeting of the American Academy of Child & Adolescent Psychiatry;
- European Congress of Psychiatry;
- European College of Neuropsychopharmacology Congress;
- International Congress on Psychopharmacology and International Symposium on Child and Adolescent Psychopharmacology;
- International Congress of European Society for Child and Adolescent Psychiatry;
- World Congress of the International Association for Child and Adolescent Psychiatry and Allied Professions;
- International Conference on Pharmacoepidemiology and Therapeutic Risk;
- World Congress of the International Association for the Scientific Study of Intellectual and Developmental Disabilities;
- Annual Meeting of the College of Psychiatric and Neurologic Pharmacists;
- Annual Conference of the American College of Neuropsychopharmacology;
- Annual National Institute of Mental Health;
- Annual Meeting of the International College of Spectrum Disorders.
**Use of second-generation antipsychotics in Autism Spectrum Disorder: a systematic review and meta-analysis protocol**

<table>
<thead>
<tr>
<th>Journal</th>
<th>BMJ Open</th>
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<td>bmjopen-2022-069114.R1</td>
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<tr>
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<td>Protocol</td>
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<tr>
<td>Date Submitted by the Author</td>
<td>11-Feb-2023</td>
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<tr>
<td>Complete List of Authors:</td>
<td>Lopes, Luis; Universidade da Sorocaba, de Oliveira, Jardel; Secretaria Municipal de Saúde, Médico de Família e Comunidade, Especialista em Saúde da Família, Geriatria e Gerontologia Bergamaschi, Cristiane; Universidade de Sorocaba, Pharmaceutical Science Fulone, Izabela; Universidade de Sorocaba, Pharmaceutical Science Lima, Elisangela; Federal University of Rio de Janeiro Pharmacy School Abe, Flávia; University of Sorocaba Mazzei, Lauren; Universidade da Sorocaba Figueiró, Mabel; Hospital do Coração Lopes, Luciane; Universidade de Sorocaba, Pharmaceutical Science</td>
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<td>Mental health</td>
</tr>
<tr>
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<td><strong>Keywords</strong></td>
<td>MENTAL HEALTH, Developmental neurology &amp; neurodisability &lt; PAEDIATRICS, EPIDEMIOLOGY</td>
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Use of second-generation antipsychotics in Autism Spectrum Disorder: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction: Atypical antipsychotics have been studied to treat Autism Spectrum Disorder (ASD). However, little is known whether these drugs are effective and safety comparing controlled and not controlled settings. This study aims to assess the efficacy and safety of second-generation antipsychotics in ASD in randomized controlled trials (RCT) and observational studies.

Methods and Analysis: This Systematic Review will include RCT and prospective cohorts evaluating second-generation antipsychotics in people five years and older diagnosed with ASD. Searches will be conducted in Medline, Embase, Cochrane Library, Epistemonikos, Lilacs, CINAHL, PsycINFO, trial registries, and gray literature databases without restriction on publication status, year of publication, and language. The primary outcomes will be symptoms of aggressive behavior, quality of life for the individual or their careers, and discontinuation or dropouts/withdrawals of antipsychotics due to adverse events. The secondary outcomes are other not serious adverse events and adherence to pharmacotherapy. Selection, data extraction, and quality assessment will be performed by pairs of reviewers, independently. The Risk of Bias 2 (RoB 2) and Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tools will be used to assess the risk of bias in the included studies. If appropriate, a meta-analysis and network meta-analysis will be conducted to synthesize the results. The overall quality of the evidence for each outcome will be determined by the Recommendation, Assessment, Development, and Evaluation (GRADE) approach.

Ethics and dissemination: This study will systematically summarize the existing evidence evaluating the use of second-generation antipsychotics for treating ASD, in controlled and uncontrolled studies. The results of this review will be disseminated through peer-reviewed publications and conference presentations.

Protocol Registration: PROSPERO – CRD42022353795

Keywords: Autism Spectrum Disorder. Antipsychotic Agents. Real-World Evidence. Systematic Review.
STRENGTHS AND LIMITATIONS OF THIS STUDY

- The search will be performed with the help of a specialized librarian experienced in medical literature searching;
- This systematic review will include stakeholders from refining the question to discussing and implementing the findings.
- Our systematic review proposal may have limitations inherent to the methodological quality of the included studies, especially non-randomized studies, which will be discussed.
- Some important outcomes such as quality of life and adherence to pharmacotherapy may not have been assessed in primary studies.
INTRODUCTION

Autism Spectrum Disorder (ASD), or simply autism, is a unique clinical condition with different levels of severity, characterized by two main symptom domains: 1) deficits in social communication and social interaction and 2) restricted repetitive behaviors (RRBs), interests and activities and sensory anomalies[1].

Estimates of the prevalence of ASD vary. About 52 million people live with ASD worldwide [2]. Studies indicate approximately 1% to 2% of children in the US and other developed countries [3,4,2,5]. A systematic review of prevalence studies of ASD identified an overall estimate of the prevalence of 7.1 per 10,000 for autism and 20 per 10,000 for all ASD [6]. Another systematic review found that the average worldwide prevalence of ASD was 17 per 100,000, with a range of 2.8 to 94 per 100,000 across all age groups [7]. Hispanic and African-American children are underdiagnosed compared to non-Hispanic white children [6]. People with higher socioeconomic status and better access to health care are diagnosed earlier [7].

ASD is considered a brain-based neurodevelopmental disorder that lasts for life [8]. The three characteristic manifestations of ASD are impaired social interaction, impaired communication, and restricted repetitive and stereotyped patterns of behavior [9]. Challenging behavior has a great impact on the quality of life of individuals with ASD, family members, and the people they live with [10,11]. It is a situation that encompasses irritability, aggression, and self-harm [12]. These symptoms are the main causes of psychiatric hospitalization, and the use of antipsychotics is recommended in the absence of effectiveness of behavioral interventions [13,14,15].

Despite the claims of curative interventions, there is no specific treatment for autism and therapies target the symptoms of the disease. Pharmacological interventions have been used as adjuncts to behavioral treatments in both children and adults and may reduce specific autistic symptoms and behaviors such as self-injury and aggression [15]. There is evidence of widespread prescribing of psychotropic drugs to people with ASD [16]. Antipsychotic drugs generally tranquilize and relieve psychotic symptoms without impairing
consciousness [15]. Second-generation antipsychotics tend to cause fewer unwanted motor adverse effects than typical ones [17].

Typical (first-generation) and atypical (second-generation) antipsychotics have been evaluated for the treatment of behavioral symptoms in individuals with ASD. It is well established in the literature that first-generation antipsychotics are not recommended for treating symptoms in ASD due to their adverse effects. First-generation antipsychotics have been associated with drug-induced movement disorders [15]. Haloperidol, for example, has been evaluated for the treatment of ASD in several trials and has been associated with improvements in withdrawal and stereotypies [18] and positive effects on learning. However, it has also been related to extrapyramidal side effects such as acute dystonic reactions, withdrawal dyskinesias, and tardive dyskinesia in this population [19].

However, short-term randomized controlled trials (RCTs) have suggested the efficacy of second-generation antipsychotics to ameliorate some challenging symptoms of ASD in children and adolescents [20]. A systematic review investigated the use of risperidone for ASD and demonstrated the efficacy of this drug in treating symptoms of aggression, irritability, and repetitive behavior. Notable adverse events, including weight gain, increased appetite, and sedation, were described [21].

In addition, evidence from two RCTs suggests that aripiprazole can be effective as a short-term medication for some behavioral aspects of ASD in children/adolescents [22–24]. The participants presented less irritability and hyperactivity and fewer stereotypies such as repetitive and purposeless actions. However, weight gain, sedation, drooling, and tremors occurrence must also be considered [25]. Another systematic review [17] found that antipsychotics (aripiprazole, clozapine, haloperidol, levosulpiride, lurasidone, olanzapine, risperidone, trifluoperazine) for children and adolescents with ASD were more efficacious than placebo in reducing stereotypies, hyperactivity, irritability and obsessions, compulsions, and increasing social communication and global functioning.

Systematic reviews published evaluating the use of antipsychotics presented important methodological limitations. An overview of systematic
reviews on aripiprazole and risperidone found 16 systematic reviews of critically low methodological quality [26]. Published Cochrane systematic reviews have only evaluated the pediatric population and have not included all second-generation antipsychotics [21,25].

This systematic review will evaluate the performance of second-generation antipsychotics in the treatment of ASD in controlled and not-controlled settings.

METHODS AND ANALYSIS

Study design, protocol, and registration

This systematic review (SR) will be performed according to the recommendations of the Cochrane Handbook for Intervention Reviews [27]. This protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [28] (Supplementary Material 1), and registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under registration nº. CRD42022353795

Patient and public involvement

Stakeholders were involved in the development and refinement of the research question. We involved decision-makers from the Brazilian Ministry of Health, primary care physicians, psychiatrists, and key stakeholders.

When the systematic review is completed, the results will be discussed in a dissemination workshop with the same stakeholders. We will involve users in classifying outcomes’ importance and interpretation of evidence [29]. We will summarize the evidence in plain language.

Eligibility criteria

The research question was structured using the Population, Intervention, Comparison, and Outcomes (PICO) structure.
Types of participants

Participants regardless of age group diagnosed with ASD using a standardized diagnostic tool or established diagnostic criteria from DSM-4 or DSM-5.

Studies involving other mental disorders will be included as long as the results are separate or at least 80% of the population has a confirmed diagnosis of ASD

Type of interventions

Second-generation antipsychotics (amisulpride, aripiprazole, asenapine, brexiprazole, cariprazine, clozapine, iloperidone, lumateperone, lurasidone, olanzapine, paliperidone, pimavanserine, quetiapine, risperidone, sulpiride, ziprasidone), without restriction as to dose, route of administration, frequency or duration of treatment.

Types of comparators

1. Second-generation antipsychotics other than intervention;
2. Placebo.

Types of outcome measures

We will include studies regardless of the scales used to measure outcomes.

Primary outcomes

1. Number of participants with aggressive behavior and degree of aggressiveness (agitation; irritability; and self-aggression), measured using validated scales reported by the patient, physician or parents;
2. Quality of life for the individual or their caregivers;
3. Number of participants who had Discontinuation or dropouts/withdrawals of antipsychotics due to adverse events.

Secondary outcomes
1. Number of participants with Adverse events of interest according to the Guideline on the clinical development of medicinal products for the treatment of ASD [30]:
   - Central Nervous System adverse events;
   - Endocrinological adverse events;
   - Other adverse events, for example, somnolence, insomnia, headache, rash and constipation.

2. Adherence to pharmacotherapy measured by validated scales, or reported by the patient, physician and parents.

Types of studies

We will include RCTs and pragmatic trials irrespective status of publication (online clinical trials results, summaries of unpublished clinical trials, abstracts, reports from pharmaceutical companies, since that they contain sufficient data for analysis), year of publication and language. Observational studies (cohorts) will be included additionally, only if they are prospective and have a comparator arm for the intervention of interest.

The RCTs will be included because they are the best study designs for evaluating the effectiveness of health interventions and cohorts will be considered especially for safety outcomes as they generally have a longer follow-up. We will not impose any limitation regarding the length of follow-up.

We will exclude non-randomized studies such databases with data from claims or medical records, cases series, retrospective cohorts, case-control, control before and after, and times series.

Search methods for identification of studies

The search strategy will use DeCS/MeSH descriptors and synonyms, being adapted according to each database searched ([Supplementary Material 2](#)). The searches will be conducted by an experienced librarian and will be reviewed by another professional librarian, according to the Peer Review of Electronic Search Strategies (PRESS) [31].
Electronic searches

A structured search for eligible primary studies will be conducted in the main electronic databases: MEDLINE via PubMed, Embase via Elsevier, Cochrane Central Register of Controlled Trials (Central), Epistemonikos, Latin American and Caribbean Health Sciences Literature (Lilacs) via Virtual Health Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and PsycINFO.

Searching other resources

1. Gray literature


2. Trial registries:


3. Hand searches

Appropriate journals and conference proceedings (Supplementary Material 3) relating to second-generation antipsychotic treatment for ASD will be hand searches and incorporated.

4. Personal communication

Pharmaceutical companies and experts in the fields will be asked if they knew of any studies that met the inclusion criteria of this review.

5. Reference checking
Reference lists of the included studies, previous systematic reviews, systematic scoping reviews, and narrative reviews of ASD will be checked for published reports and citations of unpublished research.

6. Automatic alerts

We set automatic alerts in each database to receive notifications of published new studies. We monitored the medical literature and kept the review as current as possible.

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved through an electronic database search to a reference management database <https://www.covidence.org/> and remove duplicates. Pairs of reviewers will independently screen titles and abstracts for inclusion. We will retrieve the full text of potentially relevant references, and pairs of reviewer’s authors will independently assess the full-text articles for inclusion. We will record reasons for exclusion from studies following the full-text review. Any disagreements will be resolved through discussion or, if required, by consulting a third review author.

For the two selection stages, the reviewers will carry out a pilot exercise for consensus on the eligibility criteria.

Data extraction and management

A pre-piloted and standardized form will be used to extract data from the included studies. The reviewers will be calibrated by extracting at least three articles, in pairs and independently, and, afterward, they will carry out a consensus. This process will take place until the standardization of the extracted data. The overlap of two articles in all teams of reviewers will be adopted to assess the reliability between reviewers in extracting data in the different teams.

After this stage, two reviewers will extract the data independently, and any discrepancies will be identified and resolved with a third author, when necessary.

The data collected will be a) bibliometric information (year of study publication, authors, title); b) characteristics of studies (funding, follow-up time,
design: randomized or non-randomized, scales used; clinical setting: hospitals, specialty clinics, primary care, research centers; countries, country, registered number, number of sites, duration of the study, the timing of outcome measurement: weeks or months, numbers of participants in each arm); c) characteristics of patients (inclusion and exclusion criteria, age, antipsychotics: naive vs experienced, psychiatric comorbidities, other treatments, drug regimen, route and frequency of medication administration and adverse events); d) outcome (total number of participants in each arm, the total number of participants who presented the outcome, name of the scale used to measure the outcome, numerical value to measure the outcome - mean, median, standard deviation - and time point used). We will extract data comprehensively to cover all relevant outcomes and methods reported across studies.

Where key data are missing from the study reports, we will attempt to contact the authors to obtain such information. Where multiple reports of the same trial are published, we will extract data from those we deem to be most complete.

Assessment of methodological quality of individual studies

The quality of RCTs will be assessed using Cochrane's Risk of Bias (RoB) tool version 2.0 for randomized trials on bias arising from the randomization process, deviations from intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result [32].

The quality of observational studies will be assessed using Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool on bias arising from the confounding, selection bias, information bias and reporting bias [33].

Two reviewers will assess the risk of bias. Reviewers will resolve disagreements through discussion, and a third person will judge unresolved disagreements.

Statistical analysis

Measures of treatment effect
We will use the standardized mean difference (SMD) to summarise continuous outcomes and the odds ratio (OR) to summarise binary outcomes. We will use results based on the intention-to-treat analysis (ITT) whenever available.

We will convert standardized mean differences to log-odds ratios (or vice-versa) using established methods when necessary. Depending on the data availability, we will convert sample sizes, means and standard deviations directly to 2x2 tables – under the assumption of an approximately normal distribution and a cutoff. The thresholds that separate the continuous outcome into two categories (e.g., event and non-event) will be defined by current guidelines and an expert group of psychiatrists and clinical pharmacologists.

**Missing data**

We will employ standard techniques to back-calculate the necessary statistics from reported confidence intervals, standard errors, z, t or P values. We will use approximate Bayesian computation models to derive the necessary information for meta-analysis when reported data are more complex [34] (e.g., median and interquartile range, continuous variables divided into mutually exclusive groups based on cutoffs). We will extract data from figures if data are reported graphically.

**Pair-wise meta-analysis**

We will use fully Bayesian random-effects models. Throughout our analyses, we will use only random-effects models. The choice of a random-effects model is based on the anticipated clinical and methodological heterogeneity across studies [35].

We will use the binomial likelihood for binary outcomes and model the log odds ratio. If results in primary studies are available as odds ratios (95% confidence interval), we will model binary outcomes using the normal likelihood. We will use the normal likelihood and the identity link for continuous outcomes. As suggested, statistical heterogeneity will be interpreted based on the between-study variance ($\tau^2$) [36,37].
Network meta-analysis

We will use the generalized linear model framework (the "NICE" model) described previously [38]. If feasible, we will use the arm-based approach. The model preserves randomization, assumes consistency and allows for multi-arm trials. However, if necessary, we will employ an adapted model that uses arm-level and comparison-level data. For binary outcomes, we will use the binomial likelihood. We will use the normal likelihood and the identity link for continuous outcomes [39].

To evaluate the plausibility of the transitivity assumption, we will investigate the distribution of presumed effect modifiers across treatment comparisons. The list of potential effect modifiers will be defined by listing all covariates investigated at the baseline. This list will be evaluated by a multidisciplinary panel of practicing psychiatrists and clinical pharmacologists, who will rank the importance of each covariate regarding the treatment effect. Transitivity will be judged based on the five most relevant potential effect modifiers.

We will compare the fit of the consistency model to the fit of a random-effects model that relaxes the consistency assumption ("inconsistency model"). Models will be compared via the posterior mean of the residual deviance and the deviance information criterion (DIC), with lower DIC values indicating a better model fit [39]. If appropriate, we will fit the node split model and compare direct, indirect, and network estimates for all treatments [40, 38].

We will present summary treatment effect estimates and between-trial variance derived from the median and 95% credibility intervals (Crls) from the 2.5th and 97.5th percentile of the posterior distribution. Treatment rankings (with 95% Crl) and the probability that each treatment is the best will be calculated from the posterior distributions.

Meta-regression models

If pertinent, we will examine the association between the magnitude of treatment effects and study-level characteristics, via random-effects Bayesian
meta-regression models. We will not employ average patient-level characteristics to avoid ecological fallacy [41].

Priors

We will assume non-informative, but biologically plausible priors for treatment effects for all models and between-study variances. However, in sensitivity analyses, we will also use informative priors for the between-study variances [41,42].

Funnel plot asymmetry and small-study bias in pair-wise meta-analysis

Whenever feasible (i.e., ten or more estimates), we will investigate funnel plot asymmetry using graphical and statistical approaches. For pair-wise meta-analyses, we will employ contour-enhanced plots and generate Doi plots [43]. We will calculate the LFK [44] index and conduct Egger’s linear regression test or Peter’s test.

Funnel plot asymmetry and small-study bias in network meta-analysis

For network meta-analysis, we will create a comparison-adjusted funnel plot, as suggested by Chaimani et al. We will also use the recently proposed Risk of Bias due to Missing Evidence in Network meta-analysis (ROB-MEN) approach [45].

Implementation

All Bayesian models will be implemented in MultiBUGS 2.0 (Cambridge, UK), and estimates will be obtained via Markov chain Monte Carlo methods [46]. Models will be fitted with three chains (166667 simulations each), totaling 500,000 iterations. The burn-in period will be 100,000 simulations. Convergence will be checked graphically by running three chains and using the Gelman-Rubin statistic, R. We will check autocorrelation and density of the posterior estimates graphically in Stata 16 (College Station, TX, USA).

Subgroup analysis and investigation of heterogeneity
If appropriate, we will perform subgroup analyses or meta-regression to investigate differences among two or more subgroups according to each of the following characteristics of participants, which might have an effect on the outcomes: type of clinical conditions: Infantile autism (F84.0); Atypical autism (F84.1); Other childhood disintegrative disorder (F84.3); Asperger's Syndrome (F84.5); and Other pervasive developmental disorders (F84.8); participants’ mean age; types of scales used to measure outcomes; duration of follow-up; sex; dose of antipsychotics; presence of comorbidities.

If additional analyses cannot be conducted by RevMan 5, we will perform analyses in Stata Statistical Software (Stata 2015).

Sensitivity analysis

We will perform sensitivity analyses of outcomes to assess the robustness of the findings. If feasible, we will restrict the analysis of outcomes to studies of low risk of bias, impute missing data considering worst-case scenario, and effects of fixed-effect or random-effects methods [47].

Summary of findings and assessment of the certainty of the evidence

After the results have been grouped, two reviewers will independently assess the overall certainty of the evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [48]. The main results of the review will be presented in outcome tables (Summary of Findings - SoF), as recommended by The Cochrane Collaboration [49]. This table will be built with the aid of the GRADEpro software program [48].

ETHICS AND DISSEMINATION

Since it is a literature-based study, ethical approval is not required. The results will be shared through publication in scientific journals of high impact, peer reviewed and also published in national and international conferences.
DISCUSSION

The results of this systematic review could highlight engagement findings in decision-making considering the use of antipsychotics in treating ASD in different age groups.

The analysis of evidence from observational studies can improve the understanding of the use of antipsychotics in the treatment of ASD and support more assertive decisions about the actual performance of these interventions.

Our future results may impact public policy for ASD patients, healthcare professionals, and decision-makers by providing evidence that can highlight challenges and areas for improvement, with a special look at pharmacological interventions in ASD.

This is the first systematic review with a robust proposal for controlled and not controlled settings involving the use of second-generation antipsychotics in ASD. However, there are potential limitations. Primary studies may bring limitations to this review considering the confounders present in observational studies; meta-analyses may be hampered by a lack of standardization in the measurement of efficacy outcomes and diagnostic criteria for ASD.

The methodological rigor and data analysis plan proposed in this review will provide transparency to the evidence found and may demonstrate the degree of confidence in the estimates found. To refine the construction of the final protocol of this systematic review, we are proposing the involvement of stakeholders such as patient representatives, decision-makers, and health professionals who work in the treatment of ASD. Upon completing the systematic review, the results will be disseminated among healthcare professionals, patients, and their representatives through a virtual meeting. Stakeholder perspectives will be incorporated into the systematic review.

AUTHOR CONTRIBUTIONS

LPNL is the principal investigator and wrote the protocol and the final version. JCdO, IF, CCB, ECL, FCA, LGM, and MFF reviewed and edited the
manuscript. LCL is the review guarantor, advised on background, helped to write the protocol, and revised the manuscript.

ACKNOWLEDGEMENTS

The authors would like to thank Thaiane de Lima Alexandre and Ana Carolina de Freitas Lopes for their contributions to the research questions and to the choice of drugs to be included, and to Ph.D. Tiago Veiga Pereira for his contribution to the statistical analyses.

FUNDING

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COMPETING INTERESTS

None to declare.

WORD COUNT

3837

REFERENCES


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tool=bestpractice.bmj.com)


Rhodes KM, Turner RM, Higgins JPT. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. J Clin Epidemiol [Internet]. 2015 Jan 1 [cited 2022 Sep 23];68(1):52. Available from: /pmc/articles/PMC4270451/


# SUPPLEMENTARY MATERIAL 1 - Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist: recommended items to address in a systematic review protocol*

<table>
<thead>
<tr>
<th>Section and topic</th>
<th>Item No</th>
<th>Checklist item</th>
<th>Page No</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADMINISTRATIVE INFORMATION</td>
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</tr>
<tr>
<td>Title: Identification</td>
<td>1a</td>
<td>Identify the report as a protocol of a systematic review</td>
<td>1</td>
</tr>
<tr>
<td>Update</td>
<td>1b</td>
<td>If the protocol is for an update of a previous systematic review, identify as such</td>
<td>N/A</td>
</tr>
<tr>
<td>Registration</td>
<td>2</td>
<td>If registered, provide the name of the registry (such as PROSPERO) and registration number</td>
<td>3</td>
</tr>
<tr>
<td>Authors: Contact</td>
<td>3a</td>
<td>Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author</td>
<td>1-2</td>
</tr>
<tr>
<td>Contributions</td>
<td>3b</td>
<td>Describe contributions of protocol authors and identify the guarantor of the review</td>
<td>17-18</td>
</tr>
<tr>
<td>Amendments</td>
<td>4</td>
<td>If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments</td>
<td>N/A</td>
</tr>
<tr>
<td>Support: Sources</td>
<td>5a</td>
<td>Indicate sources of financial or other support for the review</td>
<td>18</td>
</tr>
<tr>
<td>Sponsor</td>
<td>5b</td>
<td>Provide name for the review funder and/or sponsor</td>
<td>18</td>
</tr>
<tr>
<td>Role of sponsor or funder</td>
<td>5c</td>
<td>Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol</td>
<td>N/A</td>
</tr>
<tr>
<td>INTRODUCTION</td>
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<tr>
<td>Rationale</td>
<td>6</td>
<td>Describe the rationale for the review in the context of what is already known</td>
<td>5-7</td>
</tr>
<tr>
<td>Objectives</td>
<td>7</td>
<td>Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)</td>
<td>7</td>
</tr>
<tr>
<td>METHODS</td>
<td></td>
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<tr>
<td>Eligibility criteria</td>
<td>8</td>
<td>Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review</td>
<td>7-9</td>
</tr>
<tr>
<td>Information sources</td>
<td>9</td>
<td>Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage</td>
<td>9-11</td>
</tr>
<tr>
<td>Search strategy</td>
<td>10</td>
<td>Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated</td>
<td>Suppl. Material 2</td>
</tr>
<tr>
<td>Study records: Data management</td>
<td>11a</td>
<td>Describe the mechanism(s) that will be used to manage records and data throughout the review</td>
<td>11-12</td>
</tr>
</tbody>
</table>
### Selection process 11b
State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)

### Data collection process 11c
Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators

### Data items 12
List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications

### Outcomes and prioritization 13
List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale

### Risk of bias in individual studies 14
Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis

### Data synthesis

<table>
<thead>
<tr>
<th>15a</th>
<th>Describe criteria under which study data will be quantitatively synthesised</th>
<th>12-16</th>
</tr>
</thead>
<tbody>
<tr>
<td>15b</td>
<td>If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I², Kendall’s τ)</td>
<td>12-16</td>
</tr>
<tr>
<td>15c</td>
<td>Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)</td>
<td>12-16</td>
</tr>
<tr>
<td>15d</td>
<td>If quantitative synthesis is not appropriate, describe the type of summary planned</td>
<td>N/A</td>
</tr>
</tbody>
</table>

### Meta-bias(es) 16
Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)

### Confidence in cumulative evidence 17
Describe how the strength of the body of evidence will be assessed (such as GRADE)

*It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.*

### SUPPLEMENTARY MATERIAL 2 – Search strategies

Database Portal da BVS e Lilacs <April, 2022> Results: 548 (Portal da BVS) e 16 (Lilacs). Search Strategy

| 1. | "Transtorno Autístico" or "Autistic Disorder" |
| 2. | "Autismo" or "Autism" |
| 3. | "Autismo Infantil" or "Child Autism" |
| 4. | "Transtorno do Espectro Autista" or "Autism Spectrum Disorder" or "Transtorno do Espectro do Autismo" |
| 5. | or/1-4 |
| 6. | Antipsicóticos |
| 7. | "Agente Antipsicótico" or "Antipsychotic Agents" |
| 8. | "Agente Neuroléptico" or "Medicamento Neuroléptico" or "Medicamento Antipsicótico" |
| 9. | "Agentes Antipsicóticos" |
| 10. | "Droga Antipsicótica" or "Drogas Antipsicóticas" |
| 11. | "Fármaco Antipsicótico" |
| 12. | "Droga Neuroléptica" or "Fármaco Neuroléptico" |
| 13. | "Efeito Antipsicótico" |
| 14. | "Tranquilizante Maior" |
| 15. | “Risperidona” or “Risperidone” |
| 16. | Aripiprazol or aripiprazole |
| 17. | Clozapina or clozapine |
| 18. | Lurasidona or lurasidone |
| 19. | Quetiapina or quetiapine |
| 20. | Olanzapina or olanzapine |
| 21. | Ziprasidona or ziprasidone |
| 22. | Paliperidona or paliperidone |
| 23. | Brexiprazol or brexiprazole |
| 24. | Asenapina or asenapine |
| 25. | Cariprazina or cariprazine |
| 26. | Iloperidona or iloperidone |
| 27. | Lumateperona or lumateperone |
| 28. | Pimavanserina or pimavanserine |
| 29. | or/6-28 |
| 30. | 5 AND 29 |

Database MEDLINE <April, 2022> Results: 1303. Search Strategy

| 1. | “Autistic Disorder” or “(Disorder, Autistic)” or “(Disorders, Autistic)” |
2. “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early”
3. “Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autism Spectrum” or “Autistic Disorder” or "Autism Spectrum Disorder" or “Disorder, Autistic” OR “Disorders, Autistic”
4. "Child Development Disorders, Pervasive"
5. “Asperger Syndrome”
6. “Kanner’s Syndrome” or “Kanner Syndrome” or “Kanners Syndrome”
7. “Autism, Infantile” or “Infantile Autism” or Autism or “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early" or “Autism Spectrum Disorders”
8. “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum”
9. “Pervasive Child Development Disorders” or “Pervasive Development Disorders”
10. “Syndrome, Asperger” or “Asperger's Disease” or “Asperger's Diseases” or “Aspergers Disease” or “Disease, Asperger's” OR “Diseases, Asperger's” or “Asperger Disease” or “Asperger Diseases” or “Disease, Asperger” or “Diseases, Asperger” or “Asperger Disorder” or “Asperger Disorders” or “Disorder, Asperger” or “Disorders, Asperger” or “Asperger's Disorder” or “Aspergers Disorder” or “Disorder, Asperger's” or “Disorders, Asperger” or “Asperger's Syndrome” or “Aspergers Syndrome” or “Syndrome, Asperger’s” or “Syndrome, Asperger's”
11. or/1-10
12. “Tranquilizing Agents, Major” or “Major Tranquilizing Agents” or “Major Tranquilizer” or “Tranquilizer, Major”
13. “Antipsychotic Drug” or “Drug, Antipsychotic” or “Antipsychotic Agent” OR “Agent, Antipsychotic”
14. “Antipsychotic Medication” or “Medication, Antipsychotic”
15. “Neuroleptic Agent” or “Agent, Neuroleptic” or “Neuroleptic Drug” or “Drug, Neuroleptic” or Neuroleptic or Antipsychotic
16. “Antipsychotic Drugs” or Antipsychotics or “Major Tranquilizers” or “Neuroleptic Agents” or “Neuroleptic Drugs” or Neuroleptics or “Tranquilizing Agents, Major” or “Major Tranquilizing Agents”
17. “Antipsychotic Effect” or “Effect, Antipsychotic” or “Antipsychotic Effects” or “Antipsychotic Agents”
18. “Dopamine Antagonists” or “Antagonists, Dopamine” or “Antagonists, Dopamine Receptor” or “Antagonists, Dopaminergic” or “Dopamine Blockers” or “Blockers, Dopamine” or “Dopamine Receptor Antagonists” or “Receptor Antagonists, Dopamine” or “Dopamine Blocker” or “Blocker, Dopamine” or “Dopamine Receptor Antagonist” or “Antagonist, Dopamine Receptor” or “Receptor Antagonist, Dopamine” or “Dopaminergic Antagonists” or “Antagonist, Dopaminergic” or “Dopaminergic Antagonists” or “Dopamine Antagonist” or “Antagonist, Dopamine”
19. aripiprazole
20. clozapine
21. lurasidone
22. quetiapine
23. olanzapine
24. risperidone
25. ziprasidone
26. paliperidone
27. brexiprazole
28. asenapine
29. cariprazine
30. iloperidone
31. Lumateperone
32. pimavanserine
33. or/12-32
34. 11 AND 33

Database EMBASE <April, 2022> Results: 2683. Search strategy

1. 'autistic disorder'/exp or 'autistic disorder' or 'autism spectrum disorder'/exp or 'autism spectrum disorder'
2. 'child development disorders, pervasive'/exp or 'child development disorders, pervasive'
3. 'asperger syndrome'/exp or 'asperger syndrome' or 'disorder, autistic' or 'disorders, autistic'
4. 'syndrome, asperger' or 'aspergers diseases' or 'aspergers disease' or 'disease, aspergers' or 'diseases, aspergers' or 'asperger disease' or 'disease, aspergers' or 'diseases, aspergers' or 'asperger disease' or 'disease, aspergers' or 'diseases, aspergers' or 'asperger diseases' or 'disease, asperger' or 'diseases, asperger' or 'asperger disorder'/exp or 'asperger disorder' or 'aspergers disorder' or 'disorder, asperger' or 'disorders, asperger' or 'aspergers syndrome'/exp or 'aspergers syndrome' or 'syndrome, aspergers'
5. 'kanner syndrome'/exp or 'kanner syndrome' or 'kanners syndrome'
6. 'autism, infantile'/exp or 'autism, infantile' or 'infantile autism'/exp or 'infantile autism' OR 'autism'/exp
7. 'autism, early infantile'/exp or 'autism, early infantile' or 'early infantile autism'/exp OR 'early infantile autism' or 'infantile autism, early' or 'autism spectrum disorders'/exp or 'autism spectrum disorders' or 'autistic spectrum disorder'/exp or 'autistic spectrum disorders' or 'disorder, autistic spectrum'
8. 'pervasive child development disorders'/exp or 'pervasive child development disorders' or 'pervasive development disorders'
9. or/1-8
10. 'tranquilizing agents, major' or 'major tranquilizing agents' or 'major tranquilizer' or 'tranquilizer, major'
11. 'antipsychotic drug' or 'drug, antipsychotic' or 'antipsychotic agent' or 'agent, antipsychotic' or 'antipsychotic medication' or 'medication, antipsychotic'
12. 'neuroleptic agent' or 'agent, neuroleptic' or 'neuroleptic drug' or 'drug, neuroleptic' or neuroleptic
13. antipsychotic or 'antipsychotic drugs' or antipsychotics or 'major tranquilizers'
14. 'neuroleptic agents' or 'neuroleptic drugs' or neuroleptics
15. 'tranquilizing agents, major' or 'major tranquilizing agents'
16. 'antipsychotic effect' or 'effect, antipsychotic' or 'antipsychotic effects' or 'antipsychotic agents'
17. 'dopamine antagonists' or 'antagonists, dopamine' or 'antagonists, dopamine receptor' or 'antagonists, dopaminergic' or 'dopamine blockers' or 'blockers, dopamine' or 'dopamine receptor antagonists' or 'receptor antagonists, dopamine' or 'dopamine blocker' or 'blocker, dopamine' or 'dopamine receptor antagonist' or 'antagonist, dopaminergic' or 'dopaminergic antagonist' or 'dopamine antagonist' or 'antagonist, dopamine'
18. aripiprazole
19. clozapine
20. lurasidone
21. quetiapine
22. olanzapine
23. risperidone
24. ziprasidone
25. paliperidone
26. brexiprazole
27. asenapine
28. cariprazine
29. iloperidone
30. Lumateperone
31. pimavanserin
32. or/10-31
33. 9 AND 32

Database CINAHL <April, 2022> Results: 1800. Search strategy

1. “Autistic Disorder” or “(Disorder, Autistic)” or “(Disorders, Autistic)”
2. “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early”
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

3. “Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autism Spectrum” or “Autistic Disorder” or “Autism Spectrum Disorder” or “Disorder, Autistic” OR “Disorders, Autistic”

4. “Child Development Disorders, Pervasive”

5. “Asperger Syndrome”

6. “Kanner's Syndrome” or “Kanner Syndrome” or “Kanners Syndrome”

7. “Autism, Infantile” or “Infantile Autism” or Autism or “Infantile Autism, Early” or “Early Infantile Autism” or “Infantile Autism, Early” or “Autism Spectrum Disorders”

8. “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum”

9. “Pervasive Child Development Disorders” or “Pervasive Development Disorders”

10. “Syndrome, Asperger” or “Asperger's Disease” or “Asperger's Diseases” or “Aspergers Disease” or “Disease, Asperger's” OR “Diseases, Asperger's” or “Asperger Disease” or “Asperger Diseases” or “Disease, Asperger” or “Diseases, Asperger” or “Asperger Disorder” or “Asperger Disorders” or “Disorder, Asperger” or “Disorders, Asperger” or “Asperger's Disorder” or “Disorder, Asperger’s” or “Aspergers Syndrome” or “Syndrome, Asperger's”

11. or/1-10

12. “Tranquillizing Agents, Major” or “Major Tranquillizing Agents” or “Major Tranquilizer” or “Tranquilizer, Major”

13. “Antipsychotic Drug” or “Drug, Antipsychotic” or “Antipsychotic Agent” OR “Agent, Antipsychotic”

14. “Antipsychotic Medication” or “Medication, Antipsychotic”

15. “Neuroleptic Agent” or “Agent, Neuroleptic” or “Neuroleptic Drug” or “Drug, Neuroleptic” or Neuroleptic or Antipsychotic

16. “Antipsychotic Drugs” or Antipsychotics or “Major Tranquilizers” or “Neuroleptic Agents” or “Neuroleptic Drugs” or Neuroleptics or “Tranquilizing Agents, Major” or “Major Tranquilizing Agents”

17. “Antipsychotic Effect” or “Effect, Antipsychotic” or “Antipsychotic Effects” or “Antipsychotic Agents”

18. “Dopamine Antagonists” or “Antagonists, Dopamine” or “Antagonists, Dopamine Receptor” or “Antagonists, Dopaminergic” or “Dopamine Blockers” or “Blockers, Dopamine” or “Dopamine Receptor Antagonists” or “Receptor Antagonists, Dopamine” or “Dopamine Blocker” or “Blocker, Dopamine” or “Dopamine Receptor Antagonist” or “Antagonist, Dopamine Receptor” or “Receptor Antagonist, Dopamine” or “Dopaminergic Antagonist” or “Antagonist, Dopaminergic” or “Dopaminergic Antagonists” or “Dopamine Antagonist” or “Antagonist, Dopamine”

19. aripiprazole

20. clozapine

21. lurasidone
22. quetiapine
23. olanzapine
24. risperidone
25. ziprasidone
26. paliperidone
27. brexiprazole
28. asenapine
29. cariprazine
30. iloperidone
31. Lumateperone
32. pimavanserine
33. or/12-32
34. 11 AND 33

Database PSYCINFO <April, 2022> Results: 1898. search strategy

1. “Autistic Disorder” or “(Disorder, Autistic)” or “(Disorders, Autistic)"
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3. “Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum” or “Autistic Disorder” or “Autism Spectrum Disorder” or “Disorder, Autistic” OR “Disorders, Autistic”
4. "Child Development Disorders, Pervasive"
5. “Asperger Syndrome”
6. “Kanner's Syndrome” or “Kanner Syndrome” or “Kanners Syndrome”
7. “Autism, Infantile” or “Infantile Autism” or Autism or “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early” or “Autism Spectrum Disorders”
8. “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum”
9. “Pervasive Child Development Disorders” or “Pervasive Development Disorders”
10. “Syndrome, Asperger” or “Asperger's Disease” or “Asperger's Diseases” or “Aspergers Disease” or “Disease, Asperger's” OR “Diseases, Asperger's” or “Asperger Disease” or “Asperger Diseases” or “Disease, Asperger” or “Diseases, Asperger” or “Asperger Disorder” or “Asperger Disorders” or “Disorder, Asperger” or “Disorders, Asperger” or “Asperger's Disorder” or “Aspergers Disorder” or “Disorder, Asperger's” or “Asperger's Syndrome” or “Aspergers Syndrome” or “Syndrome, Asperger's”
11. or/1-10
12. “Tranquillizing Agents, Major” or “Major Tranquillizing Agents” or “Major Tranquilizer” or “Tranquilizer, Major”
13. “Antipsychotic Drug” or “Drug, Antipsychotic” or “Antipsychotic Agent” OR “Agent, Antipsychotic”
14. “Antipsychotic Medication” or “Medication, Antipsychotic”
15. “Neuroleptic Agent” or “Agent, Neuroleptic” or “Neuroleptic Drug” or “Drug, Neuroleptic” or Neuroleptic or Antipsychotic
16. “Antipsychotic Drugs” or Antipsychotics or “Major Tranquilizers” or “Neuroleptic Agents” or “Neuroleptic Drugs” or Neuroleptics or “Tranquilizing Agents, Major” or “Major Tranquilizing Agents”
17. “Antipsychotic Effect” or “Effect, Antipsychotic” or “Antipsychotic Effects” or “Antipsychotic Agents”
18. “Dopamine Antagonists” or “Antagonists, Dopamine” or “Antagonists, Dopamine Receptor” or “Antagonists, Dopaminergic” or “Dopamine Blockers” or “Blockers, Dopamine” or “Dopamine Receptor Antagonists” or “Receptor Antagonists, Dopamine” or “Dopamine Blocker” or “Blocker, Dopamine” or “Dopamine Receptor Antagonist” or “Antagonist, Dopamine Receptor” or “Dopaminergic Antagonist” or “Antagonist, Dopaminergic” or “Dopaminergic Antagonists” or “Dopamine Antagonist” or “Antagonist, Dopamine”
19. aripiprazole
20. clozapine
21. lurasidone
22. quetiapine
23. olanzapine
24. risperidone
25. ziprasidone
26. paliperidone
27. brexiprazole
28. asenapine
29. cariprazine
30. iloperidone
31. Lumateperone
32. pimavanserine
33. or/12-32
34. 11 AND 33

Database Cochrane <April, 2022> Results: 459. Search strategy

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1. Autism or “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early”
2. “Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum” or "Autistic Disorder" or "Autism Spectrum Disorder"
3. or/1-2
4. aripiprazole
5. clozapine
6. lurasidone
7. quetiapine
8. olanzapine
9. risperidone
10. ziprasidone
11. paliperidone
12. brexiprazole
13. asenapine
14. cariprazine
15. iloperidone
16. Lumateperone
17. pimavanserine
18. “Antipsychotic Drug” or “Drug, Antipsychotic”
19. “Antipsychotic Agent” or “Agent, Antipsychotic”
20. “Antipsychotic Medication” OR “Medication, Antipsychotic”
21. or/4-20
22. 3 AND 21

Database EPISTEMONIKOS <April, 2022> Results: 800. Estratégia de busca

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2. “Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum” or “Autistic Disorder” or “Autism Spectrum Disorder”
3. or/1-2
4. Risperidone
5. aripiprazole
6. clozapine
7. lurasidone
8. quetiapine
9. olanzapine
10. risperidone
11. ziprasidone
12. paliperidone
13. brexiprazole
14. asenapine
15. cariprazine
16. iloperidone
17. Lumateperone
18. pimavanserine
19. “Antipsychotic Drug” or “Drug, Antipsychotic”
20. “Antipsychotic Agent” or “Agent, Antipsychotic”
21. “Antipsychotic Medication” OR “Medication, Antipsychotic”
22. or/4-21
23. 3 AND 22

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CLINICAL TRIALS <April, 2022> Results: 192. Search strategy

1. Autism
2. Antipsychotic
3. 1 AND 2

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WHO International Clinical Trials Registry Platform <April, 2022> Results: 126. Search strategy

1. Autism
2. Antipsychotic
3. 1 AND 2

******************************************************************************

EU Clinical Trials Register <April, 2022> Results: 100. Search strategy

1. Autism
2. Antipsychotic
3. 1 AND 2

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Portal CAPES (Teses e Dissertações) <April, 2022>. Results: 619. Search strategy

1. Autismo
2. Antipsicótico
3. 1 AND 2
4. Filtro: Ciências da Saúde

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ProQuest <April, 2022>. Results: 80. Search strategy
1. Autism
2. Antipsychotic
3. 1 AND 2
SUPPLEMENTARY MATERIAL 3 - Journals and Conference

- International Congress on Psychopharmacology;
- Annual Meeting of the American Academy of Child & Adolescent Psychiatry;
- European Congress of Psychiatry;
- European College of Neuropsychopharmacology Congress;
- International Congress on Psychopharmacology and International Symposium on Child and Adolescent Psychopharmacology;
- International Congress of European Society for Child and Adolescent Psychiatry
- World Congress of the International Association for Child and Adolescent Psychiatry and Allied Professions;
- International Conference on Pharmacoepidemiology and Therapeutic Risk
- World Congress of the International Association for the Scientific Study of Intellectual and Developmental Disabilities;
- Annual Meeting of the College of Psychiatric and Neurologic Pharmacists;
- Annual Conference of the American College of Neuropsychopharmacology;
- Annual National Institute of Mental Health;
- Annual Meeting of the International College of Spectrum Disorders.
## Use of second-generation antipsychotics in Autism Spectrum Disorder: a systematic review and meta-analysis protocol

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<th>BMJ Open</th>
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<td>Lopes, Luis; Universidade da Sorocaba, de Oliveira, Jardel; Secretaria Municipal de Saúde, Médico de Família e Comunidade, Especialista em Saúde da Família, Geriatria e Gerontologia Bergamaschi, Cristiane; Universidade de Sorocaba, Pharmaceutical Science Fulone, Izabela; Universidade de Sorocaba, Pharmaceutical Science Lima, Elisangela; Federal University of Rio de Janeiro Pharmacy School Abe, Flávia; University of Sorocaba Mazzei, Lauren; Universidade da Sorocaba Figueiró, Mabel; Hospital do Coração Lopes, Luciane; Universidade de Sorocaba, Pharmaceutical Science</td>
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Use of second-generation antipsychotics in Autism Spectrum Disorder: a systematic review and meta-analysis protocol

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Phone: 55 19 99781-8441 Fax: 55 15 2101-7074
ABSTRACT

Introduction: Atypical antipsychotics have been studied to treat Autism Spectrum Disorder (ASD). However, little is known whether these drugs are effective and safety comparing controlled and non-controlled settings. This study aims to assess the efficacy and safety of second-generation antipsychotics in ASD in randomized controlled trials (RCT) and observational studies.

Methods and Analysis: This Systematic Review will include RCT and prospective cohorts evaluating second-generation antipsychotics in people five years and older diagnosed with ASD. Searches will be conducted in Medline, Embase, Cochrane Library, Epistemonikos, Lilacs, CINAHL, PsycINFO, trial registries, and grey literature databases without restriction on publication status, year of publication, and language. The primary outcomes will be symptoms of aggressive behavior, quality of life for the individual or their careers, and discontinuation or dropouts/withdrawals of antipsychotics due to adverse events. The secondary outcomes are other not serious adverse events and adherence to pharmacotherapy. Selection, data extraction, and quality assessment will be performed by pairs of reviewers, independently. The Risk of Bias 2 (RoB 2) and Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tools will be used to assess the risk of bias in the included studies. If appropriate, a meta-analysis and network meta-analysis will be conducted to synthesize the results. The overall quality of the evidence for each outcome will be determined by the Recommendation, Assessment, Development, and Evaluation (GRADE) approach.

Ethics and dissemination: This study will systematically summarize the existing evidence evaluating the use of second-generation antipsychotics for treating ASD, in controlled and uncontrolled studies. The results of this review will be disseminated through peer-reviewed publications and conference presentations.

Protocol Registration: PROSPERO – CRD42022353795

Keywords: Autism Spectrum Disorder. Antipsychotic Agents. Real-World Evidence. Systematic Review.
STRENGTHS AND LIMITATIONS OF THIS STUDY

- The search will be performed with the help of a specialized librarian experienced in medical literature searching;
- This systematic review will include stakeholders from refining the question to discussing and implementing the findings.
- Our systematic review proposal may have limitations inherent to the methodological quality of the included studies, especially non-randomized studies, which will be discussed.
- Some important outcomes such as quality of life and adherence to pharmacotherapy may not have been assessed in primary studies.
INTRODUCTION

Autism Spectrum Disorder (ASD), or simply autism, is a unique clinical condition with different levels of severity, characterized by two main symptom domains: 1) deficits in social communication and social interaction and 2) restricted repetitive behaviors (RRBs), interests and activities and sensory anomalies[1].

Estimates of the prevalence of ASD vary. About 52 million people live with ASD worldwide [2]. Studies indicate approximately 1% to 2% of children in the US and other developed countries [3,4,2,5]. A systematic review of prevalence studies of ASD identified an overall estimate of the prevalence of 7.1 per 10,000 for autism and 20 per 10,000 for all ASD [6]. Another systematic review found that the average worldwide prevalence of ASD was 17 per 100,000, with a range of 2.8 to 94 per 100,000 across all age groups [7]. Hispanic and African-American children are underdiagnosed compared to non-Hispanic white children [6]. People with higher socioeconomic status and better access to health care are diagnosed earlier [7].

ASD is considered a brain-based neurodevelopmental disorder that lasts for life [8]. The three characteristic manifestations of ASD are impaired social interaction, impaired communication, and restricted repetitive and stereotyped patterns of behavior [9]. Interfering behavior has a great impact on the quality of life of individuals with ASD, family members, and the people they live with [10,11]. Interfering behaviors may include irritability, aggression, and self-harm [12]. These symptoms are the main causes of psychiatric hospitalization, and the use of antipsychotics is recommended in the absence of effectiveness of behavioral interventions [13,14,15].

Despite the claims of curative interventions, there is no specific treatment for autism and therapies target the symptoms of the disease. Pharmacological interventions have been used as adjuncts to behavioral treatments in both children and adults and may reduce specific autistic symptoms and behaviors such as self-injury and aggression [15]. There is evidence of widespread prescribing of psychotropic drugs to people with ASD [16]. Antipsychotic drugs generally tranquilize and relieve psychotic symptoms without impairing
consciousness [15]. Second-generation antipsychotics tend to cause fewer unwanted motor adverse effects than typical ones [17].

Typical (first-generation) and atypical (second-generation) antipsychotics have been evaluated for the treatment of behavioral symptoms in individuals with ASD. It is well established in the literature that first-generation antipsychotics are not recommended for treating symptoms in ASD due to their adverse effects. First-generation antipsychotics have been associated with drug-induced movement disorders [15]. Haloperidol, for example, has been evaluated for the treatment of ASD in several trials and has been associated with improvements in withdrawal and stereotypies [18] and positive effects on learning. However, it has also been related to extrapyramidal side effects such as acute dystonic reactions, withdrawal dyskinesias, and tardive dyskinesia in this population [19].

Randomized controlled trials (RCTs) have suggested the efficacy of second-generation antipsychotics to ameliorate some interfering symptoms of ASD in children and adolescents [20]. A systematic review investigated the use of risperidone for ASD and demonstrated the efficacy of this drug in treating symptoms of aggression, irritability, and repetitive behavior. Notable adverse events, including weight gain, increased appetite, and sedation, were described [21].

In addition, evidence from two RCTs suggests that aripiprazole can be effective as a short-term medication for some behavioral aspects of ASD in children/adolescents [22–24]. Participants included in both RCTs who received aripiprazole had reduced significantly irritability when compared to the placebo groups. Nevertheless, weight gain, sedation, drooling, and tremors occurrence must also be considered [25]. Another systematic review [17] found that antipsychotics (aripiprazole, clozapine, haloperidol, levosulpiride, lurasidone, olanzapine, risperidone, trifluoperazine) for children and adolescents with ASD were more efficacious than placebo in reducing stereotypies, hyperactivity, irritability and obsessions, compulsions, and increasing social communication and global functioning.

Systematic reviews published evaluating the use of antipsychotics presented important methodological limitations. An overview of systematic
reviews on aripiprazole and risperidone found 16 systematic reviews of critically low methodological quality [26]. Published Cochrane systematic reviews have only evaluated the pediatric population and have not included all second-generation antipsychotics [21,25].

This systematic review will evaluate the performance of second-generation antipsychotics in the treatment of ASD in controlled and non-controlled settings.

METHODS AND ANALYSIS

Study design, protocol, and registration

This systematic review (SR) will be performed according to the recommendations of the Cochrane Handbook for Intervention Reviews [27]. This protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [28] (Supplementary Material 1), and registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under registration nº. CRD42022353795

Patient and public involvement

Stakeholders were involved in the development and refinement of the research question. We involved decision-makers from the Brazilian Ministry of Health, primary care physicians, psychiatrists, and key stakeholders.

When the systematic review is completed, the results will be discussed in a dissemination workshop with the same stakeholders. We will involve users in classifying outcomes’ importance and interpretation of evidence [29]. We will summarize the evidence in plain language.

Eligibility criteria

The research question was structured using the Population, Intervention, Comparison, and Outcomes (PICO) structure.
Types of participants

Participants regardless of age group diagnosed with ASD using a standardized diagnostic tool or established diagnostic criteria from DSM-4 or DSM-5.

Studies involving other mental disorders will be included as long as the results are separate or at least 80% of the population has a confirmed diagnosis of ASD.

Type of interventions

Second-generation antipsychotics (amisulpride, aripiprazole, asenapine, brexiprazole, cariprazine, clozapine, iloperidone, lumateperone, lurasidone, olanzapine, paliperidone, pimavanserin, quetiapine, risperidone, sulpiride, ziprasidone), without restriction as to dose, route of administration, frequency or duration of treatment.

Types of comparators

1. Second-generation antipsychotics other than intervention;
2. Placebo.

Types of outcome measures

We will include studies regardless of the scales used to measure outcomes.

Primary outcomes

1. Number of participants with aggressive behavior and degree of aggressiveness (agitation; irritability; and self-aggression), measured using validated scales reported by the patient, physician or parents;
2. Quality of life for the individual and/or their caregivers;
3. Number of participants who had Discontinuation or dropouts/withdrawals of antipsychotics due to adverse events.

Secondary outcomes
1. Number of participants with Adverse events of interest according to the Guideline on the clinical development of medicinal products for the treatment of ASD [30]:

- Central Nervous System adverse events;
- Endocrinological adverse events;
- Other adverse events, for example, somnolence, insomnia, headache, rash and constipation.

2. Adherence to pharmacotherapy measured by validated scales, or reported by the patient, physician and parents.

Types of studies

We will include RCTs and pragmatic trials irrespective status of publication (online clinical trials results, summaries of unpublished clinical trials, abstracts, reports from pharmaceutical companies, since that they contain sufficient data for analysis), year of publication and language. Observational studies (cohorts) will be included additionally, only if they are prospective and have a comparator arm for the intervention of interest.

The RCTs will be included because they are the best study designs for evaluating the effectiveness of health interventions and cohorts will be considered especially for safety outcomes as they generally have a longer follow-up. We will not impose any limitation regarding the length of follow-up.

We will exclude non-randomized studies such databases with data from claims or medical records, cases series, retrospective cohorts, case-control, control before and after, and times series.

Search methods for identification of studies

The search strategy will use DeCS/MeSH descriptors and synonyms, being adapted according to each database searched (Supplementary Material 2). The searches will be conducted by an experienced librarian and will be reviewed by another professional librarian, according to the Peer Review of Electronic Search Strategies (PRESS) [31].
Electronic searches

A structured search for eligible primary studies will be conducted in the main electronic databases: MEDLINE via PubMed, Embase via Elsevier, Cochrane Central Register of Controlled Trials (Central), Epistemonikos, Latin American and Caribbean Health Sciences Literature (Lilacs) via Virtual Health Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and PsycINFO.

Searching other resources

1. Grey literature


2. Trial registries:


3. Hand searches

   Appropriate journals and conference proceedings (Supplementary Material 3) relating to second-generation antipsychotic treatment for ASD will be hand searches and incorporated.

4. Personal communication

   Pharmaceutical companies and experts in the fields will be asked if they knew of any studies that met the inclusion criteria of this review.

5. Reference checking
Reference lists of the included studies, previous systematic reviews, systematic scoping reviews, and narrative reviews of ASD will be checked for published reports and citations of unpublished research.

6. Automatic alerts

We set automatic alerts in each database to receive notifications of published new studies. We monitored the medical literature and kept the review as current as possible.

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved through an electronic database search to a reference management database <https://www.covidence.org/> and remove duplicates. Pairs of reviewers will independently screen titles and abstracts for inclusion. We will retrieve the full text of potentially relevant references, and pairs of reviewer’s authors will independently assess the full-text articles for inclusion. We will record reasons for exclusion from studies following the full-text review. Any disagreements will be resolved through discussion or, if required, by consulting a third review author.

For the two selection stages, the reviewers will carry out a pilot exercise for consensus on the eligibility criteria.

Data extraction and management

A pre-piloted and standardized form will be used to extract data from the included studies. The reviewers will be calibrated by extracting at least three articles, in pairs and independently, and, afterward, they will carry out a consensus. This process will take place until the standardization of the extracted data. The overlap of two articles in all teams of reviewers will be adopted to assess the reliability between reviewers in extracting data in the different teams.

After this stage, two reviewers will extract the data independently, and any discrepancies will be identified and resolved with a third author, when necessary.

The data collected will be a) bibliometric information (year of study publication, authors, title); b) characteristics of studies (funding, follow-up time,
design: randomized or non-randomized, scales used; clinical setting: hospitals, specialty clinics, primary care, research centers; countries, country, registered number, number of sites, duration of the study, the timing of outcome measurement: weeks or months, numbers of participants in each arm); c) characteristics of patients (inclusion and exclusion criteria, age, antipsychotics: naive vs experienced, psychiatric comorbidities, other treatments, drug regimen, route and frequency of medication administration and adverse events); d) outcome (total number of participants in each arm, the total number of participants who presented the outcome, name of the scale used to measure the outcome, numerical value to measure the outcome - mean, median, standard deviation - and time point used). We will extract data comprehensively to cover all relevant outcomes and methods reported across studies.

Where key data are missing from the study reports, we will attempt to contact the authors to obtain such information. Where multiple reports of the same trial are published, we will extract data from those we deem to be most complete.

Assessment of methodological quality of individual studies

The quality of RCTs will be assessed using Cochrane's Risk of Bias (RoB) tool version 2.0 for randomized trials on bias arising from the randomization process, deviations from intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result [32].

The quality of observational studies will be assessed using Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool on bias arising from the confounding, selection bias, information bias and reporting bias [33].

Two reviewers will assess the risk of bias. Reviewers will resolve disagreements through discussion, and a third person will judge unresolved disagreements.

Statistical analysis

Measures of treatment effect
We will use the standardized mean difference (SMD) to summarise continuous outcomes and the odds ratio (OR) to summarise binary outcomes. We will use results based on the intention-to-treat analysis (ITT) whenever available.

We will convert standardized mean differences to log-odds ratios (or vice-versa) using established methods when necessary. Depending on the data availability, we will convert sample sizes, means and standard deviations directly to 2x2 tables – under the assumption of an approximately normal distribution and a cutoff. The thresholds that separate the continuous outcome into two categories (e.g., event and non-event) will be defined by current guidelines and an expert group of psychiatrists and clinical pharmacologists.

**Missing data**

We will employ standard techniques to back-calculate the necessary statistics from reported confidence intervals, standard errors, z, t or P values. We will use approximate Bayesian computation models to derive the necessary information for meta-analysis when reported data are more complex [34] (e.g., median and interquartile range, continuous variables divided into mutually exclusive groups based on cutoffs). We will extract data from figures if data are reported graphically.

**Pair-wise meta-analysis**

We will use fully Bayesian random-effects models. Throughout our analyses, we will use only random-effects models. The choice of a random-effects model is based on the anticipated clinical and methodological heterogeneity across studies [35].

We will use the binomial likelihood for binary outcomes and model the log odds ratio. If results in primary studies are available as odds ratios (95% confidence interval), we will model binary outcomes using the normal likelihood. We will use the normal likelihood and the identity link for continuous outcomes. As suggested, statistical heterogeneity will be interpreted based on the between-study variance ($\tau^2$) [36,37].
Network meta-analysis

We will use the generalized linear model framework (the "NICE" model) described previously [38]. If feasible, we will use the arm-based approach. The model preserves randomization, assumes consistency and allows for multi-arm trials. However, if necessary, we will employ an adapted model that uses arm-level and comparison-level data. For binary outcomes, we will use the binomial likelihood. We will use the normal likelihood and the identity link for continuous outcomes [39].

To evaluate the plausibility of the transitivity assumption, we will investigate the distribution of presumed effect modifiers across treatment comparisons. The list of potential effect modifiers will be defined by listing all covariates investigated at the baseline. This list will be evaluated by a multidisciplinary panel of practicing psychiatrists and clinical pharmacologists, who will rank the importance of each covariate regarding the treatment effect. Transitivity will be judged based on the five most relevant potential effect modifiers.

We will compare the fit of the consistency model to the fit of a random-effects model that relaxes the consistency assumption ("inconsistency model"). Models will be compared via the posterior mean of the residual deviance and the deviance information criterion (DIC), with lower DIC values indicating a better model fit [39]. If appropriate, we will fit the node split model and compare direct, indirect, and network estimates for all treatments [40, 38].

We will present summary treatment effect estimates and between-trial variance derived from the median and 95% credibility intervals (Crls) from the 2.5th and 97.5th percentile of the posterior distribution. Treatment rankings (with 95% Crl) and the probability that each treatment is the best will be calculated from the posterior distributions.

Meta-regression models

If pertinent, we will examine the association between the magnitude of treatment effects and study-level characteristics, via random-effects Bayesian
meta-regression models. We will not employ average patient-level characteristics to avoid ecological fallacy [41].

Priors

We will assume non-informative, but biologically plausible priors for treatment effects for all models and between-study variances. However, in sensitivity analyses, we will also use informative priors for the between-study variances [41,42].

Funnel plot asymmetry and small-study bias in pair-wise meta-analysis

Whenever feasible (i.e., ten or more estimates), we will investigate funnel plot asymmetry using graphical and statistical approaches. For pair-wise meta-analyses, we will employ contour-enhanced plots and generate Doi plots [43]. We will calculate the LFK [44] index and conduct Egger’s linear regression test or Peter’s test.

Funnel plot asymmetry and small-study bias in network meta-analysis

For network meta-analysis, we will create a comparison-adjusted funnel plot, as suggested by Chaimani et al. We will also use the recently proposed Risk of Bias due to Missing Evidence in Network meta-analysis (ROB-MEN) approach [45].

Implementation

All Bayesian models will be implemented in MultiBUGS 2.0 (Cambridge, UK), and estimates will be obtained via Markov chain Monte Carlo methods [46]. Models will be fitted with three chains (166667 simulations each), totalizing 500,000 iterations. The burn-in period will be 100,000 simulations. Convergence will be checked graphically by running three chains and using the Gelman-Rubin statistic, $R$. We will check autocorrelation and density of the posterior estimates graphically in Stata 16 (College Station, TX, USA).

Subgroup analysis and investigation of heterogeneity
If appropriate, we will perform subgroup analyses or meta-regression to investigate differences among two or more subgroups according to each of the following characteristics of participants, which might have an effect on the outcomes: type of clinical conditions: Infantile autism (F84.0); Atypical autism (F84.1); Other childhood disintegrative disorder (F84.3); Asperger’s Syndrome (F84.5); and Other pervasive developmental disorders (F84.8); participants’ mean age; types of scales used to measure outcomes; duration of follow-up; sex; dose of antipsychotics; presence of comorbidities.

If additional analyses cannot be conducted by RevMan 5, we will perform analyses in Stata Statistical Software (Stata 2015).

**Sensitivity analysis**

We will perform sensitivity analyses of outcomes to assess the robustness of the findings. If feasible, we will restrict the analysis of outcomes to studies of low risk of bias, impute missing data considering worst-case scenario, and effects of fixed-effect or random-effects methods [47].

**Summary of findings and assessment of the certainty of the evidence**

After the results have been grouped, two reviewers will independently assess the overall certainty of the evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [48]. The main results of the review will be presented in outcome tables (Summary of Findings - SoF), as recommended by The Cochrane Collaboration [49]. This table will be built with the aid of the GRADEpro software program [48].

**ETHICS AND DISSEMINATION**

Since it is a literature-based study, ethical approval is not required. The results will be shared through publication in scientific journals of high impact, peer reviewed and also published in national and international conferences.
DISCUSSION

The results could inform decision-making processes in the use of antipsychotics for the treatment of ASD. The evidence systematized in this study may contribute to improvements in health care based on the best evidence on the use of antipsychotics in the treatment of ASD. Our future results may impact public policy for ASD patients, healthcare professionals, and decision-makers by providing evidence that can highlight challenges and areas for improvement, with a special look at pharmacological interventions in ASD.

The analysis of evidence from observational studies can improve the understanding of the use of antipsychotics in the treatment of ASD and support more assertive decisions about the actual performance of these interventions.

This is the first systematic review with a robust proposal for controlled and non-controlled settings involving the use of second-generation antipsychotics in ASD. Nevertheless, there are potential limitations. Primary studies may bring limitations to this review considering the confounders present in observational studies; meta-analyses may be hampered by a lack of standardization in the measurement of efficacy outcomes and diagnostic criteria for ASD.

The methodological rigor and data analysis plan proposed in this review will provide transparency to the evidence found and may demonstrate the degree of confidence in the estimates found. To refine the construction of the final protocol of this systematic review, we are proposing the involvement of stakeholders such as patient representatives, decision-makers, and health professionals who work in the treatment of ASD. Upon completing the systematic review, the results will be disseminated among healthcare professionals, patients, and their representatives through a virtual meeting. Stakeholder perspectives will be incorporated into the systematic review.

AUTHOR CONTRIBUTIONS
LPNL is the principal investigator and wrote the protocol and the final version. JCdO, IF, CCB, ECL, FCA, LGM, and MFF reviewed and edited the manuscript. LCL is the review guarantor, advised on background, helped to write the protocol, and revised the manuscript.

ACKNOWLEDGEMENTS

The authors would like to thank Thaiane de Lima Alexandre and Ana Carolina de Freitas Lopes for their contributions to the research questions and to the choice of drugs to be included, and to Ph.D. Tiago Veiga Pereira for his contribution to the statistical analyses.

FUNDING

This research received funding from the Ministry of Health of Brazil (MoH) and National Council for Scientific and Technological Development (CNPq), nº 423543/2021-0. Furthermore, this project was funded by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)—PROSUC—CAPES/UNISO. Grant number not applicable.

COMPETING INTERESTS

None to declare.

WORD COUNT

3837

REFERENCES


31. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre


42. Rhodes KM, Turner RM, Higgins JPT. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. J Clin Epidemiol [Internet]. 2015 Jan 1 [cited 2022 Sep 23];68(1):52. Available from: /pmc/articles/PMC4270451/


# SUPPLEMENTARY MATERIAL 1 - Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist: recommended items to address in a systematic review protocol*

<table>
<thead>
<tr>
<th>Section and topic</th>
<th>Item No</th>
<th>Checklist item</th>
<th>Page No</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADMINISTRATIVE INFORMATION</td>
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</tr>
<tr>
<td>Title:</td>
<td>1a</td>
<td>Identify the report as a protocol of a systematic review</td>
<td>1</td>
</tr>
<tr>
<td>Identification</td>
<td>1b</td>
<td>If the protocol is for an update of a previous systematic review, identify as such</td>
<td>N/A</td>
</tr>
<tr>
<td>Registration</td>
<td>2</td>
<td>If registered, provide the name of the registry (such as PROSPERO) and registration number</td>
<td>3</td>
</tr>
<tr>
<td>Authors:</td>
<td>3a</td>
<td>Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author</td>
<td>1-2</td>
</tr>
<tr>
<td>Contributions</td>
<td>3b</td>
<td>Describe contributions of protocol authors and identify the guarantor of the review</td>
<td>17-18</td>
</tr>
<tr>
<td>Amendments</td>
<td>4</td>
<td>If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments</td>
<td>N/A</td>
</tr>
<tr>
<td>Support:</td>
<td>5a</td>
<td>Indicate sources of financial or other support for the review</td>
<td>18</td>
</tr>
<tr>
<td>Sources</td>
<td>5b</td>
<td>Provide name for the review funder and/or sponsor</td>
<td>18</td>
</tr>
<tr>
<td>Sponsor</td>
<td>5c</td>
<td>Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol</td>
<td>N/A</td>
</tr>
<tr>
<td>Role of sponsor or funder</td>
<td></td>
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<tr>
<td>INTRODUCTION</td>
<td>6</td>
<td>Describe the rationale for the review in the context of what is already known</td>
<td>5-7</td>
</tr>
<tr>
<td>Rationale</td>
<td>7</td>
<td>Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)</td>
<td>7</td>
</tr>
<tr>
<td>Objectives</td>
<td></td>
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<tr>
<td>METHODS</td>
<td>8</td>
<td>Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review</td>
<td>7-9</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td></td>
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<tr>
<td>Information sources</td>
<td>9</td>
<td>Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage</td>
<td>9-11</td>
</tr>
<tr>
<td>Search strategy</td>
<td>10</td>
<td>Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated</td>
<td>Suppl. Material 2</td>
</tr>
<tr>
<td>Study records:</td>
<td></td>
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<tr>
<td>Data management</td>
<td>11a</td>
<td>Describe the mechanism(s) that will be used to manage records and data throughout the review</td>
<td>11-12</td>
</tr>
<tr>
<td>Selection process</td>
<td>11b</td>
<td>State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)</td>
<td>11-12</td>
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<tr>
<td>Data collection process</td>
<td>11c</td>
<td>Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators</td>
<td>11-12</td>
</tr>
<tr>
<td>Data items</td>
<td>12</td>
<td>List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications</td>
<td>11-12</td>
</tr>
<tr>
<td>Outcomes and prioritization</td>
<td>13</td>
<td>List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale</td>
<td>8-9</td>
</tr>
<tr>
<td>Risk of bias in individual studies</td>
<td>14</td>
<td>Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis</td>
<td>12</td>
</tr>
<tr>
<td>Data synthesis</td>
<td>15a</td>
<td>Describe criteria under which study data will be quantitatively synthesised</td>
<td>12-16</td>
</tr>
<tr>
<td></td>
<td>15b</td>
<td>If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I², Kendall’s τ)</td>
<td>12-16</td>
</tr>
<tr>
<td></td>
<td>15c</td>
<td>Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)</td>
<td>12-16</td>
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<tr>
<td></td>
<td>15d</td>
<td>If quantitative synthesis is not appropriate, describe the type of summary planned</td>
<td>N/A</td>
</tr>
<tr>
<td>Meta-bias(es)</td>
<td>16</td>
<td>Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)</td>
<td>15-16</td>
</tr>
<tr>
<td>Confidence in cumulative evidence</td>
<td>17</td>
<td>Describe how the strength of the body of evidence will be assessed (such as GRADE)</td>
<td>16</td>
</tr>
</tbody>
</table>

*It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

SUPPLEMENTARY MATERIAL 2 – Search strategies

Database Portal da BVS e Lilacs <April, 2022> Results: 548 (Portal da BVS) e 16 (Lilacs). Search Strategy

1. "Transtorno Autístico" or "Autistic Disorder"
2. "Autismo" or "Autism"
3. "Autismo Infantil" or "Child Autism"
4. "Transtorno do Espectro Autista" or "Autism Spectrum Disorder" or "Transtorno do Espectro do Autismo"
5. or/1-4
6. Antipsicóticos
7. "Agente Antipsicótico" or "Antipsychotic Agents"
8. "Agente Neuroléptico" or "Medicamento Neuroléptico" or "Medicamento Antipsicótico"
9. "Agentes Antipsicóticos"
10. "Droga Antipsicótica" or "Drogas Antipsicóticas"
11. "Fármaco Antipsicótico"
12. "Droga Neuroléptica" or "Fármaco Neuroléptico"
13. "Efeito Antipsicótico"
14. "Tranquilizante Maior"
15. "Risperidona" or "Risperidone"
16. Aripiprazol or aripiprazole
17. Clozapina or clozapine
18. Lurasidona or lurasidone
19. Quetiapina or quetiapine
20. Olanzapina or olanzapine
21. Ziprasidona or ziprasidone
22. Paliperidona or paliperidone
23. Brexiprazol or brexiprazole
24. Asenapina or asenapine
25. Cariprazina or cariprazine
26. Iloperidona or iloperidone
27. Lumateperona or lumateperone
28. Pimavanserina or pimavanserine
29. or/6-28
30. 5 AND 29

Database MEDLINE <April, 2022> Results: 1303. Search Strategy

1. “Autistic Disorder” or “(Disorder, Autistic)” or “(Disorders, Autistic)”
2. “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early”
3. “ Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autism Spectrum” or “Autistic Disorder” or “Autism Spectrum Disorder” or “Disorder, Autism” OR “Disorders, Autism”
4. "Child Development Disorders, Pervasive"
5. “Asperger Syndrome”
6. “Kanner's Syndrome” or “Kanner Syndrome” or “Kanners Syndrome”
7. “ Autism, Infantile” or “Infantile Autism” or Autism or “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early” or “Autism Spectrum Disorders”
8. “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum”
9. “Pervasive Child Development Disorders” or “Pervasive Development Disorders”
10. "Syndrome, Asperger" or “Asperger's Disease” or “Asperger's Diseases” or “Aspergers Disease” or “Disease, Asperger's” OR “Diseases, Asperger's” or “Asperger Disease” or “Asperger Diseases” or “Disease, Asperger” or “Diseases, Asperger” or “Asperger Disorder” or “Asperger Disorders” or “Disorder, Asperger” or “Disorders, Asperger” or “Asperger's Disorder” or “Aspergers Disorder” or “Disorder, Asperger’s” or “Disorders, Asperger” or “Asperger's Syndrome” or “Aspergers Syndrome” or “Syndrome, Asperger’s”
11. or/1-10
12. “Tranquilizing Agents, Major” or “Major Tranquilizing Agents” or “Major Tranquilizer” or “Tranquilizer, Major”
13. “Antipsychotic Drug” or “Drug, Antipsychotic” or “Antipsychotic Agent” OR “Agent, Antipsychotic”
14. “Antipsychotic Medication” or “Medication, Antipsychotic”
15. “Neuroleptic Agent” or “Agent, Neuroleptic” or “Neuroleptic Drug” or “Drug, Neuroleptic” or Neuroleptic or Antipsychotic
16. “Antipsychotic Drugs” or Antipsychotics or “Major Tranquilizers” or “Neuroleptic Agents” or “Neuroleptic Drugs” or Neuroleptics or “Tranquilizing Agents, Major” or “Major Tranquilizing Agents”
17. “Antipsychotic Effect” or “Effect, Antipsychotic” or “Antipsychotic Effects” or “Antipsychotic Agents”
18. “Dopamine Antagonists” or “Antagonists, Dopamine” or “Antagonists, Dopaminergic” or Dopamine Receptor” or “Antagonists, Dopaminergic” or Dopamine Blockers” or Blockers, Dopamine” or “Dopamine Receptor Antagonists” or “Receptor Antagonists, Dopamine” or “Dopamine Blocker” or “Blocker, Dopamine” or “Dopamine Receptor Antagonist” or “Antagonist, Dopamine” or “Dopaminergic Antagonists” or “Dopamine Antagonist” or “Antagonist, Dopamine”
19. aripипrazole
Database EMBASE <April, 2022> Results: 2683. Search strategy

1. 'autistic disorder'/exp or 'autistic disorder' or 'autism spectrum disorder'/exp or 'autism spectrum disorder'
2. 'child development disorders, pervasive'/exp or 'child development disorders, pervasive'
3. 'asperger syndrome'/exp or 'asperger syndrome' or 'disorder, autistic' or 'disorders, autistic'
4. 'syndrome, asperger' or 'aspergers diseases' or 'aspergers disease' or 'disease, aspergers' or 'diseases, aspergers' or 'asperger disease' or 'diseases, asperger' or 'diseases, aspergers' or 'asparagus syndrome'/exp or 'asparagus disease' or 'diseases, aspergers' or 'disorder, asparagus' or 'disorders, asparagus'
5. 'kanner syndrome'/exp or 'kanner syndrome' or 'kanners syndrome'
6. 'autism, infantile'/exp or 'autism, infantile' or 'infantile autism'/exp or 'infantile autism' OR 'autism'/exp
7. 'autism, early infantile'/exp or 'autism, early infantile' or 'early infantile autism'/exp OR 'early infantile autism' or 'infantile autism, early' or 'infantile autism, early' or 'autism spectrum disorders'/exp or 'autism spectrum disorders' or 'autistic spectrum disorder'/exp or 'autistic spectrum disorder' or 'autistic spectrum disorders' or 'disorder, autistic spectrum'
8. 'pervasive child development disorders'/exp or 'pervasive child development disorders' or 'pervasive development disorders'
9. or/1-8
10. 'tranquillizing agents, major' or 'major tranquillizing agents' or 'major tranquilizer' or 'tranquilizer, major'
11. 'antipsychotic drug' or 'drug, antipsychotic' or 'antipsychotic agent' or 'agent, antipsychotic' or 'antipsychotic medication' or 'medication, antipsychotic'
12. 'neuroleptic agent' or 'agent, neuroleptic' or 'neuroleptic drug' or 'drug, neuroleptic' or neuroleptic
13. antipsychotic or 'antipsychotic drugs' or antipsychotics or 'major tranquilizers'
14. 'neuroleptic agents' or 'neuroleptic drugs' or neuroleptics
15. 'tranquilizing agents, major' or 'major tranquilizing agents'
16. 'antipsychotic effect' or 'effect, antipsychotic' or 'antipsychotic effects' or 'antipsychotic agents'
17. 'dopamine antagonists' or 'antagonists, dopamine' or 'antagonists, dopamine receptor' or 'antagonists, dopaminergic' or 'dopamine blockers' or 'blockers, dopamine' or 'dopamine receptor antagonists' or 'receptor antagonists, dopamine' or 'dopamine blocker' or 'blocker, dopamine' or 'dopamine receptor antagonist' or 'antagonist, dopamine receptor' or 'receptor antagonist, dopamine' or 'dopaminergic antagonist' or 'antagonist, dopaminergic' or 'dopaminergic antagonists' or 'dopamine antagonist' or 'antagonist, dopamine'
18. aripiprazole
19. clozapine
20. lurasidone
21. quetiapine
22. olanzapine
23. risperidone
24. ziprasidone
25. paliperidone
26. brexiprazole
27. asenapine
28. cariprazine
29. iloperidone
30. Lumateperone
31. pimavanserine
32. or/10-31
33. 9 AND 32

Database CINAHL <April, 2022> Results: 1800. Search strategy
1. “Autistic Disorder” or “(Disorder, Autistic)” or “(Disorders, Autistic)"
2. “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early"
3. “Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autism Spectrum” or “Autistic Disorder” or “Autism Spectrum Disorder” or “Disorder, Autistic” OR “Disorders, Autistic”
4. “Child Development Disorders, Pervasive”
5. “Asperger Syndrome”
6. “Kanner's Syndrome” or “Kanner Syndrome” or “Kanners Syndrome”
7. “Autism, Infantile” or “Infantile Autism” or Autism or “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early” or “Autism Spectrum Disorders”
8. “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum”
9. “Pervasive Child Development Disorders” or “Pervasive Development Disorders”
10. “Syndrome, Asperger” or “Asperger's Disease” or “Asperger's Diseases” or “Aspergers Disease” or “Disease, Asperger's” OR “Diseases, Asperger's” or “Asperger Disease” or “Asperger Diseases” or “Disease, Asperger” or “Diseases, Asperger” or “Asperger Disorder” or “Asperger Disorders” or “Disorder, Asperger” or “Disorders, Asperger” or “Asperger's Disorder” or “Aspergers Disorder” or “Disorder, Asperger's” or “Asperger's Syndrome” or “Aspergers Syndrome” or “Syndrome, Asperger's”
11. or/1-10
12. “Tranquillizing Agents, Major” or “Major Tranquillizing Agents” or “Major Tranquilizer” or “Tranquilizer, Major”
13. “Antipsychotic Drug” or “Drug, Antipsychotic” or “Antipsychotic Agent” OR “Agent, Antipsychotic”
14. “Antipsychotic Medication” or “Medication, Antipsychotic”
15. “Neuroleptic Agent” or “Agent, Neuroleptic” or “Neuroleptic Drug” or “Drug, Neuroleptic” or Neuroleptic or Antipsychotic
16. “Antipsychotic Drugs” or Antipsychotics or “Major Tranquilizers” or “Neuroleptic Agents” or “Neuroleptic Drugs” or Neuroleptics or “Tranquilizing Agents, Major” or “Major Tranquilizing Agents”
17. “Antipsychotic Effect” or “Effect, Antipsychotic” or “Antipsychotic Effects” or “Antipsychotic Agents”
18. “Dopamine Antagonists” or “Antagonists, Dopamine” or “Antagonists, Dopaminergic” or “Dopamine Receptor” or “Antagonists, Dopaminergic” or “Dopamine Blockers” or “Blockers, Dopamine” or “Dopamine Receptor Antagonists” or “Receptor Antagonists, Dopamine” or “Dopamine Blocker” or “Blocker, Dopamine” or “Dopamine Receptor Antagonist” or “Antagonist, Dopamine” or “Dopaminergic Antagonist” or “Antagonist, Dopaminergic” or “Dopaminergic Antagonists” or “Dopamine Antagonist” or “Antagonist, Dopamine”
19. aripiprazole
20. clozapine
21. lurasidone
22. quetiapine
23. olanzapine
24. risperidone
25. ziprasidone
26. paliperidone
27. brexiprazole
28. asenapine
29. cariprazine
30. iloperidone
31. Lumateperone
32. pimavanserine
33. or/12-32
34. 11 AND 33

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Database PSYCINFO <April, 2022> Results: 1898. search strategy

1. “Autistic Disorder” or “(Disorder, Autistic)” or “(Disorders, Autistic)”
2. “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early”
3. “Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum” or “Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Disorder, Autistic” OR “Disorders, Autistic”
4. “Child Development Disorders, Pervasive”
5. “Asperger Syndrome”
6. “Kanner's Syndrome” or “Kanner Syndrome” or “Kanners Syndrome”
7. “Autism, Infantile” or “Infantile Autism” or Autism or “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early” or “Autism Spectrum Disorders”
8. “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum”
9. “Pervasive Child Development Disorders” or “Pervasive Development Disorders”
10. “Syndrome, Asperger” or “Asperger's Disease” or “Asperger's Diseases” or “Aspergers Disease” or “Disease, Asperger's” OR “Diseases, Asperger's” or “Asperger Disease” or “Asperger Diseases” or “Disease, Asperger” or “Diseases, Asperger” or “Asperger Disorder” or “Asperger Disorders” or “Disorder, Asperger” or “Disorders, Asperger” or “Asperger's Disorder” or “Aspergers Disorder” or “Disorder, Asperger's” or “Asperger's Syndrome” or “Aspergers Syndrome” or “Syndrome, Asperger's”
11. or/1-10
12. “Tranquillizing Agents, Major” or “Major Tranquillizing Agents” or “Major Tranquilizer” or “Tranquilizer, Major”
13. “Antipsychotic Drug” or “Drug, Antipsychotic” or “Antipsychotic Agent” OR  
   “Agent, Antipsychotic”  
14. “Antipsychotic Medication” or “Medication, Antipsychotic”  
15. “Neuroleptic Agent” or “Agent, Neuroleptic” or “Neuroleptic Drug” or  
   “Drug, Neuroleptic” or Neuroleptic or Antipsychotic  
16. “Antipsychotic Drugs” or Antipsychotics or “Major Tranquilizers” or  
   “Neuroleptic Agents” or “Neuroleptic Drugs” or Neuroleptics or  
   “Tranquilizing Agents, Major” or “Major Tranquilizing Agents”  
17. “Antipsychotic Effect” or “Effect, Antipsychotic” or “Antipsychotic Effects”  
   or “Antipsychotic Agents”  
18. “Dopamine Antagonists” or “Antagonists, Dopamine” or “Antagonists,  
   Dopamine Receptor” or “Antagonists, Dopaminergic” or “Dopamine  
   Blockers” or “Blockers, Dopamine” or “Dopamine Receptor Antagonists”  
   or “Receptor Antagonists, Dopamine” or “Dopamine Blocker” or “Blocker,  
   Dopamine” or “Dopamine Receptor Antagonist” or “Antagonist,  
   Dopamine Receptor” or “Receptor Antagonist, Dopamine” or  
   “Dopaminergic Antagonist” or “Antagonist, Dopaminergic” or  
   “Dopaminergic Antagonists” or “Dopamine Antagonist” or “Antagonist,  
   Dopamine”  
19. aripiprazole  
20. clozapine  
21. lurasidone  
22. quetiapine  
23. olanzapine  
24. risperidone  
25. ziprasidone  
26. paliperidone  
27. brexiprazole  
28. asenapine  
29. cariprazine  
30. iloperidone  
31. Lumateperone  
32. pimavanserine  
33. or/12-32  
34. 11 AND 33  

Database Cochrane <April, 2022> Results: 459. Search strategy  

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1. Autism or “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile  
   Autism, Early”  
2. “Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Autistic  
   Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder,  
   Autistic Spectrum” or “Autistic Disorder” or "Autism Spectrum Disorder"  
3. or/1-2  

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4. aripiprazole
5. clozapine
6. lurasidone
7. quetiapine
8. olanzapine
9. risperidone
10. ziprasidone
11. paliperidone
12. brexiprazole
13. asenapine
14. cariprazine
15. iloperidone
16. Lumateperone
17. pimavanserine
18. “Antipsychotic Drug” or “Drug, Antipsychotic”
19. “Antipsychotic Agent” or “Agent, Antipsychotic”
20. “Antipsychotic Medication” OR “Medication, Antipsychotic”
21. or/4-20
22. 3 AND 21

Database EPISTEMONIKOS <April, 2022> Results: 800. Estratégia de busca

1. Autism or “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early”
2. “Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum” or “Autistic Disorder” or "Autism Spectrum Disorder"
3. or/1-2
4. Risperidone
5. aripiprazole
6. clozapine
7. lurasidone
8. quetiapine
9. olanzapine
10. risperidone
11. ziprasidone
12. paliperidone
13. brexiprazole
14. asenapine
15. cariprazine
16. iloperidone
17. Lumateperone
18. pimavanserine
19. “Antipsychotic Drug” or “Drug, Antipsychotic”
20. “Antipsychotic Agent” or “Agent, Antipsychotic”
21. “Antipsychotic Medication” OR “Medication, Antipsychotic”
22. or/4-21
23. 3 AND 22

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CLINICAL TRIALS <April, 2022> Results: 192. Search strategy

1. Autism
2. Antipsychotic
3. 1 AND 2

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WHO International Clinical Trials Registry Platform <April, 2022> Results: 126. Search strategy

1. Autism
2. Antipsychotic
3. 1 AND 2

***************************************

EU Clinical Trials Register <April, 2022> Results: 100. Search strategy

1. Autism
2. Antipsychotic
3. 1 AND 2

***************************************

Portal CAPES (Teses e Dissertações) <April, 2022>. Results: 619. Search strategy

1. Autismo
2. Antipsicótico
3. 1 AND 2
4. Filtro: Ciências da Saúde

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ProQuest <April, 2022>. Results: 80. Search strategy
1. Autism
2. Antipsychotic
3. 1 AND 2
SUPPLEMENTARY MATERIAL 3 - Journals and Conference

- International Congress on Psychopharmacology;
- Annual Meeting of the American Academy of Child & Adolescent Psychiatry;
- European Congress of Psychiatry;
- European College of Neuropsychopharmacology Congress;
- International Congress on Psychopharmacology and International Symposium on Child and Adolescent Psychopharmacology;
- International Congress of European Society for Child and Adolescent Psychiatry;
- World Congress of the International Association for Child and Adolescent Psychiatry and Allied Professions;
- International Conference on Pharmacoepidemiology and Therapeutic Risk;
- World Congress of the International Association for the Scientific Study of Intellectual and Developmental Disabilities;
- Annual Meeting of the College of Psychiatric and Neurologic Pharmacists;
- Annual Conference of the American College of Neuropsychopharmacology;
- Annual National Institute of Mental Health;
- Annual Meeting of the International College of Spectrum Disorders.
# Use of second-generation antipsychotics in Autism Spectrum Disorder: a systematic review and meta-analysis protocol

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Use of second-generation antipsychotics in Autism Spectrum Disorder: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction: Atypical antipsychotics have been studied to treat Autism Spectrum Disorder (ASD). However, like little is known about whether these drugs are effective and safe when compared in controlled and non-controlled settings. This study aims to assess the efficacy and safety of second-generation antipsychotics in ASD in randomized controlled trials (RCT) and observational studies.

Methods and Analysis: This Systematic Review will include RCT and prospective cohorts evaluating second-generation antipsychotics in people five years and older diagnosed with ASD. Searches will be conducted in Medline, Embase, Cochrane Library, Epistemonikos, Lilacs, CINAHL, PsycINFO, trial registries, and grey literature databases without restriction on publication status, year of publication, and language. The primary outcomes will be symptoms of aggressive behavior, quality of life for the individual or their careers, and discontinuation or dropouts/withdrawals of antipsychotics due to adverse events. The secondary outcomes are other not serious adverse events and adherence to pharmacotherapy. Selection, data extraction, and quality assessment will be performed by pairs of reviewers, independently. The Risk of Bias 2 (RoB 2) and Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tools will be used to assess the risk of bias in the included studies. If appropriate, a meta-analysis and network meta-analysis will be conducted to synthesize the results. The overall quality of the evidence for each outcome will be determined by the Recommendation, Assessment, Development, and Evaluation (GRADE) approach.

Ethics and dissemination: This study will systematically summarize the existing evidence evaluating the use of second-generation antipsychotics for treating ASD, in controlled and uncontrolled studies. The results of this review will be disseminated through peer-reviewed publications and conference presentations.

Protocol Registration: PROSPERO – CRD42022353795

Keywords: Autism Spectrum Disorder. Antipsychotic Agents. Real-World Evidence. Systematic Review.
STRENGTHS AND LIMITATIONS OF THIS STUDY

- The search will be performed with the help of a specialized librarian experienced in medical literature searching;
- This systematic review will include stakeholders from refining the question to discussing and implementing the findings.
- Our systematic review proposal may have limitations inherent to the methodological quality of the included studies, especially non-randomized studies, which will be discussed.
- Some important outcomes such as quality of life and adherence to pharmacotherapy may not have been assessed in primary studies.
INTRODUCTION

Autism Spectrum Disorder (ASD), or simply autism, is a unique clinical condition with different levels of severity, characterized by two main symptom domains: 1) deficits in social communication and social interaction and 2) restricted repetitive behaviors (RRBs), interests and activities and sensory anomalies[1].

Estimates of the prevalence of ASD vary. About 52 million people live with ASD worldwide [2]. Studies indicate approximately 1% to 2% of children in the US and other developed countries [3,4,2,5]. A systematic review of prevalence studies of ASD identified an overall estimate of the prevalence of 7.1 per 10,000 for autism and 20 per 10,000 for all ASD [6]. Another systematic review found that the average worldwide prevalence of ASD was 17 per 100,000, with a range of 2.8 to 94 per 100,000 across all age groups [7]. Hispanic and African-American children are underdiagnosed compared to non-Hispanic white children [6]. People with higher socioeconomic status and better access to health care are diagnosed earlier [7].

ASD is considered a brain-based neurodevelopmental disorder that lasts for life [8]. The three characteristic manifestations of ASD are impaired social interaction, impaired communication, and restricted repetitive and stereotyped patterns of behavior [9]. Interfering behavior has a great impact on the quality of life of individuals with ASD, family members, and the people they live with [10,11]. Interfering behaviors may include irritability, aggression, and self-harm [12]. These symptoms are the main causes of psychiatric hospitalization, and the use of antipsychotics is recommended in the absence of effectiveness of behavioral interventions [13,14,15].

Despite the claims of curative interventions, there is no specific treatment for autism and therapies target the symptoms of the disease. Pharmacological interventions have been used as additional to behavioral treatments in both children and adults and may reduce specific autistic symptoms and behaviors such as self-injury and aggression [15]. There is evidence of widespread prescribing of psychotropic drugs to people with ASD [16]. Antipsychotic drugs
generally tranquilize and relieve psychotic symptoms without impairing consciousness [15]. Second-generation antipsychotics tend to cause fewer unwanted motor adverse effects than typical ones [17].

Typical (first-generation) and atypical (second-generation) antipsychotics have been evaluated for the treatment of behavioral symptoms in individuals with ASD. It is well established in the literature that first-generation antipsychotics are not recommended for treating symptoms in ASD due to their adverse effects. First-generation antipsychotics have been associated with drug-induced movement disorders [15]. Haloperidol, for example, has been evaluated for the treatment of ASD in several trials and has been associated with improvements in withdrawal and stereotypies [18] and positive effects on learning. However, it has also been related to extrapyramidal side effects such as acute dystonic reactions, withdrawal dyskinesias, and tardive dyskinesia in this population [19].

Randomized controlled trials (RCTs) have suggested the efficacy of second-generation antipsychotics to ameliorate some interfering symptoms of ASD in children and adolescents [20]. A systematic review investigated the use of risperidone for ASD and demonstrated the efficacy of this drug in treating symptoms of aggression, irritability, and repetitive behavior. Notable adverse events, including weight gain, increased appetite, and sedation, were described [21].

In addition, evidence from two RCTs suggests that aripiprazole can be effective as a short-term medication for some behavioral aspects of ASD in children/adolescents [22–24]. Participants included in both RCTs who received aripiprazole had reduced significantly irritability when compared to the placebo groups. Nevertheless, weight gain, sedation, drooling, and tremors occurrence must also be considered [25]. Another systematic review [17] found that antipsychotics (aripiprazole, clozapine, haloperidol, levosulpiride, lurasidone, olanzapine, risperidone, trifluoperazine) for children and adolescents with ASD were more efficacious than placebo in reducing stereotypies, hyperactivity, irritability and obsessions, compulsions, and increasing social communication and global functioning.
Systematic reviews published evaluating the use of antipsychotics presented important methodological limitations. An overview of systematic reviews on aripiprazole and risperidone found 16 systematic reviews of critically low methodological quality [26]. Published Cochrane systematic reviews have only evaluated the pediatric population and have not included all second-generation antipsychotics [21,25].

This systematic review will evaluate the performance of second-generation antipsychotics in the treatment of ASD in controlled and non-controlled settings.

METHODS AND ANALYSIS

Study design, protocol, and registration

This systematic review (SR) will be performed according to the recommendations of the Cochrane Handbook for Intervention Reviews [27]. This protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [28] (Supplementary Material 1), and registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under registration nº. CRD42022353795

Patient and public involvement

Stakeholders were involved in the development and refinement of the research question. We involved decision-makers from the Brazilian Ministry of Health, primary care physicians, psychiatrists, and key stakeholders.

When the systematic review is completed, the results will be discussed in a dissemination workshop with the same stakeholders. We will involve users in classifying outcomes' importance and interpretation of evidence [29]. We will summarize the evidence in plain language.

Eligibility criteria
The research question was structured using the Population, Intervention, Comparison, and Outcomes (PICO) structure.

**Types of participants**

Participants regardless of age group diagnosed with ASD using a standardized diagnostic tool or established diagnostic criteria from DSM-4 or DSM-5.

Studies involving other mental disorders will be included as long as the results are separate or at least 80% of the population has a confirmed diagnosis of ASD.

**Type of interventions**

Second-generation antipsychotics (amisulpride, aripiprazole, asenapine, brexiprazole, cariprazine, clozapine, iloperidone, lumateperone, lurasidone, olanzapine, paliperidone, pimavanserine, quetiapine, risperidone, sulpiride, ziprasidone), without restriction as to dose, route of administration, frequency or duration of treatment.

**Types of comparators**

1. Second-generation antipsychotics other than intervention;
2. Placebo.

**Types of outcome measures**

We will include studies regardless of the scales used to measure outcomes.

**Primary outcomes**

1. Number of participants with aggressive behavior and degree of aggressiveness (agitation; irritability; and self-aggression), measured using validated scales reported by the patient, physician or parents;
2. Quality of life for the individual and/or their caregivers;
3. Number of participants who had Discontinuation or dropouts/withdrawals of antipsychotics due to adverse events.

**Secondary outcomes**

1. Number of participants with Adverse events of interest according to the Guideline on the clinical development of medicinal products for the treatment of ASD [30]:
   - Central Nervous System adverse events;
   - Endocrinological adverse events;
   - Other adverse events, for example, somnolence, insomnia, headache, rash and constipation.

2. Adherence to pharmacotherapy measured by validated scales, or reported by the patient, physician and parents.

**Types of studies**

We will include RCTs and pragmatic trials irrespective status of publication (online clinical trials results, summaries of unpublished clinical trials, abstracts, reports from pharmaceutical companies, since that they contain sufficient data for analysis), year of publication and language. Observational studies (cohorts) will be included additionally, only if they are prospective and have a comparator arm for the intervention of interest.

The RCTs will be included because they are the best study designs for evaluating the effectiveness of health interventions and cohorts will be considered especially for safety outcomes as they generally have a longer follow-up. We will not impose any limitation regarding the length of follow-up.

We will exclude non-randomized studies such databases with data from claims or medical records, cases series, retrospective cohorts, case-control, control before and after, and times series.

**Search methods for identification of studies**

The search strategy will use DeCS/MeSH descriptors and synonyms, being adapted according to each database searched (Supplementary Material...
2). The searches will be conducted by an experienced librarian and will be reviewed by another professional librarian, according to the Peer Review of Electronic Search Strategies (PRESS) [31].

**Electronic searches**

A structured search for eligible primary studies will be conducted in the main electronic databases: MEDLINE via PubMed, Embase via Elsevier, Cochrane Central Register of Controlled Trials (Central), Epistemonikos, Latin American and Caribbean Health Sciences Literature (Lilacs) via Virtual Health Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and PsycINFO.

**Searching other resources**

1. Grey literature

We will adapt a specific structured search strategy for the grey literature, including: ProQuest Dissertations and Theses [https://about.proquest.com/en/products-services/pqdtglobal/], Portal Capes [https://catalogodeteses.capes.gov.br/catalogo-teses/#t/], and Open Grey [https://opengrey.eu/].

2. Trial registries:

Clinical Trials: [www.ClinicalTrials.gov]; International Clinical Trials Platform: [www.who.int/ictrp]; Registry Platform Current Controlled Trials: [www.isrctn.com]; EU Clinical Trials Register: [www.clinicaltrialsregister.eu] and Brazilian Registry of Clinical Trials: [www.ensaiosclinicos.gov.br/]

3. Hand searches

Appropriate journals and conference proceedings (Supplementary Material 3) relating to second-generation antipsychotic treatment for ASD will be hand searches and incorporated.

4. Personal communication
Pharmaceutical companies and experts in the fields will be asked if they knew of any studies that met the inclusion criteria of this review.

5. Reference checking

Reference lists of the included studies, previous systematic reviews, systematic scoping reviews, and narrative reviews of ASD will be checked for published reports and citations of unpublished research.

6. Automatic alerts

We set automatic alerts in each database to receive notifications of published new studies. We monitored the medical literature and kept the review as current as possible.

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved through an electronic database search to a reference management database <https://www.covidence.org/> and remove duplicates. Pairs of reviewers will independently screen titles and abstracts for inclusion. We will retrieve the full text of potentially relevant references, and pairs of reviewer’s authors will independently assess the full-text articles for inclusion. We will record reasons for exclusion from studies following the full-text review. Any disagreements will be resolved through discussion or, if required, by consulting a third review author.

As described in detail previously [32], for the two selection stages, the reviewers will carry out a pilot exercise for consensus on the eligibility criteria.

Data extraction and management

As described in detail previously A pre-piloted and standardized form will be used to extract data from the included studies [32]. The reviewers will be calibrated by extracting at least three articles, in pairs and independently, and, afterward, they will carry out a consensus. This process will take place until the standardization of the extracted data. The overlap of two articles in all teams of reviewers will be adopted to assess the reliability between reviewers in extracting data in the different teams.
After this stage, two reviewers will extract the data independently, and any discrepancies will be identified and resolved with a third author, when necessary.

The data collected will be a) bibliometric information (year of study publication, authors, title); b) characteristics of studies (funding, follow-up time, design: randomized or non-randomized, scales used; clinical setting: hospitals, specialty clinics, primary care, research centers; countries, country, registered number, number of sites, duration of the study, the timing of outcome measurement: weeks or months, numbers of participants in each arm); c) characteristics of patients (inclusion and exclusion criteria, age, antipsychotics: naive vs experienced, psychiatric comorbidities, other treatments, drug regimen, route and frequency of medication administration and adverse events); d) outcome (total number of participants in each arm, the total number of participants who presented the outcome, name of the scale used to measure the outcome, numerical value to measure the outcome - mean, median, standard deviation - and time point used). We will extract data comprehensively to cover all relevant outcomes and methods reported across studies.

Where key data are missing from the study reports, we will attempt to contact the authors to obtain such information [33]. Where multiple reports of the same trial are published, we will extract data from those we deem to be most complete.

Assessment of methodological quality of individual studies

The quality of RCTs will be assessed using Cochrane’s Risk of Bias (RoB) tool version 2.0 for randomized trials on bias arising from the randomization process, deviations from intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result [34].

The quality of observational studies will be assessed using Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool on bias arising from the confounding, selection bias, information bias and reporting bias [35].

Two reviewers will assess the risk of bias. Reviewers will resolve disagreements through discussion, and a third person will judge unresolved disagreements.
Statistical analysis

Measures of treatment effect

We will use the standardized mean difference (SMD) to summarise continuous outcomes and the odds ratio (OR) to summarise binary outcomes. We will use results based on the intention-to-treat analysis (ITT) whenever available.

We will convert standardized mean differences to log-odds ratios (or vice-versa) using established methods when necessary. Depending on the data availability, we will convert sample sizes, means and standard deviations directly to 2x2 tables – under the assumption of an approximately normal distribution and a cutoff. The thresholds that separate the continuous outcome into two categories (e.g., event and non-event) will be defined by current guidelines and an expert group of psychiatrists and clinical pharmacologists.

Missing data

We will employ standard techniques to back-calculate the necessary statistics from reported confidence intervals, standard errors, z, t or P values. We will use approximate Bayesian computation models to derive the necessary information for meta-analysis when reported data are more complex [36] (e.g., median and interquartile range, continuous variables divided into mutually exclusive groups based on cutoffs). We will extract data from figures if data are reported graphically.

Pair-wise meta-analysis

We will use fully Bayesian random-effects models. Throughout our analyses, we will use only random-effects models. The choice of a random-effects model is based on the anticipated clinical and methodological heterogeneity across studies [37].

We will use the binomial likelihood for binary outcomes and model the log odds ratio. If results in primary studies are available as odds ratios (95% confidence interval), we will model binary outcomes using the normal likelihood.
We will use the normal likelihood and the identity link for continuous outcomes.
As suggested, statistical heterogeneity will be interpreted based on the between-
study variance ($\tau^2$) [38,39].

**Network meta-analysis**

We will use the generalized linear model framework (the "NICE" model)
described previously [40]. If feasible, we will use the arm-based approach. The
model preserves randomization, assumes consistency and allows for multi-arm
trials. However, if necessary, we will employ an adapted model that uses arm-
level and comparison-level data. For binary outcomes, we will use the binomial
likelihood. We will use the normal likelihood and the identity link for continuous
outcomes [41].

To evaluate the plausibility of the transitivity assumption, we will
investigate the distribution of presumed effect modifiers across treatment
comparisons. The list of potential effect modifiers will be defined by listing all
covariates investigated at the baseline. This list will be evaluated by a
multidisciplinary panel of practicing psychiatrists and clinical pharmacologists,
who will rank the importance of each covariate regarding the treatment effect.
Transitivity will be judged based on the five most relevant potential effect
modifiers.

We will compare the fit of the consistency model to the fit of a random-
effects model that relaxes the consistency assumption ("inconsistency model").
Models will be compared via the posterior mean of the residual deviance and the
deviance information criterion (DIC), with lower DIC values indicating a better
model fit [41]. If appropriate, we will fit the node split model and compare direct,
indirect, and network estimates for all treatments [42, 40].

We will present summary treatment effect estimates and between-trial
variance derived from the median and 95% credibility intervals (CrIs) from the
2.5th and 97.5th percentile of the posterior distribution. Treatment rankings (with
95% CrI) and the probability that each treatment is the best will be calculated
from the posterior distributions.
Meta-regression models

If pertinent, we will examine the association between the magnitude of treatment effects and study-level characteristics, via random-effects Bayesian meta-regression models. We will not employ average patient-level characteristics to avoid ecological fallacy [43].

Priors

We will assume non-informative, but biologically plausible priors for treatment effects for all models and between-study variances. However, in sensitivity analyses, we will also use informative priors for the between-study variances [43,44].

Funnel plot asymmetry and small-study bias in pair-wise meta-analysis

Whenever feasible (i.e., ten or more estimates), we will investigate funnel plot asymmetry using graphical and statistical approaches. For pair-wise meta-analyses, we will employ contour-enhanced plots and generate Doi plots [45]. We will calculate the LFK [46] index and conduct Egger’s linear regression test or Peter’s test.

Funnel plot asymmetry and small-study bias in network meta-analysis

For network meta-analysis, we will create a comparison-adjusted funnel plot, as suggested by Chaimani et al. We will also use the recently proposed Risk of Bias due to Missing Evidence in Network meta-analysis (ROB-MEN) approach [47].

Implementation

All Bayesian models will be implemented in MultiBUGS 2.0 (Cambridge, UK), and estimates will be obtained via Markov chain Monte Carlo methods [48]. Models will be fitted with three chains (166667 simulations each), totalizing 500,000 iterations. The burn-in period will be 100,000 simulations. Convergence will be checked graphically by running three chains and using the Gelman-Rubin
statistic, R. We will check autocorrelation and density of the posterior estimates graphically in Stata 16 (College Station, TX, USA).

**Subgroup analysis and investigation of heterogeneity**

If appropriate, we will perform subgroup analyses or meta-regression to investigate differences among two or more subgroups according to each of the following characteristics of participants, which might have an effect on the outcomes: type of clinical conditions: Infantile autism (F84.0); Atypical autism (F84.1); Other childhood disintegrative disorder (F84.3); Asperger's Syndrome (F84.5); and Other pervasive developmental disorders (F84.8); participants’ mean age; types of scales used to measure outcomes; duration of follow-up; sex; dose of antipsychotics; presence of comorbidities.

If additional analyses cannot be conducted by RevMan 5, we will perform analyses in Stata Statistical Software (Stata 2015).

**Sensitivity analysis**

We will perform sensitivity analyses of outcomes to assess the robustness of the findings. If feasible, we will restrict the analysis of outcomes to studies of low risk of bias, impute missing data considering worst-case scenario, and effects of fixed-effect or random-effects methods [49].

**Summary of findings and assessment of the certainty of the evidence**

After the results have been grouped, two reviewers will independently assess the overall certainty of the evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [50]. The main results of the review will be presented in outcome tables (Summary of Findings - SoF), as recommended by The Cochrane Collaboration [51]. This table will be built with the aid of the GRADEpro software program [50].

**ETHICS AND DISSEMINATION**
Since it is a literature-based study, ethical approval is not required. The results will be shared through publication in scientific journals of high impact, peer reviewed and also published in national and international conferences.

DISCUSSION

The results could inform decision-making processes in the use of antipsychotics for the treatment of ASD. The evidence systematized in this study may contribute to improvements in health care based on the best evidence on the use of antipsychotics in the treatment of ASD. Our future results may impact public policy for ASD patients, healthcare professionals, and decision-makers by providing evidence that can highlight challenges and areas for improvement, with a special look at pharmacological interventions in ASD.

The analysis of evidence from observational studies can improve the understanding of the use of antipsychotics in the treatment of ASD and support more assertive decisions about the actual performance of these interventions.

This is the first systematic review with a robust proposal for controlled and non-controlled settings involving the use of second-generation antipsychotics in ASD. Nevertheless, there are potential limitations. Primary studies may bring limitations to this review considering the confounders present in observational studies; meta-analyses may be hampered by a lack of standardization in the measurement of efficacy outcomes and diagnostic criteria for ASD.

The methodological rigor and data analysis plan proposed in this review will provide transparency to the evidence found and may demonstrate the degree of confidence in the estimates found. To refine the construction of the final protocol of this systematic review, we are proposing the involvement of stakeholders such as patient representatives, decision-makers, and health professionals who work in the treatment of ASD. Upon completing the systematic review, the results will be disseminated among healthcare professionals,
patients, and their representatives through a virtual meeting. Stakeholder perspectives will be incorporated into the systematic review.

AUTHOR CONTRIBUTIONS

LPNL is the principal investigator and wrote the protocol and the final version. JCdO, IF, CCB, ECL, FCA, LGM, and MFF reviewed and edited the manuscript. LCL is the review guarantor, advised on background, helped to write the protocol, and revised the manuscript.

ACKNOWLEDGEMENTS

The authors would like to thank Thaiane de Lima Alexandre and Ana Carolina de Freitas Lopes for their contributions to the research questions and to the choice of drugs to be included, and to Ph.D. Tiago Veiga Pereira for his contribution to the statistical analyses.

FUNDING

This research received funding from the Ministry of Health of Brazil (MoH) and National Council for Scientific and Technological Development (CNPq), nº 423543/2021-0. Furthermore, this project was funded by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)—PROSUC—CAPES/UNISO. Grant number not applicable.

COMPETING INTERESTS

None to declare.

WORD COUNT

3837
REFERENCES


SUPPLEMENTARY MATERIAL 1 - Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist: recommended items to address in a systematic review protocol*

<table>
<thead>
<tr>
<th>Section and topic</th>
<th>Item No</th>
<th>Checklist item</th>
<th>Page No</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADMINISTRATIVE INFORMATION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title: Identification</td>
<td>1a</td>
<td>Identify the report as a protocol of a systematic review</td>
<td>1</td>
</tr>
<tr>
<td>Update</td>
<td>1b</td>
<td>If the protocol is for an update of a previous systematic review, identify as such</td>
<td>N/A</td>
</tr>
<tr>
<td>Registration</td>
<td>2</td>
<td>If registered, provide the name of the registry (such as PROSPERO) and registration number</td>
<td>3</td>
</tr>
</tbody>
</table>

| Authors: Contact | 3a      | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1-2     |
| Contributions 3b |        | Describe contributions of protocol authors and identify the guarantor of the review | 17-18   |

| Amendments | 4      | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | N/A     |

| Support: Sources | 5a | Indicate sources of financial or other support for the review | 18 |
| Sponsor 5b |        | Provide name for the review funder and/or sponsor | 18 |
| Role of sponsor or funder 5c |        | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | N/A |

| INTRODUCTION |         |                                                                 |         |
| Rationale | 6      | Describe the rationale for the review in the context of what is already known | 5-7     |
| Objectives | 7      | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 7       |

| METHODS |         |                                                                 |         |
| Eligibility criteria | 8      | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | 7-9     |
| Information sources | 9      | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | 9-11    |

| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | Suppl. Material 2 |

<p>| Study records: Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | 11-12 |</p>
<table>
<thead>
<tr>
<th>Selection process</th>
<th>11b</th>
<th>State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)</th>
<th>11-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data collection process</td>
<td>11c</td>
<td>Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators</td>
<td>11-12</td>
</tr>
<tr>
<td>Data items</td>
<td>12</td>
<td>List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications</td>
<td>11-12</td>
</tr>
<tr>
<td>Outcomes and prioritization</td>
<td>13</td>
<td>List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale</td>
<td>8-9</td>
</tr>
<tr>
<td>Risk of bias in individual studies</td>
<td>14</td>
<td>Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis</td>
<td>12</td>
</tr>
<tr>
<td>Data synthesis</td>
<td>15a</td>
<td>Describe criteria under which study data will be quantitatively synthesised</td>
<td>12-16</td>
</tr>
<tr>
<td></td>
<td>15b</td>
<td>If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I², Kendall’s τ)</td>
<td>12-16</td>
</tr>
<tr>
<td></td>
<td>15c</td>
<td>Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)</td>
<td>12-16</td>
</tr>
<tr>
<td></td>
<td>15d</td>
<td>If quantitative synthesis is not appropriate, describe the type of summary planned</td>
<td>N/A</td>
</tr>
<tr>
<td>Meta-bias(es)</td>
<td>16</td>
<td>Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)</td>
<td>15-16</td>
</tr>
<tr>
<td>Confidence in cumulative evidence</td>
<td>17</td>
<td>Describe how the strength of the body of evidence will be assessed (such as GRADE)</td>
<td>16</td>
</tr>
</tbody>
</table>

*It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

SUPPLEMENTARY MATERIAL 2 – Search strategies

Database Portal da BVS e Lilacs <April, 2022> Results: 548 (Portal da BVS) e 16 (Lilacs). Search Strategy

1. "Transtorno Autístico" or "Autistic Disorder"
2. "Autismo" or "Autism"
3. "Autismo Infantil" or "Child Autism"
4. "Transtorno do Espectro Autista" or "Autism Spectrum Disorder" or "Transtorno do Espectro do Autismo"
5. or/1-4
6. Antipsicóticos
7. "Agente Antipsicótico" or "Antipsychotic Agents"
8. "Agente Neuroléptico" or "Medicamento Neuroléptico" or "Medicamento Antipsicótico"
9. "Agentes Antipsicóticos"
10. "Droga Antipsicótica" or "Drogas Antipsicóticas"
11. "Fármaco Antipsicótico"
12. "Droga Neuroléptica" or "Fármaco Neuroléptico"
13. "Efeito Antipsicótico"
14. "Tranquilizante Maior"
15. “Risperidona” or “Risperidone”
16. Aripiprazol or aripiprazole
17. Clozapina or clozapine
18. Lurasidona or lurasidone
19. Quetiapina or quetiapine
20. Olanzapina or olanzapine
21. Ziprasidona or ziprasidone
22. Paliperidona or paliperidone
23. Brexiprazol or brexiprazole
24. Asenapina or asenapine
25. Cariprazina or cariprazine
26. Iloperidona or iloperidone
27. Lumateperona or lumateperone
28. Pimavanserina or pimavanserine
29. or/6-28
30. 5 AND 29

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Database MEDLINE <April, 2022> Results: 1303. Search Strategy

1. “Autistic Disorder” or “(Disorder, Autistic)” or “(Disorders, Autistic)”
2. “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early”
3. “Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum” or “Autistic Disorder” or “Autism Spectrum Disorder” or “Disorder, Autistic” OR “Disorders, Autistic”
4. “Child Development Disorders, Pervasive”
5. “Asperger Syndrome”
6. “Kanner's Syndrome” or “Kanner Syndrome” or “Kanners Syndrome”
7. “Autism, Infantile” or “Infantile Autism” or Autism or “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early” or “Autism Spectrum Disorders”
8. “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum”
9. “Pervasive Child Development Disorders” or “Pervasive Development Disorders”
10. “Syndrome, Asperger” or “Asperger's Disease” or “Asperger's Diseases” or “Aspersers Disease” or “Disease, Asperger's” OR “Diseases, Asperger's” or “Asperger Disease” or “Asperger Diseases” or “Disease, Asperger” or “Diseases, Asperger” or “Asperger Disorder” or “Asperger Disorders” or “Disorder, Asperger” or “Disorders, Asperger” or “Asperger's Disorder” or “Aspersers Disorder” or “Disorder, Asperger's” or “Asperger's Syndrome” or “Aspersers Syndrome” or “Syndrome, Asperger's”
11. or/1-10
12. “Tranquilizing Agents, Major” or “Major Tranquillizing Agents” or “Major Tranquilizer” or “Tranquilizer, Major”
13. “Antipsychotic Drug” or “Drug, Antipsychotic” or “Antipsychotic Agent” OR “Agent, Antipsychotic”
14. “Antipsychotic Medication” or “Medication, Antipsychotic”
15. “Neuroleptic Agent” or “Agent, Neuroleptic” or “Neuroleptic Drug” or “Drug, Neuroleptic” or Neuroleptic or Antipsychotic
16. “Antipsychotic Drugs” or Antipsychotics or “Major Tranquilizers” or “Neuroleptic Agents” or “Neuroleptic Drugs” or Neuroleptics or “Tranquilizing Agents, Major” or “Major Tranquilizing Agents”
17. “Antipsychotic Effect” or “Effect, Antipsychotic” or “Antipsychotic Effects” or “Antipsychotic Agents”
18. “Dopamine Antagonists” or “Antagonists, Dopamine” or “Antagonists, Dopamine Receptor” or “Antagonists, Dopaminergic” or “Dopamine Blockers” or “Blockers, Dopamine” or “Dopamine Receptor Antagonists” or “Receptor Antagonists, Dopamine” or “Dopamine Blocker” or “Blocker, Dopamine” or “Dopamine Receptor Antagonist” or “Antagonist, Dopamine” or “Receptor Antagonist, Dopamine” or “Dopaminergic Antagonists” or “Dopaminergic Antagonist” or “Antagonist, Dopamine”
19. aripiprazole
20. clozapine
21. lurasidone
22. quetiapine
23. olanzapine
24. risperidone
25. ziprasidone
26. paliperidone
27. brexiprazole
28. asenapine
29. cariprazine
30. iloperidone
31. Lumateperone
32. pimavanserine
33. or/12-32
34. 11 AND 33

Database EMBASE <April, 2022> Results: 2683. Search strategy

1. 'autistic disorder'/exp or 'autistic disorder' or 'autism spectrum disorder'/exp or 'autism spectrum disorder'
2. 'child development disorders, pervasive'/exp or 'child development disorders, pervasive'
3. 'asperger syndrome'/exp or 'asperger syndrome' or 'disorder, autistic' or 'disorders, autistic'
4. 'syndrome, asperger' or 'aspergers diseases' or 'aspergers disease' or 'disease, aspergers' or 'diseases, aspergers' or 'asperger disease' or 'disease, asperger' or 'diseases, asperger' or 'asperger disorder'/exp or 'asperger disorder' or 'asperger disorders' or 'disorder, asperger' or 'disorders, asperger' or 'aspergers disorder'/exp or 'aspergers syndrome'/exp or 'aspergers syndrome' or 'syndrome, aspergers'
5. 'kanner syndrome'/exp or 'kanner syndrome' or 'kanners syndrome'
6. 'autism, infantile'/exp or 'autism, infantile' or 'infantile autism'/exp or 'infantile autism' OR 'autism'/exp
7. 'autism, early infantile'/exp or 'autism, early infantile' or 'early infantile autism'/exp OR 'early infantile autism' or 'infantile autism, early' or 'autism spectrum disorders'/exp or 'autism spectrum disorders' or 'autistic spectrum disorder'/exp or 'autistic spectrum disorder' or 'autistic spectrum disorders' or 'disorder, autistic spectrum'
8. 'pervasive child development disorders'/exp or 'pervasive child development disorders' or 'pervasive development disorders'
9. or/1-8
10. ‘tranquillizing agents, major’ or ‘major tranquilizing agents’ or ‘major tranquilizer’ or ‘tranquilizer, major’
11. ‘antipsychotic drug’ or ‘drug, antipsychotic’ or ‘antipsychotic agent’ or ‘agent, antipsychotic’ or ‘antipsychotic medication’ or ‘medication, antipsychotic’
12. ‘neuroleptic agent’ or ‘agent, neuroleptic’ or ‘neuroleptic drug’ or ‘drug, neuroleptic’ or ‘neuroleptic’
13. antipsychotic or ‘antipsychotic drugs’ or antipsychotics or ‘major tranquilizers’
14. ‘neuroleptic agents’ or ‘neuroleptic drugs’ or neuroleptics
15. ‘tranquilizing agents, major’ or ‘major tranquilizing agents’
16. ‘antipsychotic effect’ or ‘effect, antipsychotic’ or ‘antipsychotic effects’ or ‘antipsychotic agents’
17. ‘dopamine antagonists’ or ‘antagonists, dopamine’ or ‘antagonists, dopamine receptor’ or ‘antagonists, dopaminergic’ or ‘dopamine blockers’ or ‘blockers, dopamine’ or ‘dopamine receptor antagonists’ or ‘receptor antagonists, dopamine’ or ‘dopamine blocker’ or ‘blocker, dopamine’ or ‘dopamine receptor antagonist’ or ‘antagonist, dopamine receptor’ or ‘receptor antagonist, dopamine’ or ‘dopaminergic antagonist’ or ‘antagonist, dopaminergic’ or ‘dopaminergic antagonists’ or ‘dopamine antagonist’ or ‘antagonist, dopamine’
18. aripiprazole
19. clozapine
20. lurasidone
21. quetiapine
22. olanzapine
23. risperidone
24. ziprasidone
25. paliperidone
26. brexiprazole
27. asenapine
28. cariprazine
29. iloperidone
30. Lumateperone
31. pimavanserine
32. or/10-31
33. 9 AND 32

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Database CINAHL <April, 2022> Results: 1800. Search strategy
*******************************************************************************
1. “Autistic Disorder” or “(Disorder, Autistic)” or “(Disorders, Autistic)”
2. “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early”
3. “Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autism Spectrum” or “Autism Spectrum Disorder” or “Disorder, Autistic” OR “Disorders, Autistic”
4. “Child Development Disorders, Pervasive”
5. “Asperger Syndrome”
6. “Kanner's Syndrome” or “Kanner Syndrome” or “Kanners Syndrome”
7. “Autism, Infantile” or “Infantile Autism” or Autism or “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early” or “Autism Spectrum Disorders”
8. “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum”
9. “Pervasive Child Development Disorders” or “Pervasive Development Disorders”
10. “Syndrome, Asperger” or “Asperger's Disease” or “Asperger's Diseases” or “Aspergers Disease” or “Disease, Asperger's” OR “Diseases, Asperger's” or “Asperger Disease” or “Asperger Diseases” or “Disease, Asperger” or “Diseases, Asperger” or “Asperger Disorder” or “Asperger Disorders” or “Disorder, Asperger” or “Disorders, Asperger” or “Asperger's Disorder” or “Disorder, Asperger's” or “Asperger's Syndrome” or “Aspergers Syndrome” or “Syndrome, Asperger's”
11. or/1-10
12. “Tranquillizing Agents, Major” or “Major Tranquillizing Agents” or “Major Tranquilizer” or “Tranquilizer, Major”
13. “Antipsychotic Drug” or “Drug, Antipsychotic” or “Antipsychotic Agent” OR “Agent, Antipsychotic”
14. “Antipsychotic Medication” or “Medication, Antipsychotic”
15. “Neuroleptic Agent” or “Agent, Neuroleptic” or “Neuroleptic Drug” or “Drug, Neuroleptic” or Neuroleptic or Antipsychotic
16. “Antipsychotic Drugs” or Antipsychotics or “Major Tranquilizers” or “Neuroleptic Agents” or “Neuroleptic Drugs” or Neuroleptics or “Tranquilizing Agents, Major” or “Major Tranquilizing Agents”
17. “Antipsychotic Effect” or “Effect, Antipsychotic” or “Antipsychotic Effects” or “Antipsychotic Agents”
18. “Dopamine Antagonists” or “Antagonists, Dopamine” or “Antagonists, Dopamine Receptor” or “Antagonists, Dopaminergic” or “Dopamine Blockers” or “Blockers, Dopamine” or “Dopamine Receptor Antagonists” or “Receptor Antagonists, Dopamine” or “Dopamine Blocker” or “Blocker, Dopamine” or “Dopamine Receptor Antagonist” or “Antagonist, Dopamine Receptor” or “Receptor Antagonist, Dopamine” or “Dopaminergic Antagonist” or “Antagonist, Dopaminergic” or “Dopaminergic Antagonists” or “Dopamine Antagonist” or “Antagonist, Dopamine”
19. aripiprazole
20. clozapine
21. lurasidone
22. quetiapine
23. olanzapine
24. risperidone
25. ziprasidone
26. paliperidone
27. brexiprazole
28. asenapine
29. cariprazine
30. iloperidone
31. Lumateperone
32. pimavanserine
33. or/12-32
34. 11 AND 33

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Database PSYCINFO <April, 2022> Results: 1898. search strategy
1. "Autistic Disorder" or "(Disorder, Autistic)" or "(Disorders, Autistic)"
2. "Autism, Early Infantile" or "Early Infantile Autism" or "Infantile Autism, Early"
3. "Autism Spectrum Disorder" or "Autism Spectrum Disorders" or "Autistic Spectrum Disorder" or "Autistic Spectrum Disorders" or "Disorder, Autistic Spectrum" or "Disorder, Autistic Spectrum Disorders" or "Disorder, Autistic Spectrum OR "Disorders, Autistic"
4. "Child Development Disorders, Pervasive"
5. "Asperger Syndrome"
6. "Kanner's Syndrome" or "Kanner Syndrome" or "Kanners Syndrome"
7. "Autism, Infantile" or "Infantile Autism" or Autism or "Autism, Early Infantile" or "Early Infantile Autism" or "Infantile Autism, Early" or "Autism Spectrum Disorders"
8. "Autistic Spectrum Disorder" or "Autistic Spectrum Disorders" or "Disorder, Autistic Spectrum"
9. "Pervasive Child Development Disorders" or "Pervasive Development Disorders"
10. "Syndrome, Asperger" or "Asperger's Disease" or "Asperger's Diseases" or "Aspergers Disease" or "Disease, Asperger's" OR "Diseases, Asperger's" or "Asperger Disease" or "Asperger Diseases" or "Disease, Asperger" or "Diseases, Asperger" or "Asperger Disorder" or "Asperger Disorders" or "Disorder, Asperger" or "Disorders, Asperger" or "Asperger's Disorder" or "Aspergers Disorder" or "Disorder, Asperger's" or "Asperger's Syndrome" or "Aspergers Syndrome" or "Syndrome, Asperger's"
11. or/1-10
12. "Tranquillizing Agents, Major" or "Major Tranquillizing Agents" or "Major Tranquilizer" or "Tranquilizer, Major"
13. “Antipsychotic Drug” or “Drug, Antipsychotic” or “Antipsychotic Agent” OR
   “Agent, Antipsychotic”
14. “Antipsychotic Medication” or “Medication, Antipsychotic”
15. “Neuroleptic Agent” or “Agent, Neuroleptic” or “Neuroleptic Drug” or
    “Drug, Neuroleptic” or Neuroleptic or Antipsychotic
16. “Antipsychotic Drugs” or Antipsychotics or “Major Tranquilizers” or
    “Neuroleptic Agents” or “Neuroleptic Drugs” or Neuroleptics or
    “Tranquilizing Agents, Major” or “Major Tranquilizing Agents”
17. “Antipsychotic Effect” or “Effect, Antipsychotic” or “Antipsychotic Effects”
    or “Antipsychotic Agents”
18. “Dopamine Antagonists” or “Antagonists, Dopamine” or “Antagonists,
    Dopamine Receptor” or “Antagonists, Dopaminergic” or “Dopamine
    Blockers” or “Blockers, Dopamine” or “Dopamine Receptor Antagonists”
    or “Receptor Antagonists, Dopamine” or “Dopamine Blocker” or “Blocker,
    Dopamine” or “Dopamine Receptor Antagonist” or “Antagonist,
    Dopamine Receptor” or “Receptor Antagonist, Dopamine” or
    “Dopaminergic Antagonist” or “Antagonist, Dopaminergic” or
    “Dopaminergic Antagonists” or “Dopamine Antagonist” or “Antagonist,
    Dopamine”
19. aripiprazole
20. clozapine
21. lurasidone
22. quetiapine
23. olanzapine
24. risperidone
25. ziprasidone
26. paliperidone
27. brexiprazole
28. asenapine
29. cariprazine
30. iloperidone
31. Lumateperone
32. pimavanserine
33. or/12-32
34. 11 AND 33

Database Cochrane <April, 2022> Results: 459. Search strategy

1. Autism or “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile
   Autism, Early”
2. “Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Autistic
   Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder,
   Autistic Spectrum” or "Autistic Disorder" or "Autism Spectrum Disorder"
3. or/1-2
4. aripiprazole
5. clozapine
6. lurasidone
7. quetiapine
8. olanzapine
9. risperidone
10. ziprasidone
11. paliperidone
12. brexiprazole
13. asenapine
14. cariprazine
15. iloperidone
16. Lumateperone
17. pimavanserine
18. “Antipsychotic Drug” or “Drug, Antipsychotic”
19. “Antipsychotic Agent” or “Agent, Antipsychotic”
20. “Antipsychotic Medication” OR “Medication, Antipsychotic”
21. or/4-20
22. 3 AND 21

Database EPISTEMONIKOS <April, 2022> Results: 800. Estratégia de busca

1. Autism or “Autism, Early Infantile” or “Early Infantile Autism” or “Infantile Autism, Early”
2. “Autism Spectrum Disorder” or “Autism Spectrum Disorders” or “Autistic Spectrum Disorder” or “Autistic Spectrum Disorders” or “Disorder, Autistic Spectrum” or “Autistic Disorder” or “Autism Spectrum Disorder”
3. or/1-2
4. Risperidone
5. aripiprazole
6. clozapine
7. lurasidone
8. quetiapine
9. olanzapine
10. risperidone
11. ziprasidone
12. paliperidone
13. brexiprazole
14. asenapine
15. cariprazine
16. iloperidone
17. Lumateperone
18. pimavanserine
19. “Antipsychotic Drug” or “Drug, Antipsychotic”
20. “Antipsychotic Agent” or “Agent, Antipsychotic”
21. “Antipsychotic Medication” OR “Medication, Antipsychotic”
22. or/4-21
23. 3 AND 22

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CLINICAL TRIALS <April, 2022> Results: 192. Search strategy

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1. Autism
2. Antipsychotic
3. 1 AND 2

WHO International Clinical Trials Registry Platform <April, 2022> Results: 126. Search strategy

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1. Autism
2. Antipsychotic
3. 1 AND 2

EU Clinical Trials Register <April, 2022> Results: 100. Search strategy

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1. Autism
2. Antipsychotic
3. 1 AND 2

Portal CAPES (Teses e Dissertações) <April, 2022>. Results: 619. Search strategy

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1. Autismo
2. Antipsicótico
3. 1 AND 2
4. Filtro: Ciências da Saúde

ProQuest <April, 2022>. Results: 80. Search strategy
1. Autism
2. Antipsychotic
3. 1 AND 2
SUPPLEMENTARY MATERIAL 3 - Journals and Conference

- International Congress on Psychopharmacology;
- Annual Meeting of the American Academy of Child & Adolescent Psychiatry;
- European Congress of Psychiatry;
- European College of Neuropsychopharmacology Congress;
- International Congress on Psychopharmacology and International Symposium on Child and Adolescent Psychopharmacology;
- International Congress of European Society for Child and Adolescent Psychiatry
- World Congress of the International Association for Child and Adolescent Psychiatry and Allied Professions;
- International Conference on Pharmacoepidemiology and Therapeutic Risk
- World Congress of the International Association for the Scientific Study of Intellectual and Developmental Disabilities;
- Annual Meeting of the College of Psychiatric and Neurologic Pharmacists;
- Annual Conference of the American College of Neuropsychopharmacology;
- Annual National Institute of Mental Health;
- Annual Meeting of the International College of Spectrum Disorders.