Use of second-generation antipsychotics in autism spectrum disorder: a systematic review and meta-analysis protocol

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INTRODUCTION
Atypical antipsychotics have been studied to treat autism spectrum disorder (ASD). However, 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 randomised controlled trials (RCT) and observational studies.

Methods and analysis
This systematic review will include RCT and prospective cohorts evaluating second-generation antipsychotics in people 5 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 behaviour, 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 non-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 (RoB) 2 and Risk of Bias in Non-Randomised 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 synthesise the results. The overall quality of the evidence for each outcome will be determined by the Recommendation, Assessment, Development and Evaluation approach.

Ethics and dissemination
This study will systematically summarise 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.

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STRENGTHS AND LIMITATIONS OF THIS STUDY
⇒ The search will be performed with the help of a specialised librarian experienced in medical literature searching.
⇒ This systematic review (SR) will include stakeholders from refining the question to discussing and implementing the findings.
⇒ Our SR proposal may have limitations inherent to the methodological quality of the included studies, especially non-randomised 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, characterised by two main symptom domains: (a) deficits in social communication and social interaction and (b) restricted repetitive behaviours, interests and activities and sensory anomalies.

Estimates of the prevalence of ASD vary. About 52 million people live with ASD worldwide. Studies indicate approximately 1%–2% of children in the USA and other developed countries. A systematic review (SR) 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. Another SR found that the average worldwide prevalence of ASD was 17 per 10 000, with a range of 2.8–94 per 10 000 across all age groups. Hispanic and African-American children are underdiagnosed compared with non-Hispanic white children. People with higher socioeconomic status and better access to healthcare are diagnosed earlier.

ASD is considered a brain-based neurodevelopmental disorder that lasts for life. The three characteristic manifestations of ASD are impaired social interaction, impaired communication, and restricted repetitive and


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stereotyped patterns of behaviour. Interfering behaviour has a great impact on the quality of life of individuals with ASD, family members and the people they live with. Interfering behaviours may include irritability, aggression and self-harm. These symptoms are the main causes of psychiatric hospitalisation, and the use of antipsychotics is recommended in the absence of effectiveness of behavioural interventions.

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 behavioural treatments in both children and adults and may reduce specific autistic symptoms and behaviours such as self-injury and aggression. There is evidence of widespread prescribing of psychotropic drugs to people with ASD. Antipsychotic drugs generally tranquillise and relieve psychotic symptoms without impairing consciousness. Second-generation antipsychotics tend to cause fewer unwanted motor adverse effects than typical ones.

Typical (first-generation) and atypical (second-generation) antipsychotics have been evaluated for the treatment of behavioural 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. Haloperidol, for example, has been evaluated for the treatment of ASD in several trials and has been associated with improvements in withdrawal and stereotypies 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.

Randomised controlled trials (RCTs) have suggested the efficacy of second-generation antipsychotics to ameliorate some interfering symptoms of ASD in children and adolescents. An SR investigated the use of risperidone for ASD and demonstrated the efficacy of this drug in treating symptoms of aggression, irritability and repetitive behaviour. Notable adverse events, including weight gain, increased appetite and sedation, were described.

In addition, evidence from two RCTs suggests that aripiprazole can be effective as a short-term medication for some behavioural aspects of ASD in children/adolescents. Participants included in both RCTs who received aripiprazole had reduced significantly irritability when compared with the placebo groups. Nevertheless, weight gain, sedation, drooling and tremors occurrence must also be considered. Another SR 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.

SRs published evaluating the use of antipsychotics presented important methodological limitations. An overview of SRs on aripiprazole and risperidone found 16 SRs of critically low methodological quality. Published Cochrane SRs have only evaluated the paediatric population and have not included all second-generation antipsychotics.

This SR 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 SR (SR) will be performed according to the recommendations of the Cochrane Handbook for Intervention Reviews. This protocol is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (online supplemental material 1), and registered in the International Prospective Register of Systematic Reviews (PROSPERO) database.

**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.

**Eligibility criteria**

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

**Types of participants**

Participants regardless of age group diagnosed with ASD using a standardised 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, brexpiprazole, 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 behaviour 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:
   - 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 of the 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-randomised studies such databases with data from claims or medical records, case 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 (online supplemental 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.

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/catalogoteses/#1/) and Open Grey (https://opengrey.eu/).
2. Trial registers
   - 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 (online supplemental 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 SRs, 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, 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 standardised 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 standardisation 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: randomised or non-randomised, scales used; clinical setting: hospitals, specialty clinics, primary care, research centres; 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, SD—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 randomised trials on bias arising from the randomisation process, deviations from intended intervention, missing outcome data, measurement of the outcome and selection of the reported result.

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

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

We will convert SMDs to log-OR (or vice-versa) using established methods when necessary. Depending on the data availability, we will convert sample sizes, means and SD directly to 2×2 tables—under the assumption of an approximately normal distribution and a cut-off. The thresholds that separate the continuous outcome into two categories (eg, 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 CIs, SEs, 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 (eg, median and IQR, continuous variables divided into mutually exclusive groups based on cut-offs). 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.

We will use the binomial likelihood for binary outcomes and model the log OR. If results in primary studies are available as ORs (95% CI), 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 ($\tau^2$).

Network meta-analysis

We will use the generalised linear model framework (the ‘NICE’ model) described previously. If feasible, we will use the arm-based approach. The model preserves randomisation, 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.

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. If appropriate, we will fit the node split model and compare direct, indirect and network estimates for all treatments.

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.

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.

Funnel plot asymmetry and small-study bias in pair-wise meta-analysis
Whenever feasible (ie, 10 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. We will calculate the LFK 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 Chiuocchia et al. We will also use the recently proposed Risk of Bias due to Missing Evidence in Network meta-analysis approach.

Implementation
All Bayesian models will be implemented in MultiBUGS 2.0 (Cambridge, UK), and estimates will be obtained via Markov chain Monte Carlo methods. Models will be fitted with three chains (166667 simulations each), totalling 500000 iterations. The burn-in period will be 100000 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 V.16.

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.

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. The main results of the review will be presented in outcome tables (Summary of Findings—SoF), as recommended by The Cochrane Collaboration. This table will be built with the aid of the GRADEpro software programme.

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 systematised in this study may contribute to improvements in healthcare 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 SR 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 standardisation in the measurement of efficacy outcomes and diagnostic criteria for ASD.

The methodological rigour 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 SR, we are proposing the involvement of stakeholders such as patient representatives, decision-makers and health professionals who work in the treatment of ASD. On completing the SR, the results will be disseminated among healthcare professionals, patients and their representatives through a virtual meeting. Stakeholder perspectives will be incorporated into the SR.

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Contributors LPNL is the principal investigator and wrote the protocol and the final version. JCCdO, IF, CdCB, EdCL, 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.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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