PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Use of second-generation antipsychotics in Autism Spectrum Disorder: a systematic review and meta-analysis protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>Lopes, Luis; de Oliveira, Jardel; Bergamaschi, Cristiane; Fulone, Izabela; Lima, Elisangela; Abe, Flávia; Mazzei, Lauren; Figueiró, Mabel; Lopes, Luciane</td>
</tr>
</tbody>
</table>

VERSION 1 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Amsbary, Jessica</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>University of North Carolina System, Frank Porter Graham Child Development Institute</td>
</tr>
<tr>
<td>REVIEW RETURNED</td>
<td>13-Dec-2022</td>
</tr>
</tbody>
</table>

GENERAL COMMENTS

Thank you for the opportunity to review the manuscript, “Use of second-generation antipsychotics in Autism Spectrum Disorder: A systematic review and meta-analysis protocol”. This sounds like an interesting review that could contribute to the existing literature on antipsychotics used to treat autism.

As a terminology note, many are referring to ASD as just “autism” now as preferred by a number of self-advocates (less focus on the disorder), but this terminology change is up to the authors.

Abstract: Claiming the medications work in real life may be beyond the scope of this systematic review. It is also a little confusing to differentiate between withdrawal due to adverse events and adverse events as a secondary outcome.

Strengths and limitations – please explain how and when the study will consider key stakeholders?

Introduction:
There are no longer categorical distinctions in autism (in the DSM 5). There are also only two listed manifestation categories (social communication impairments and RRB). I think the authors will include studies that refer to autism as the different categorical classifications that were published prior to DSM-5, but they should clarify the written content to reflect this.

Methods:
The stakeholder description is still a little unclear – will outcomes change following their meetings? The discussion makes it sound as if stakeholders will only be consulted after the review is complete. Clarification here and in the discussion would be helpful.

Additional information that explains and operationalizes outcome data being collected would be helpful. Maybe some examples?
Please clarify when the authors use the term “if warranted” – it would be helpful to explicitly state what would warrant additional analyses.

Comparators – what about nonrandomized studies included? Will they all have control groups? If yes, disregard it, but if no, please explain how those will be addressed.

For consistency with English, change year "de" publication to “of”

Discussion:

The sentence at the bottom of page 17 “In addition to being to date,….” does not sound like a complete sentence.

Overall, this sounds like a well-designed systematic review that could contribute new knowledge to the field.

REVIEWER

HASSIOTIS, ANGELA
ROYAL FREE and UNIVERSITY COLLEGE MEDICAL SCHOOL, PSYCHIATRY and BEHAVIOURAL SCIENCES

REVIEW RETURNED

16-Dec-2022

GENERAL COMMENTS

This is a very interesting topic and I expect it to have impact in terms of prescribing for autistic people. I particularly like the inclusion of PPI

There are a few issues that need to be addressed:

1. whilst the language is overall free of mistakes and typos, there are a few places where it needs attention; e.g. in a few places the text suggests that some action has taken place and in others that this is work to be carried out; grey literature is also written as gray; make sure the tense is present or past throughout

2. please clarify if ASD also includes intellectual disabilities; would these children/adults be included/excluded?

3. ICD10 is now superseded by ICD11; would you consider switching?

4. there is mention of a network meta-analysis but no mention is made till the statistical analysis section; perhaps consider this being mentioned earlier as a stated objective

REVIEWER

Sera, Francesco
London School of Hygiene and Tropical Medicine, Social and Environmental Health Research

REVIEW RETURNED

22-Dec-2022

GENERAL COMMENTS

I applaud the authors for the rigour and clarity of this paper presenting the protocol for a systematic review and meta-analysis on the use of second-generation antipsychotics in Autism Spectrum Disorder.

I think that the use of a Bayesian inferential approach with the possibility of modelling network meta-analysis is a strength of the analysis plan.

One aspect that I found not very clear is how the different effect size measures (e.g. Odds ratios and standardised mean differences) can be harmonised in this Bayesian framework. Perhaps the authors could specify more in detail this aspect.
Reviewer: 1 Dr. Jessica Amsbary, University of North Carolina System Comments to the Author: #2.

Thank you for the opportunity to review the manuscript, “Use of second-generation antipsychotics in Autism Spectrum Disorder: A systematic review and meta-analysis protocol”. This sounds like an interesting review that could contribute to the existing literature on antipsychotics used to treat autism.

R: Thank you! Reviewer: 1 #3. As a terminology note, many are referring to ASD as just “autism” now as preferred by a number of self-advocates (less focus on the disorder), but this terminology change is up to the authors. Thank you for your comment! We agree with this, but we have decided to be consistent with the terminology adopted in official guidelines (e.g NICE, CADTH, etc).

#4. Abstract:

Claiming the medications work in real life may be beyond the scope of this systematic review. It is also a little confusing to differentiate between withdrawal due to adverse events and adverse events as a secondary outcome. Thanks for the contribution! We change as follows: “However, little is known whether these drugs are effective and safety comparing controlled and not controlled settings” Also, we understand that Real-world evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product. RWE can be generated by different study designs or analyses, including but not limited to, pragmatic trials, and observational studies (prospective and/or retrospective). We clarify the difference between adverse events and discontinuation or dropouts/withdrawals of antipsychotics due to adverse events. The last one is considering serious adverse events that’s why we include this as the primary outcome. The other one is a common adverse event included as a secondary outcome.

#5. Strengths and limitations – please explain how and when the study will consider key stakeholders.

R: Many thanks for the observation! 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 summarize the evidence in plain language.

#6. Introduction: There are no longer categorical distinctions in autism (in the DSM 5). There are also only two listed manifestation categories (social communication impairments and RRB). I think the authors will include studies that refer to autism as the different categorical classifications that were published prior to DSM-5, but they should clarify the written content to reflect this.

R: Thank you! We added information about the DSM-5 in the introduction and clarified the study population in the method: Introduction: “Autism Spectrum Disorder (ASD) 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” Method: “Participants regardless of age group diagnosed with ASD using a standardized diagnostic tool or established diagnostic criteria from DSM-4 or DSM-5” #7. Methods:
The stakeholder description is still a little unclear – will outcomes change following their meetings? The discussion makes it sound as if stakeholders will only be consulted after the review is complete. Clarification here and in the discussion would be helpful.

R: Thank you! Before elaborating on the systematic review protocol, the stakeholders were consulted to refine the question considering mainly the outcomes of interest in two online meetings. Upon completing the systematic review, the results will be disseminated among healthcare professionals, decision-makers, patients, and their representatives through a virtual meeting. Stakeholder perspectives will be incorporated into the systematic review text.

Additional information that explains and operationalizes outcome data being collected would be helpful. Maybe some examples?

R: We change as follows: 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]; Data extraction and management: 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). #9. Please clarify when the authors use the term “if warranted” – it would be helpful to explicitly state what would warrant additional analyses. R: Sorry, we don’t follow. We already added the explanation of when the additional analysis would be necessary. Could you please let us know which part of the method section this information is missing? #10. Comparators – what about nonrandomized studies included? Will they all have control groups? If yes, disregard it, but if no, please explain how those will be addressed. R: Thank you! Single-arm non-randomized studies, such as series and case reports, will be excluded. We will only include studies with a comparator group. We included the following sentences to clarify it: “Observational studies (cohorts) will be included additionally, only if they are prospective and have a comparator arm for the intervention of interest. 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” #11. For consistency with English, change the year “de” publication to “of” R: Thank you very much! Corrections have been made. #12. Discussion: The sentence at the bottom of page 17 “In addition to being to date,…” does not sound like a complete sentence. R: Thanks for your contribution! That was a typo mistake. Adjustments have been made to the text. “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.” #13. Overall, this sounds like a well-designed systematic review that could contribute new knowledge to the field. R: Thank you! Reviewer: 2 Dr. ANGELA HASSIOTIS, ROYAL FREE and UNIVERSITY COLLEGE MEDICAL SCHOOL Comments to the Author: #14. This is a very interesting topic and I expect it to have an impact in terms of prescribing for autistic people. I particularly like the inclusion of PPI There are a few issues that need to be addressed: R: Thank you! #15. whilst the language is overall free of mistakes and typos, there are a few places where it needs attention; e.g. in a few places the text suggests that some action has taken place and in others that this works to be carried out; grey literature is also written as gray; make sure the tense is present or past throughout R: Thank you very much for your contribution! We carefully proofread all text to correct any tense errors or typo mistakes. #16. please clarify if ASD also includes intellectual disabilities; would these children/adults be included/excluded? R: Thank you! To clarify the study population we added the following sentences in the introduction and methods section: Introduction: “Autism Spectrum Disorder (ASD) 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 sensory anomalies” Method: “Participants regardless of age group diagnosed with ASD using a standardized diagnostic tool or established diagnostic criteria from DSM-4 or DSM-5.” We will not exclude studies where patients with ASD have intellectual disabilities. Our statistical analysis provides for subgroup analyses for associated psychiatric comorbidities. #17. ICD10 is now superseded by ICD11; would you consider switching? R: Thanks for your contribution! #18. #19. #20. #21. #22.
harmonised in this Bayesian framework. Perhaps the authors could specify more in detail this aspect.

R: We thank the reviewer for the positive remark and constructive criticisms regarding our statistical methods. On remark #20 on data harmonization, we will use previous techniques to convert standardized mean differences to log-odds ratios and vice-versa (if pertinent). These approaches employ the relation between the logit of a proportion and the normal distribution. Furthermore, we will use the properties of the normal distribution to compute 2x2 tables directly from sample sizes, means and standard deviations. Recently, there has been a great deal of support and use of these methods. To address the reviewer’s criticism, we amended the main text as follows: “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.”

References

VERSIGN 2 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Sera, Francesco</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>London School of Hygiene and Tropical Medicine, Social and Environmental Health Research</td>
</tr>
</tbody>
</table>

| REVIEW RETURNED   | 27-Feb-2023                |

| GENERAL COMMENTS  | The authors answered positively to all my comments. I have no further comments |

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Amsbary, Jessica</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>University of North Carolina System, Frank Porter Graham Child Development Institute</td>
</tr>
</tbody>
</table>

| REVIEW RETURNED   | 28-Feb-2023                |

| GENERAL COMMENTS  | Thank you for the opportunity to review the revised manuscript, “Use of second-generation antipsychotics in Autism Spectrum Disorder: a systematic review and meta-analysis protocol”. The authors have addressed several concerns and improved the clarity of the manuscript and the study protocol. A few minor suggestions are noted below. When discussing the presentation of ASD on line 22 p. 6, the authors may consider an alternative word to “situation”… maybe something like “Interfering behaviors may include irritability…. As a side note, some researchers in the field are moving away from calling behaviors “challenging” and using “interfering” instead to reduce the level of blame implied in the terminology. Small note for line 13 p. 7 – the authors may choose an alternative to “however” to avoid the same sentence starter for two sentences in a row. |

|                   |                                           |
On line 22, p. 7, please add clarification that the participants who received the treatment showed improvements (or if both groups showed the improvements, clarify that)

Line 6, p. 8 – consider using non-controlled as opposed to not-controlled
For the quality of life primary outcomes, I wonder if the authors should specify individual and/or caregiver instead of just or (I imagine some studies may report on both?)

The first sentence in the discussion is a little confusing – not sure what engagement findings means. The authors may consider explaining this terminology or simply saying the results could inform decision-making processes in the use of antipsychotics for clarity (unless there is an additional point that could be clarified).

It would still be helpful to have a little more detail about stakeholder perspectives and their benefits in the discussion.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3 Dr. Francesco Sera, London School of Hygiene and Tropical Medicine Comments to the Author: #02 The authors answered positively to all my comments. I have no further comments R: Thank you! #03 Dr. Jessica Amsbary, University of North Carolina System Comments to the Author: #04 When discussing the presentation of ASD on line 22 p. 6, the authors may consider an alternative word to “situation”… maybe something like “Interfering behaviors may include irritability….” As a side note, some researchers in the field are moving away from calling behaviors “challenging” and using “interfering” instead to reduce the level of blame implied in the terminology. R: Thank you for your comment! We updated according your suggestion. #05 Small note for line 13 p. 7 – the authors may choose an alternative to “however” to avoid the same sentence starter for two sentences in a row. R: Thank you! We changed the sentence as you suggested. #06 On line 22, p. 7, please add clarification that the participants who received the treatment showed improvements (or if both groups showed the improvements, clarify that) R: Thanks for the contribution! We change as follows: “Participants included in the studies who received aripiprazole had reduced irritability when compared to the placebo group” #07 Line 6, p. 8 – consider using non-controlled as opposed to not-controlled R: Thank you! #08 For the quality of life primary outcomes, I wonder if the authors should specify individual and/or caregiver instead of just or (I imagine some studies may report on both?) R: Thank you! We corrected it. #09 The first sentence in the discussion is a little confusing – not sure what engagement findings means. The authors may consider explaining this terminology or simply saying the results could inform decision-making processes in the use of antipsychotics for clarity (unless there is an additional point that could be clarified). R: Thank you We change as follows: “The results could inform decision-making processes in the use of antipsychotics for the treatment of ASD” #10 It would still be helpful to have a little more detail about stakeholder perspectives and their benefits in the discussion. R: Thanks for the contribution! We change as follows: “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.

Reviewer: 3 Competing interests of Reviewer: None Reviewer: 1 Competing interests of Reviewer: None

VERSION 3 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Amsbary, Jessica</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of North Carolina System, Frank Porter Graham Child Development Institute</td>
<td></td>
</tr>
<tr>
<td>REVIEW RETURNED</td>
<td>01-May-2023</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GENERAL COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thank you for the opportunity to review the revised manuscript, “Use of second-generation antipsychotics in Autism Spectrum Disorder: a systematic review and meta-analysis protocol”. This sounds like a feasible and important systematic review but I do have a couple minor suggestions for the authors.</td>
</tr>
<tr>
<td>In the abstract, the authors state: “However, little is known whether these drugs are effective and safety comparing controlled and non-controlled settings” – might want to reword this second part for clarity with something like little is know about whether these drugs are effective and safe when compared in controlled and non-controlled settings…if this is what the intent is (not 100% sure)</td>
</tr>
<tr>
<td>Introduction</td>
</tr>
<tr>
<td>This may just be a personal preference, but the word “adjuncts” in relation to pharmacological interventions…might a word like supplemental or additional be more clear?</td>
</tr>
<tr>
<td>Overall, I think this can be a solid systematic review with through plans, methods, and analyses. These findings could contribute to the field. I hope the authors are able to move forward with this review.</td>
</tr>
</tbody>
</table>

VERSION 3 – AUTHOR RESPONSE

Reviewer: 1
Dr. Jessica Amsbary, University of North Carolina System

#01 Thank you for the opportunity to review the revised manuscript, “Use of second-generation antipsychotics in Autism Spectrum Disorder: a systematic review and meta-analysis protocol”. This sounds like a feasible and important systematic review but I do have a couple minor suggestions for the authors.

R: Thank you!

#02 In the abstract, the authors state: “However, little is known whether these drugs are effective and safety comparing controlled and non-controlled settings” – might want to reword
this second part for clarity with something like little is know about whether these drugs are effective and safe when compared in controlled and non-controlled settings…if this is what the intent is (not 100% sure).

R: Thank you for considering our manuscript for publication. We change as follows: “However, like little is known about whether these drugs are effective and safe when compared in controlled and non-controlled settings”

Introduction

#02 This may just be a personal preference, but the word “adjuncts” in relation to pharmacological interventions…might a word like supplemental or additional be more clear? R: Thank you!

#03 Overall, I think this can be a solid systematic review with through plans, methods, and analyses. These findings could contribute to the field. I hope the authors are able to move forward with this review.

R: The suggestions were valuable for the refinement of the protocol! We hope this version is suitable for publication.