

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The Effectiveness of Lifestyle Interventions for Improving the Physical Health of Children and Adolescents Taking Antipsychotic Medications: Protocol for a Systematic Review and Meta-Analysis.
AUTHORS	Hawker, Patrick; Bellamy, Jessica; McHugh, Catherine; Wong, Tsz Ying; Williams, Katrina; Wood, Amanda; Anderson, Vicki; Tonge, Bruce J.; Ward, Philip; Sciberras, Emma; Bellgrove, Mark; Silk, Tim; Lin, Ping-I; Eapen, Valsamma

VERSION 1 – REVIEW

REVIEWER	Barnett, Erin Dartmouth-Hitchcock Medical Center
REVIEW RETURNED	27-Jul-2023

GENERAL COMMENTS	<p>Thank you for the opportunity to review this manuscript. The authors have submitted their protocol to conduct a systematic review and meta-analysis of lifestyle interventions to improve physical health for youth taking antipsychotics. This reviewer does not find it typical for protocols such as this to be published on their own accord, unless there is a significant and unique or novel methodology or analytic strategy. Part of this exclusion could be because there is a chance that too few studies will be identified, and therefore, the review would have to be significantly blunted and the meta-analysis may not be possible. This reviewer has provided feedback on the manuscript but is unsure whether the protocol, even if very strong, is worthy of publication.</p> <p>The introduction and methods presented thus far are strong. They are clear, well-organized, and well-written. A few suggestions follow.</p> <p>Before the objectives, the authors state: “By reducing the negative effects of antipsychotic medications, it may be possible to sustain their usage, leading to the optimization of critical learning and developmental periods.” To this reviewer, the main benefit would be to reduce harms or reduce the risk of harms to the child while on the antipsychotic, not necessarily to sustain the use of the medications. Another potential goal/implication might be the identification of interventions that must be provided or would be recommended to accompany antipsychotic prescriptions to youth who experience indicators of worsening physical health. Might the authors consider these goals/implications?</p> <p>Perhaps in the Intro, or somewhere else, could the authors make a brief connection between sleep (and perhaps smoking too) and physical health or BMI? Since the primary outcome is BMI, it</p>
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	<p>probably makes sense to show how sleep and smoking indicators relate to BMI.</p> <p>Current trends show that youth are at higher risk of vaping than smoking cigarettes. Depending on the years of the publications, vaping may need to be included.</p> <p>Could the research literature reviewed be useful for lifestyle interventions to improve physical health for all youth? Or is there something specific about youth receiving antipsychotics for which this is only relevant?</p>
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REVIEWER	Rashid, Nazia ACADIA Pharmaceuticals Inc
REVIEW RETURNED	14-Aug-2023

GENERAL COMMENTS	<p>This paper was a very well written and thorough paper. I am very impressed with the use of the checklists (PRISMA and GRADE). The appropriate databases were included as well. RCTs were evaluated and risk of bias assessment was completed.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1		
<p>This reviewer does not find it typical for protocols such as this to be published on their own accord, unless there is a significant and unique or novel methodology or analytic strategy. Part of this exclusion could be because there is a chance that too few studies will be identified, and therefore, the review would have to be significantly blunted and the meta-analysis may not be possible. This reviewer has provided feedback on the manuscript but is unsure whether the protocol, even if very strong, is worthy of publication.</p>	<p>We thank the reviewer for raising this point. We have chosen to publish our systematic review protocol, recognising the growing emphasis on best-practice measures which promote transparency and reproducibility in research. This not only ensures our accountability to predefined methods but will enhance the credibility of our findings. The increasing trend of publishing systematic review protocols—even those without novel methodologies or analytic strategies—supports our approach. Systematic review protocols published in BMJ Open over the recent years including Seppala et al. (2021), Lopes-Júnior et al. (2019), Corepal et al. (2019), and Hawke et al. (2022) serve as examples.</p> <p>Further addressing your concern, our preliminary literature scoping has identified at least eight articles meeting inclusion criteria for the meta-analysis, mitigating the risk of insufficient studies for our review. We trust that the merit of our publication in advancing transparent science and inviting critical peer appraisal will be appreciated.</p>	<p>n/a</p>
<p>Before the objectives, the authors state: “By reducing the negative effects of antipsychotic medications, it may be possible to sustain their usage, leading to the optimization of critical learning and developmental periods.” To this reviewer, the main benefit would be to reduce harms or reduce the risk of harms to the child while on the antipsychotic, not necessarily to sustain the use of the medications.</p>	<p>We thank the reviewer for this suggestion. This statement was added to highlight the primary goal of reducing risk of physical health decline for children and adolescents taking antipsychotics, while acknowledging the potential benefits of sustained uses in specific cases such as those with Tics/Tourette Syndrome. However, we agree that it is not the focus of the review and have removed the statement.</p>	<p>Page 6</p>

<p>Another potential goal/implication might be the identification of interventions that must be provided or would be recommended to accompany antipsychotic prescriptions to youth who experience indicators of worsening physical health. Might the authors consider these goals/implications?</p>	<p>We agree with the reviewer on this comment that the inclusion of intervention recommendations may have practical implications for clinical practice. While this is not a core objective of the study as we are yet to ascertain the quality of evidence available, we will be sure to discuss clinical implications and recommendations of our findings in the final manuscript.</p>	<p>n/a</p>
<p>Perhaps in the Intro, or somewhere else, could the authors make a brief connection between sleep (and perhaps smoking too) and physical health or BMI? Since the primary outcome is BMI, it probably makes sense to show how sleep and smoking indicators relate to BMI.</p>	<p>Thank you for your suggestion. We have added the following phrase to strengthen the rationale for evaluating programs which incorporate a multi-faceted intervention program.</p> <p>“Recent work suggests that broadening intervention scope beyond diet and exercise, specifically those that incorporate sleep improvement and nicotine reduction programs, could effectively improve metabolic parameters and lower cardiovascular risk of individuals who take antipsychotic medications.[2] [Green et al. 2015; Baker et al. 2017]”</p>	<p>Page 4</p>
<p>Current trends show that youth are at higher risk of vaping than smoking cigarettes. Depending on the years of the publications, vaping may need to be included.</p>	<p>We agree that this is a relevant measure given the increases in vaping particularly in a younger cohort. We have made adjustments throughout to include studies that address vaping in addition to smoking behaviour, and any form of nicotine reduction (inclusive of smoking and vaping) as an outcome measure for lifestyle intervention programs.</p>	<p>Pages 8 and 10</p>
<p>Could the research literature reviewed be useful for lifestyle interventions to improve physical health for all youth? Or is there something specific about youth</p>	<p>While studies such as Bondyra-Wisniewska et al. (2021) have systematically analysed the effectiveness of intervention programs for improving cardiometabolic parameters of all overweight or obese children and youth, our findings may not translate to general population norms due to the unique challenges experienced by our target group. Regardless, we agree that the lifestyle intervention programs if supported by the family would be applicable to any youth, although we would like to highlight some of the unique characteristics of this population that may make the generalisation less straight forward. Firstly, children and adolescents with intellectual</p>	<p>Page 6</p>

<p>receiving antipsychotics for which this is only relevant?</p>	<p>and developmental disability who are prescribed antipsychotic medications may be receiving the medication for specific neurodevelopmental disorders (such as ADHD, Autism Spectrum Disorder, Tourette Syndrome, or Intellectual Disability) that in itself may be associated with specific challenges such as increased restrictiveness around diet/food and routines in ASD, accompanied by pronounced behavioural dysregulation and a high likelihood of coexisting mental health diagnoses. In addition, anti-psychotic medications may have unique effects that may impact aspects of 'lifestyle' such as increased appetite or sleep. Furthermore, this cohort requires an individualised strategy involving cares/families as key participants as well as adaptations as per the developmental age and communication style/level of the young person etc. Our review seeks to pinpoint strategies uniquely suited to their needs, and specifically tailored to those on antipsychotics, thus avoiding broad interventions that might not account for individual complexities. Thus, extrapolating our findings to the wider child and youth population may not be fitting. We have further expanded on the above points in the manuscript.</p>	
<p>Reviewer 2</p>		
<p>This paper was a very well written and thorough paper. I am very impressed with the use of the checklists (PRISMA and GRADE). The appropriate databases were included as well. RCTs were evaluated and risk of bias assessment was completed.</p>	<p>We thank the reviewer for their comments.</p>	<p>n/a</p>

Additional Comment: We have corrected an oversight in our initial submission by adding Daniel Lin, who significantly contributed to drafting the manuscript, as an author for this study.

Additional formatting changes have been made to tables in line with request from the editorial team.

Removed 'Amendments to Protocol' and 'Table 1: Amendments to the Systematic Review Protocol' as these amendments were all made prior to commencing the review process and documentation is not necessary.

Removed 'Study Timeline' as this was for internal records and was not necessary/intended to be in the published manuscript

