Author's response to reviews

Title: The risk of elevated prolactin levels in pediatric patients exposed to antipsychotics for the treatment of schizophrenia and other schizophrenia spectrum disorders: protocol for a systematic review and meta-analysis

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Author's response to reviews: see over
Response to Reviewers’ Comments

Reviewer #1

1. This is an important topic, and one that has received a lot of attention. As the authors note, many antipsychotics are not licensed in children and adolescents, so they're prescribed off-label and information about adverse events has not been submitted to FDA or other regulatory bodies. Some data have been made available because of litigation. The developers of quetiapine (AstraZeneca) and risperidone (J&J) have been sued specifically because the companies underreported adverse events, and the authors should look for information about those trials on DIDA (http://dida.library.ucsf.edu/).

   Response: We thank-you kindly for your suggestion. We are familiar with the Drug Industry Document Archive (DIDA), and are aware that this database may contain relevant information that has not been formally published in a peer-reviewed journal. However, we chose not to search DIDA. As a rule, it is not typically searched in formal systematic reviews. It is potentially biased because it does not contain comparable documentation on all drugs of interest.

2. Because many important trials may not have been published at all, or may have been reported incompletely, the authors should add a comprehensive search for unpublished data (e.g. ClinicalTrials and ICTRP).

   Response: Thank-you for your suggestion. We have now included in our protocol that we will search clinicaltrials.gov and the International Clinical Trials Registry Platform.

3. I would suggest the authors also reconsider limiting the review by DSM diagnosis. It would be appropriate to broaden the inclusion criteria because the effects of interest are associated with the drug rather than the condition. Antipsychotics are also used in bipolar disorder (a dubious pediatric diagnosis) and have the same harms in this group.

   Response: We thank the reviewer for this comment. The overarching purpose of this project is to inform treatment guidelines for pediatric schizophrenia and schizophrenia spectrum disorder (which does, in fact, include bipolar disorder with psychotic features). Therefore, this is the chosen focus of our review.

   Additionally, from a statistical perspective, we have limited our review to schizophrenia and schizophrenia spectrum disorder because this population is generally homogenous compared to other psychological conditions where anti-psychotics are used. A homogenous population is extremely important when considering meta-analytic techniques such as
network meta-analysis. This is because the results are only reliable when there are little to no effect modifiers (i.e. baseline patient characteristics that can impact outcomes, both efficacy and safety).

4. Clinically, differences in AEs are probably more important than small differences in efficacy, and I'm not sure the rationale for limiting this review to one AE - could the authors also include weight and other metabolic effects, cardiac effects, etc.?

Response: Thank you for addressing this issue. We are reporting on multiple AEs that could be attributed to increased prolactin levels. The safety outcomes included are galactorrhea, gynecomastia, sexual dysfunctions (impotence/libido), menstrual irregularities (amenorrhea/dysmenorrhea), and change in prolactin levels.

5. The authors should consider if methods for NWMA of efficacy outcomes are appropriate for rare / adverse events.

Response: Thank you for this comment. We have done a cursory review of the included studies. This is what is reported in the 48 trials. We have updated the systematic review protocol to reflect this. We will also provide pooled estimates of the interventions of interest. These will be provided in our subsequent analysis.
This is an interesting topic for a systemic review, and as the authors point out, there has been little work done on the subject of prolactin and related side effects arising from the use of antipsychotic medication- typical and atypical- in young children and adolescents. However, I have found a recent review of this subject across all ages, including children and adolescents and those with first episode psychosis (Peuskens et al., 2014)

A major difficulty for any systemic review in this age group is the lack of randomised controlled trials (although expanding), and furthermore systematic data on side-effects such as those due to raised prolactin levels i.e. sexual difficulties; in the longer-term osteoporosis, menstrual irregularities. Drug companies may provide more detailed evidence of side-effects, which may include serial prolactin levels throughout the course of treatment, otherwise I suspect data will be rather scant, making comparisons and ultimately any systemic review problematic.

1. Is the study design appropriate? The problem lies with the lack of data i.e. the small number of trials carried out, and furthermore the lack of systematic coverage of side-effects in particular prolactin levels, secondary sexual characteristics. I worry particularly about the systematic collection of such data as prolactin levels can be affected by the time of day, exercise, sexual activity, and as mentioned by the authors the presence of other medications. To partly circumvent the problems, the authors propose to gather data from both observational and randomised control designed studies, which they contend can be meta-analyzed together if they report common information. As the focus is looking at side effects, and not primarily efficacy, I suspect this may be allowable, although it would be important to look at both sets of data to see if there are systematic differences between the two, which would be interesting of course, but clearly not the focus of this study.

   **Response:** Thank-you for considering this issue. We are conducting sensitivity analyses to look at both RCTs and observational studies or RCTs only.

2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing? I believe that details are provided of an network analysis and while I am not an expert on network meta-analysis, I believe the authors do detail how they are to carryout the work which should allow replication.

   **Response:** Thank you for this comment.

3. Is the planned statistical analysis appropriate? I believe the statistical analysis may be appropriate, however, I am not clear whether allowances have be made for the number of trials involved, and how this will affect the results and the effect sizes seen, particularly as the authors point out it is very likely that there will be
considerable heterogeneity. Furthermore, there is an issue of how prolactin levels vary between the sexes and at various ages across the proposed study span where there are tremendous changes i.e. puberty. Unfortunately, I am not aware of the systematic understanding of prolactin levels in normal adolescence, and how these vary with stress, exercise, time of day and, therefore, it is going to be very difficult to understand the effects of medication against a largely unknown baseline. This is not to say it is not possible to carry out the study, but to point out some of the pitfalls which may arise, and which may make any interpretation that much more difficult.

The authors state that they will use meta-regression to test and (potentially) control for effect-modification within and across comparisons by a number of relevant covariates: treatment dosage, gender distribution, age distribution, and the history of chosen clinically relevant baseline co-morbidities. That may be possible, but surely one cannot control for so many covariates of interest when the number of studies that may be identified are potentially so few.

**Response:** Thank-you for your suggestion. When interpreting our results, we will consider what has been published on prolactin levels in normal adolescence and how these may vary with stress, exercise, time of day. With regards controlling for the possible multiple covariates of interest, it may be preferable to have several models that control for single effect modifiers (e.g. age, dosage), rather than one model that controls for all effect modifiers. This will be determined once the volume of data is well understood.

4. **Is the writing acceptable?** Overall, I believe the writing is acceptable and the authors are able to make it clear what they intend to do which gives confidence that any publication arising from this work would be readable and ultimately understandable.

The authors state they will conduct our analyses using two approaches: 1) considering each drug independently, and 2) considering all drugs within a given dopamine receptor affinity class as exhibiting comparable treatment effects, which is a reasonable, and the authors highlight the considerable limitations of this – assuming that medications exhibiting specific dopamine affinity having comparable treatment effects, which is not naïve, as the authors admit, but wrong. It may be that a correction will need to be added, as the authors later indicate they can do, allowing for the differing potencies of the antipsychotics.

**Response:** Thank-you for your comment. We will consider differences in class effects either via a correction factor or conducting a sensitivity analysis examining the differing potencies of the antipsychotics.
Handling Editor

1. "The second reviewer identifies the same problem emphasized in my comments, which is the poor state of evidence the authors are likely to encounter. Including aspirational methods in a protocol is fine, but I would also encourage the authors to consider plans for dealing with a limited dataset that may include studies of different designs (which may not be comparable in a NWMA) with too few events to draw meaningful statistical inferences (much less conduct multiple regressions). Having read some of the company reports, I am confident that these harms are more commonly measured than they are reported, which the second reviewer also identifies as a concern. The authors may wish to elaborate their plans for finding and using unpublished data, and their plans for dealing with reporting bias in all the included study types.

   Response: Thank-you for considering this issue. We are using both RCTs and observational studies to populate our evidence base. Our preliminary search resulted in 48 publications. Furthermore, we included trials from conference abstracts. As for reporting bias, we are limiting our review to schizophrenia and schizophrenia spectrum disorders in the pediatric population to maintain a generally homogenous population, and to inform treatment guidelines in this population.

2. Please mention each author individually in your Authors' Contributions section. We suggest the following kind of format (please use initials to refer to each author's contribution): ?AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

   Response: Thank-you for your suggestion. We will add the contribution section to our manuscript.