Reviewer's report

**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

**Version:** 1  
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**Reviewer:** Anthony James

**Reviewer's report:**

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.

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 carry out the work which should allow replication.
3. Is the planned statistical analysis appropriate? I believe the statistical analysis may be appropriate, however, I am not clear whether allowances have been 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.

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.