Author's response to reviews

Title: Atypical antipsychotic augmentation in SSRI treatment refractory obsessive-compulsive disorder: A systematic review and meta-analysis

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Author's response to reviews: see over
Dear Dr Kantrowitz

Thank you for your review.

> We have not responded to our first reviewer as there were no substantive changes to be made. We have re-proof-read the article and tried to ensure that there are no grammatical errors. The following is our response to the review.

On the whole, this systematic review, is a worthwhile addition to the literature, finding a significant benefit for both aripiprazole and risperidone in OCD. There is a clear agenda against the use of antipsychotics that often runs contrary to the evidence presented. This has no place in a meta-analysis. I am in full agreement that antipsychotics need to be used cautiously, but the authors go too far in their assertions that these meta-analysis findings should be taken with caution, and the frequent “delegitimizing” of the aripiprazole findings, by stating that the studies were “early” and that they "may show diminished returns in the long term". This may be true, but no evidence is presented for this.

> Thank you. We are cautious about the possible diminished return over time as visual analysis of risperidone studies in Figure 5 of responders show each trial of risperidone has led to decrease in the response rate. This is a recognized pattern in some psychotropic drugs where over time the nature of the participants recruited or other factors may diminish the effect size. Compared to say the use of anti-psychotics in schizophrenia, these studies are all relatively small, conducted in the short-term and the overall GRADE of the recommendations was rated as very low. (The GRADE system is a systematic and explicit approach to making judgements about quality of evidence and strength of recommendations.)

One gets the impression that the authors had decided on the introduction and the conclusions before conducting the meta-analysis, and their dismissal of the findings and frequent reliance on the preconceived opinion makes it hard to take their legitimate safety concerns seriously. In order to maximize impact, the authors should shift their tone and simply report their findings, starting in the abstract. The first sentence of the results needs to simply state that there was a significant acute benefit of aripiprazole and risperidone.

> We disagree, whereas it is usually important for people with psychosis or bipolar disorder to remain on anti-psychotics to reduce the risk of relapse, there are different issues in OCD in which there is a small effect size with no evidence of benefit on the long term, potential adverse effects in the long term and evidence-based alternatives with CBT. Thus the mindset of many psychiatrists is to use anti-psychotics in OCD in the same way as in schizophrenia rather than to determine if there is any benefit in the absence of other interventions over 4 weeks and to then discuss with the patient whether there was any significant benefit and the potential adverse effects in the long term.
The legitimate concerns over long-term safety and efficacy, and the possible superiority of cognitive behavioral therapy should be moved to a subsection of the discussion.

> We have done this but for the reasons described above we remain cautious about the use of anti-psychotics in the discussion.

Other issues:

1. Abstract: Spell out NICE

>> Thank you. This has been corrected.

2. Copy edit the introduction and discussion. There are a number of run-on sentences, beginning with the first one.

>> Thank you we have modified and re-proof read the article.

3. The authors report that the NICE review from 2006 relied on a meta analysis from 2010. Please explain.


4. The authors cite Random house digest to support an exaggeration of effects. The authors decided not to do a funnel plot, which would be a better way to assess this.

>> The citation of the book in the introduction is an excellent summary of possible biases in RCTs and in their dissemination. We had conducted a Funnel plot and have now included it. There is some suggestion of asymmetry in the funnel plot, however as all studies included in the analysis were small it is difficult to make a firm conclusion in terms of small study bias. Asymmetries in funnel plots can also be because of heterogeneity within the sample and over-estimation of treatment in some studies.

5. Please double check the sentence on line 17 page 10. It was unclear

>> This has now been corrected.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

>> Thank you. We have re-proof-read.

Statistical review: Yes, and I have assessed the statistics in my in my report.

Declaration of competing interests: none
We note that you have been consultant to Otsuka Pharmaceuticals (manufacturer of aripiprazole) and other pharmaceutical companies in disclosing interests in other articles.

Yours sincerely,

David Veale