Author's response to reviews

Title: Towards the implementation of personalized pharmacotherapy for bipolar disorder

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Author's response to reviews: see over
Reviewer 1:

1. **Perhaps the title should be [changed]....**

   Based on the suggestion of the reviewer, we have changed the title of the work to better emphasize the genetic aspects.

Reviewer 2:

1. **[There are] now... several controlled trials..... [the authors] should...be aware of Hall-Flavin et al (2013 )...and Winner et al, (2014).**

   Thank you for pointing out the important developments in the literature. The additional references were included and discussed in the revised manuscript.

Reviewer 3:

1. **Much of the data is now...old...almost entirely collected via candidate gene studies...relevant data is not yet available from large scale GWAS of bipolar pharmacogenetics.**

   The reviewer is correct to point out that important gaps remain in the bipolar literature. Towards mitigating this, we have added in a discussion on genomic approaches in antidepressant pharmacogenetics based largely on MDD that could reasonably be extrapolated to bipolar disorder.

2. **My concern with the...review is that by reviewing...candidate gene studies of pharmacogenetics of bipolar disorder, conclusions are being drawn which are not likely to be valid or relevant**

   As the reviewer concedes, the manuscript can only discuss the published literature and we have accurately done so. Nonetheless, the concern that GWAS may overlap little with candidate gene studies is valid and has been address in the text (pg 8-9). We maintain that many candidate gene studies are still be useful, even as they are supplemented by information from newer, distinct methods. Hence, they are incomplete, but not invalid or irrelevant.

3. **There are not enough data to conduct a meta-analysis...the data is selective...**

   A quantitative meta-analysis of the entire set of 16 candidate genes is beyond the scope of this review that is intended primarily to define a novel direction of research based on
clinical utility rather than statistical association. However, in several instances of individual markers (e.g. DRD2, HTR2C, FKBP5), meta-analyses have been conducted, and where available, these are referred to in the manuscript. We were indeed selective about the genetic markers, but were systematic and transparent in the criteria applied to make our choices. We invite further input from the community on how to make these choices more effective in future iterations. In the meantime, few implementation designs have been proposed and there are no established criteria to which adherence should be followed.

4. **The authors state "...evidence already exists for a number of well replicated PGT markers"...Unfortunately I find this a specious argument.**

We have softened the tone of the sentence in question to incorporate the element of uncertainty that still surrounds the pharmacogenetic markers in question. Ultimately though, this is a difference of opinion. The reviewer is simply taking the position that others in the field have advanced, that total certainty is required before taking steps towards implementation. This position has been taken in the literature frequently, and has yet to be challenged. In fact, the entire field of psychiatric genetics is pervaded by doubt and skepticism because of the number of non-replications. For this reason, we established standards of replication in our selection, but such standards are not well established for the field in general. In short, these are some of the reasons for writing this review. We do not expect that early iterations of implementation markers and polygenic algorithms will be perfect for every situation, but instead, that by getting practical experience with the issues now, the progress made will be faster and more pertinent than it would be by waiting for perfect association studies.

5. **The authors should...apply the algorithm to the analysis of current drugs based on population frequencies...**

We appreciate the intent of this critique which is to get at practical clinical utility. However, the number of possibilities and combinations are so great that it is difficult to estimate, and we would hold suspect such an estimate because of the number of assumptions. However, to give the reader some idea of where subjects would be categorized by the algorithm, we have reported actual data from the implementation trials conducted by the Mayo clinic group to give an approximate number of people expected to be categorized as having “severe” side effect profiles (up to 25%, see pg 13), and made the point that subjects failing to have any risk associated markers (“preferential users”) may be uncommon (pg 12).
6. To be useful, the study design needs to given due consideration to what should be tested and issues of power...there is almost no data on effect size, so in fact a pre-study would be needed...the proposal of this clinical trial appears to be somewhat premature.

As in point 4 above, lack of data is the conventional argument made against genetic testing in the clinic, and the primary reason for writing this paper. The reviewer is correct that on issues of effect size, power etc, there is little data. However, as we argue in the manuscript (pg 10, 12-13), the extrapolation of statistical power from individual marker associations, to real world application of a polygenic panel may prove difficult to model and/or problematic for unexpected reasons. These issues would be better answered through direct experimentation. We do not argue with the suggestion of conducting preliminary experiments, but argue that we need to do a qualitatively different kind of trial. In fact we agree on the need to begin to determine effect size. For that reason, we are proposing a pilot study to obtain estimates of effect size.

7. Supplementary data was not reviewed.

We did not mean to submit supplementary data. Sorry for the mistake.