Reviewer's report

Title: Towards the implementation of personalized pharmacotherapy for bipolar disorder

Version: 1 Date: 8 February 2014

Reviewer: Peter R Schofield

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The authors provide a review of the pharmacogenetics of bipolar disorder and then suggest that given the relative paucity of good predictive information that a pharmacogenetics clinical trial is warranted.

Major Compulsory Revisions

1

Naturally review articles can only evaluate previously published data, but much of the data is now six or more years old, and has been almost entirely collected via candidate gene studies. This results in a methodological flaw because relevant data is not yet available from large scale GWAS of bipolar pharmacogenetics. The authors need to address this issue.

By way of analogy, a comparison of the genetics of risk for bipolar based on the same approach (ie older candidate gene studies) would reach a very different conclusion to that of the large scale collaborative GWAS studies now being undertaken by the PGC. Thus, almost no classic candidate gene studies of bipolar, including those that had been replicated and validated by meta-analysis have proven to be bona fide risk alleles when denser GWAS studies on larger cohorts have been undertaken. Thus my concern with the current review is that by reviewing now rather old candidate gene studies of pharmacogenetics of bipolar disorder, conclusions are being drawn which are not likely to be valid or relevant in the future (based on the related experience from the bipolar risk genetic studies). I acknowledge that STEP-BD did use a GWAS analysis, but this represents just a small portion of the reviewed data.

2

A second problem with the available pharmacogenetic data is that there are not sufficient studies for almost all of the candidate genes to conduct a meta analysis. Level 1 evidence only requires two studies, one more than 500 people and of similar ethnicity and a corrected p of 0.05. Thus while the review data presented in this opinion article provides a comprehensive examination of the available data, the data is selective in that it has only been garnered from candidate gene studies.

The authors need to address why the review has not included meta analysis of the candidate genes. Given my expectation that there is not sufficient data to
support a meta analysis, then one has to question the veracity of the various candidate gene reports

3
A broader issue of concern (eg introduction para 2) is that successful pharmacogenetic studies and implementation have been based on a specific drug and (eventually) a specific gene effect. The examples given for warfarin, thiopurine and abacavir all fit this model. Whereas in this article, the treatment for bipolar includes many drugs. One of the mainstay drugs after lithium, valproate, doesn’t have any pharmacogenetic data available. While this illustrates the pressing need to advance the field, it does create problems in presenting a review.

Pharmacokinetic data is well established via polymorphisms in the CYP2D6 and 2C19 genes affecting drug metabolism and thus response. However for depression the EGAPP group concluded that the field needs more work before this approach can be applied. The case for bipolar is even more pressing given the paucity of data.

The authors state "While the discovery of predictive genetic markers is just beginning, evidence already exists for a number of well replicated PGT markers". Unfortunately I find this a specious argument (having commented on risk genetic markers above) and finding that the evidence is by any objective standard still rather weak and preliminary. Rather the quote from the authors that is perhaps the most valid in this opinion piece is "Pharmacogenetics and clinical practice: Are we there yet? ..... The answer seems unclear."

Thus the authors need to address these limitations of the available data and the conceptualisation of the review and opinion sections of the paper.

4
Turning now to the opinion component of the article. I am strongly of the view that this is a topical issue to raise notwithstanding the paucity of data. This is a major clinical issue and answers would have immediate clinical benefit to the majority of patients.

To address this issue the authors propose an algorithm to prioritise drug use. However, for this to be a strong contribution to the field the authors should actually apply the algorithm to the analysis of current drugs based on population frequencies of the P450 metabolic variants. In other words, there need to be clear predictions or statements about which drugs are preferred and which have caveats regarding their use.

5
A randomised controlled trial of pharmacogenetics of bipolar is proposed and this is a laudable goal. However, the study design is both simplistic and without any specific details. To be useful, the study design needs to given due consideration to what should be tested and issues of power.
My expectation is based on the current data that there is almost no data on effect size, so in fact a prestudy would be needed to assess the effects of integrated pharmacogenetic testing, ie almost all studies to date have examined a single gene, not a range of genes. Thus it is first necessary to test the effect size of selected genes. If the selected genes show a significant effect, then they could form part of the test panel for inclusion in the proposed trial. Thus the proposal of this clinical trial appears to be somewhat premature, although again I agree it is well warranted.

Minor Essential Revisions
The authors uploaded the manuscript a second time rather than the supplementary file, so I have not been able to review this material.

Discretionary Revisions
Nil

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.