Author's response to reviews

Title: The co-administration of quetiapine or placebo to cognitive-behavior therapy in treatment refractory depression; a preliminary trial

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Author's response to reviews: see over
To the Editorial Staff,  
BMC – Psychiatry,

MS: 8312126711678731  

Thank you for reviewing, one again, my manuscript entitled ‘The co-administration of quetiapine to cognitive behavior therapy in treatment refractory depression; a preliminary placebo-controlled trail’ that I submitted for your consideration in BMC-Psychiatry on the 6th of January 2008.

To the EDITOR:

It has unfortunately taken me a bit more time to respond to the queries as I received 2 concurrent e-mails that same morning almost 4 weeks ago, one with the queries and the other with an acceptance from the Int. J. Mental Health Systems for another manuscript. As Biomedcentral does impose some of the final ‘onerous’ editing chores upon the authors, a task that I am admittedly not very good at, this did take up quite a bit of time in the past 3 weeks, which is why my present replies are at the very limit of the allotted reply allowance (the 29th of May).

In addition, I am beginning to doubt that using Endnote, with its many bugs that Biomedcentral has made me aware of, is really of any use other than in the draft stage of a manuscript. As such, I have formatted the references myself and removed the field codes in the present manuscript. If the manuscript is accepted I would be willing to use endnote in the final version.

To the REVIEWER:

One of the reviewers has recommended accepting the manuscript without revision and the other has brought up several points he feels still require attention. I will gladly address the points made by Dr Stewart (who, with the total amount of queries generated, most every one the result of attentive and careful reading, I almost feel should be a co-author!) in the following paragraphs.

THE TITLE.

The title, although improved, is still too obscure. I have modified the title which is now ‘The co-administration of quetiapine or placebo to cognitive behavior therapy in treatment refractory depression; a preliminary trail’. This title reflects the study flowchart to a “T”.

THE ABSTRACT.

All of Dr Stewart’s suggestions are now in the revised abstract.

INTRODUCING THE CONCEPT OF REMISSION IN THE INTRODUCTION.

This point is well taken and really opened up quite a few little changes that I made to the
manuscript. I have added a phrase in the opening paragraph of the INTRODUCTION. It is now the major focus, rather than ‘any antidepressant response’, as was the case in the prior version.

**THE MEDICATION QUERY.**

I address this important point (his concerns with the medication and the criteria used to assess treatment refractoriness) in the METHODS section.

Concerning this point the paragraph in the Methods section has been completely rewritten. I have finally come around to Dr Stewart point of view. He has major concerns about being as clear as possible about the medication used. He again brought it up in his queries. I think this is fully justified, both for the reasons he provides as well as for others. Medication is a somewhat fluctuating phenomenon. Yesterday’s typical dose (this protocol was actually written almost 7 years ago using the available references) is not always today’s or even tomorrow’s. If this manuscript is published, 10 years from now it is entirely possible that, for one of the antidepressants used, what I considered ‘therapeutic’ or maximum might no longer be so. I have thus added a bit of data from the STAR*D study inasmuch as the dose cut offs that I used were either equal to or above those that were typically shown to induce remission in that trial. I hope this section is clearer and it should as the vast majority of the patients had sequential venlafaxine and a reuptake blocker (or the other way around). The remaining few had a mix of the other antidepressants mentioned at the doses mentioned. They all had a third treatment (for example, a reuptake blocker at a dose lower that that used as a cut off although this did not count as an ‘adequate’ treatment). It is still mentioned as 30 mg of paroxetine or 250 mg of wellbutrin, 187.5 mg XR of venlafaxine still cannot be considered a ‘non’ treatment. Some patients do respond to these doses. This should also be clear from this paragraph. I have added a footnote to table 1 also.

**THE ‘CBT IS EFFECTIVE IN TRD’ QUERY IN THE INTRODUCTION.**

Upon reading this paragraph I feel that Dr Stewart’s point is well made. However, CBT itself has to be introduced to the reader. After all, data of its usefulness in stage II TRD is, at best, very sparse. Also and again, going back to when this protocol was initially written CBT had an extensive, 10 to 20 year history in the treatment of ‘mild to moderate’ depression, whereas the evidence for quetiapine was basically in abstract form at the APA (I presented this data in abstract form at the APA in New York). Apart from the recent STAR*D data on CBT, its use in stage II TRD is, even today, rather novel (although I would agree that it is increasing almost on a monthly basis). As such, it requires a little background and perspective.

What I have done, rather that limit the CBT discussion is insert it into a somewhat larger paragraph in the INTRODUCTION on TRD (therefore diluting a bit) while I enhanced the discussion on quetiapine in the paragraph underneath, as a preamble to the aim of the study. The reader’s focus should at least be equally (or more) on quetiapine now.

**THE COMMENTS AND QUERIES CONCERNING THE METHODS SECTION.**

I think I have answered most of this query in the ‘medication’ response above. I am not quite sure
what Dr Stewart means by ‘other’ criteria used. The only criteria I used was to open the 2001-2002 Canadian Pharmaceutical Compendium, distributed to all physicians in the country and the official guide, and looked up all of the antidepressants and wrote in the protocol what the maximum recommended dose was. The key word here is recommended. I will admit that it is a bit on the conservative side, as it is used by all physicians, specialists and GPs included. That being said the doses that were used in this study are nevertheless equal to or above those used by the STAR*D study.

I have taken Dr Stewart’s maximum dose comment as tongue in cheek (I hope that I am correct). Although the minimum treatment was 8 weeks, most every patient has much longer durations of treatment for each sequential antidepressant. In addition, no, maximum dose for 3 of the 8 weeks means just that. The dose had to be confirmed at maximum for the whole 3 weeks, not for one minute during the 3 weeks. Again, for most every patient 3 weeks was a minimum and it was often much longer. I did not re write this in the METHODS section as I really do not think that readers would interpret this in any other way. One just has to look at table 1 and the duration of the depression for most patients (close to 2 years) would suggest that this is so.

Bipolar disorders were excluded. This is mentioned on page 6 in the exclusion criteria. However, given that clinical trial reports today require about twice or three times the number of pages in the METHODS section as any other section, parsing every detail is somewhat of a chore, so this comment is quite understandable.

Regarding the lithium comment, as stated in the text some patients were excluded due to non-compliance so when the lithium level was clearly not where it should be (or just about) and for no obvious reason, patients were excluded. There is still debate as the relevance of lithium levels and the augmentation response. The initial reports (the deMontigny group) did not find a correlation. In fact, lithium augmentation was observed within 48 hrs. Later studies suggested that although responses can be observed at that time, much later (weeks rather than days) responses are also typical. In a recent review including most RCTs on lithium augmentation (with and without the inclusion of open label ones), levels were not correlated, at least when 0.5 mEq/L or more.

As such, levels of 0.6 to 0.9 mEq/L were targeted. Levels were adjusted to within this range at the first blood level, which was a week after beginning lithium treatment. As there were sufficient funds to use a private laboratory results were exceptionally fast (especially of a universal health care country) and permitted very rapid adjustments. However, one must realize that this adjustment was for the sake of protocol, given the absence of a correlation and potential early responses. Again, here we are taking about response, not remission, and the criteria for response were not exceptionally strict. Patients were not extended into the study and given, for instance, 4 rather than 3 weeks of treatment. In addition, lithium was tapered at day 21 in non responders and this afforded them a bit more than 3 weeks of continued therapy, so that for the odd patient at 0.5 for instance that was tapered up to 0.6 the total duration at 0.6 would have been a little under 3 weeks.

THE COMMENTS AND QUERIES CONCERNING THE RESULTS SECTION.

The ‘One’ has been corrected. It never ceases to amaze me that no matter how many times I read
A ‘notable’ between group difference was study completion. Here, subsequent to Dr Stewart’s prior objection to the unadjusted 2X2 OR I removed the significant connotation as well as the unadjusted OR. I downgraded it to a ‘notable’ difference. I used notable here as ‘observable’ or ‘detectable’ or ‘mentionable’ or ‘trend’ or ‘interesting’, not as significant. I feel that a 91% completion versus a 45% completion is nevertheless interesting clinically, even if just given in a naturalistic manner, and merits one of these qualifiers. No p values or given or any mention that this is significant. In addition, it is followed by a true statistic that differentiates the 2 groups on the total number of visits they finished. So the 2 groups differ in this highly related aspect (indeed, just another way of looking at basically the same data). However, if Dr Stewart objects to ‘notable’ I am perfectly willing to use one of the other qualifiers. I have replaced it with ‘interesting between group observation’ in the text, although any other suggestion would be fine.

What was the placebo count? Pills were matched exactly. There were an equal number of placebo or quetiapine pills. The pill count is the same. They were distributed in visit specific blister packs produced by Astra-Zeneca, making pill counting relatively straightforward. Pill counts were performed by the nursing staff and the interviewing investigator was not told aware of it, unless of course there was some sort of discrepancy for a given visit. In this instance the research nurse would inform the investigator. I have added a phrase in the results section.

The authors should consider deleting the last paragraph of the results section as, although not inaccurate, does not really make the case for the effectiveness of CBT in TRD. The paragraph has now been deleted.

THE COMMENTS AND QUERIES CONCERNING THE DISCUSSION SECTION.

The emphasis on the combined results have been excluded from the results section and the emphasis (although I would say ‘mention’) about the effectiveness of CBT and placebo is substantially reduced. The focus is now on the quetiapine and CBT arm. This is clearly stated as the primary finding of this study. I have also added a few phrases on the average dose of quetiapine as a limiting factor in this study. Again, this goes some way in placing the focus on quetiapine, rather than CBT. CBT remains in the discussion as it is nevertheless interesting to speculate as to its relatively poor showing.

The Keller reference may not be appropriate.
I have now rephrased this and used the reference in a more generic way to illustrate the contrast between the two Rx+psychotherapy treatments, rather that specifically CBT. It is now being used as a general intro into the discussion as to why CBT did not appear to do very well in this study. The context has been changed so that the Lower response rate is now meaning is clearer. These sections have been substantially re-written.

The references of the superiority of the combined treatment versus either alone have all been removed. Again, a lot of these paragraphs have been revised.

Table 2 has been rearranged as per Dr Stewart’s suggestion. The p values were removed from the
RESULTS section for the secondary scales and the table is referenced instead.

In the hope that this revision will meet with your satisfaction,

Yves Chaput, MD, FRCP(C), PhD