Author's response to reviews

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

Authors:

Yves JA Chaput (yveschaput@bellnet.ca)
Annick Magnan (tobedetermined@bellnet.ca)

Version: 2 Date: 7 January 2008

Author's response to reviews: see over
Thank you for reviewing my manuscript entitled ‘A double-blind, randomized, placebo controlled trial of cognitive-behaviour therapy, alone or co-administered with quetiapine, in refractory depression’ that I submitted for your consideration in BMC-Psychiatry on the 7th of November 2007.

Overall, the reviewers made many comments and queries that required quite a few modifications to the text. In fact, most of the RESULTS, DISCUSSION and CONCLUSION sections have been revised. Changes and additions have also been made to the ABSTRACT and METHODS sections, less so to the INTRODUCTION. The queries and the subsequent changes that made as a result have hopefully substantially enhanced the quality of the manuscript. Dr Khan makes two broad main points in his comments. The first is to more precisely (accurately?) interpret the data and the other is a query concerning the effect of the passage of time on our results. Dr Stewart makes quite a few specific points per manuscript section. Overall, many of Dr Stewart’s points are similar to Dr Kahn’s first point but with a major difference. Dr Stewart is much more skeptical with regards all of the open label data in this manuscript and suggests focusing almost exclusively on the double blind portion of the trial.

The major queries and comments made by the two reviewers and the changes are detailed below.

I will begin with the comments by Dr Stewart, as they are much more numerous.

**Query:** The STAR*D data is not adequately interpreted and can be misleading (second paragraph of the INTRODUCTION).

**Response:** The second paragraph of the introduction has been revised. I have re read the article in the Am J Psychiatry and, in order to eliminate all ambiguity, I have essentially quoted the authors themselves on this subject. In fact, I have probably gone as far as one can go without being accused of outright plagiarism!

**Query:** The primary aim of the study, as stated in the INTRODUCTION, is not really supported by the methodology used.

**Response:** I understand this comment although I do not fully agree with it. Clearly, the effectiveness of CBT in TRD is not part of the double-blind paradigm and represents an uncontrolled, open label assessment. This reduces its validity to the level of ‘case reports’ although does not eliminate it entirely (the lithium open label part of the trial also).

As stated earlier, I have re-written the aim section of the study in the INTRODUCTION in order to better reflect the methodology used. The open label results have been substantially downgraded to a paragraph at the end of the RESULTS section.
Query: In the METHODS section, a query about the number of patients with a screen HAMD scores. More specifically, Dr Stewart wonders ‘how many patients had entry $HAMD = 20$, and randomization $= 18$. I.e., how many had their scores inflated in order to shoe horn them into the study? Forced scores ought to drop once study entry constraints are removed, independent of treatment effects. Drops in post-randomization scores then become misleading in suggesting treatment efficacy. Thus, apparent improvement in patients treated with CBT alone might be partially attributable to such obligatory post-randomization drops in HAMD scores. Post-randomization changes in scores not required for randomization seem more meaningful. This seems especially important in their 31 patients whose mean $HRSD$ was only 23, so presumably including a lot who barely met study entry criteria.’

Response: I must admit that this query caught me a bit off guard. In response, 2 patients had HAMD randomization scores of 18. One had a screen HAMD score of 22, the other of 20. No consistent change was observed at LOCF (one was substantially improved whereas the other was substantially less well and was less well beginning at the following evaluation point). There was no predictability here or ‘obligatory post randomization drop in HAMD scores’.

Any methodology (clinical or not) can be perverted. To date (and since 1986), none of my prior publications (mostly in basic science rather than of clinical research) have been singled out as using questionable or inappropriate methodology. In fact, some, especially those concerning the physiological role of serotonin somatodendritic and terminal autoreceptors and the possible effects of antidepressant treatments on their sensitivity are still, 20 years later, actively cited in new publications. I have also participated in a host of pharmaceutical clinical trails and have always ‘passed’ the ‘peer’ inter rater reliability sessions with success using ratings instruments for depression (including the HRSD), psychosis and for anxiety. I would imagine that the only certain way of eliminating such a situation would be to record all patient interviews, as is often done for the CBT sessions, for independent review, if need be. However, this was not done for this trial.

Query: In the METHODS section. Dr Stewart wonders queries ‘They state they excluded patients with most of the common psychiatric disorders, including personality disorders. They do not state how they determined whether their patients had personality disorders. As the more reliable methods are quite time consuming, one wonders how well personality disorders were excluded. But, also, why, as apparent personality disorders sometimes disappear once a patient is no longer depressed.’

Response: This section has been slightly revised. I now state that certain personality disorders were excluded, including the type A (paranoid, schizoid, schizotypal and antisocial) and one type B (borderline). As state earlier I have participated in many clinical trails and have extensively used the M.I.N.I (Version 5, which is available in French and in English). I have, over the years, incorporated it into my clinical Evaluation although the clinical evaluation predominated here.

Second, as I was in charge of the emergency service of the university hospital where many patients were recruited from the psychiatric chart was readily available to me.
Third, as colleagues readily referred patients (for once) for this study background information (pharmacological and clinical) was readily available for those recruited outside the hospital. This is now stated briefly in the second paragraph of the METHODS.

As to why they were excluded pertains to the actual design of this study. This study actually started out as a ‘feasability’ study (of taking a group of TRD patients and withdrawing all medication within a short period of time and allocating to CBT in an open trail fashion) when I originally wrote the protocol. It was not at all clear that patients would be interested in withdrawing all meds or indeed, that an IRB would not consider it a high risk endeavor (both IRBs did). The study thus required clear and verifiable entrance criteria, both on a diagnostic and pharmacological level in order to minimized the risk to the patients. Part of minimizing this risk was to eliminate all contributing factors to possible suicide attempts, such as BPD or antisocial personality disorders and substance abuse disorders. For obvious reasons, all anxiety disorders were excluded as this was, after all, a CBT trial. In addition, with relatively modest resources (financial mostly) the the goal was essentially to obtain a measurable effect, regardless of whether it was maximal or not. This also required eliminating all possible contributing clinical factors, permitting a smaller number of N at intake. In fact, most of the patients eliminated from the initial 40 were, at a minimum, co morbid with a type B (or A) disorder.

Query: Dr Stewart stats that ‘I doubt they excluded patients allergic to penicillin, yet state that patients with “nonwn drug allergies” were excluded. Granted, the offensive sentence ends with the clause “that might contraindicate . . .” But, why not clarify that it is specifically a quetiapine drug allergy that they intended to exclude’

Response: This is correct. The purpose was not to exclude any type of allergy but rather, those that might affect the course of the study. Although after having had one patient in a prior study end up in med ICU for a month with a possible ‘related’ drug effect (ended up not being so, thankfully and the patient made a full recovery), all of those sleepless nights made me take this section quite seriously. What I tried to eliminate was any known (chart or self report) psychotropic drug allergy, including to quetiapine. I have revised this in the text. Given the nature of this study you can understand that the ICF, already voluminous, became substantially more so after the inclusion of a sponsor (and the sponsor’s internal review board) and the requirements of 2 independent IRB boards. The wording of this section is a consequence of this somewhat administrative process. I do agree however that it is ‘over inclusive’.

Query: The study group ‘really consisted on twice antidepressant refractory plus lithium augmentation refractory subjects. They state that “maximal recommended doses” were required to consider patients to be refractory. However, they never mention what medications had been used or at what doses or whose “recommended doses” were utilized. Perhaps these were ideosyncratic doses I (and possibly others) would consider grossly inadequate’.

Response: All dosages were verified, as stated above. This was an absolute requirement. Otherwise, it would have been ethically difficult to justify recommending CBT as one of the logical alternatives and withdraw all meds following lithium non-response.
In fact, the average number of documented antidepressant treatments was 3 in each group. Actually, many patients had more, however, we could usually confirm the dose (via the patient’s pharmacy or physician) but could not be certain of the duration of treatment. Bupropion is a case in point. A paragraph has been added to the METHODS section detailing all antidepressants and their average doses.

The actual reference used was the Canadian Pharmacists Association Compendium of Pharmaceutical Products. This annual publication is the most widely referenced source in Canada.

Query: ‘After demographics and illness history, next thing should be to document what the prior medications were that patients were deemed to be refractory to and what the maximal doses of these had been that they had taken for at least three weeks each. Otherwise, the reader has no idea whether he or she would agree that these are “treatment refractory” patients according to their own definition.’

Response; This has now been added in the METHODS section.

Query; Revisions to table 2. As well, the reviewer questions the ‘significance of HRSD # 14’ as well as many other parts of the table

Response; 14 was actually the minimum score for admission into the STAR*D study. 15 was the ‘response’ score for the Keller study (#25). Both somehow got lost in the many changes that I eventually made to the last version of the manuscript. This was a summary table and I tried to draw attention to the N=29 section, which was the overall response to the study, both open label and double blind. However, as this is no longer a focus of the study the table itself makes even less sense in the present manuscript so I have eliminated it altogether. Some of it was inserted in the DISCUSSION section in the text.

Query; ‘They report screening but not randomization scores.’

Response; The focus now being on the double-blind portion of the trial, both screen and randomizations are in the text (in parentheses, second paragraph of the RESULTS section).

Query The recommendation to lead ‘off with describing the population that got to randomization (as they do, but expanding on that), then jumping right into Efficacy of Quetiepine, only mentioning what occurred in the CBT only group as a contrast for the quetiepine group. Leave editorializing as to whether what occurred on CBT alone can be attributed to CBT vs. the natural course of illness to the discussion. It is a minor issue in this study, given its methodology, so why highlight it?’

Response; I have re arranged the RESULTS section accordingly. The editorializing part (which I believe was the paragraph summarizing the lithium and CBT phase) has been removed.
Query: What does “Day 70” mean?

Response: Sorry for the confusion. I have now rephrased this in a more meaningful way. I now refer to the number of CBT sessions given in parallel to the number of days post randomization (of quetiapine or placebo tx).

Query: ‘They state that quetiapine was well-tolerated. If so, I wonder why the mean dose was so low and no one reached the allowed maximum in the face of most patients not remitting. They do not report what the pills per day were for those receiving placebo. If the range in number of pills equals that of quetiapine-treated patients, one wonders about the vigor of the treaters. If most reached max or at least near max, one wonders about the statement that quetiapine was well-tolerated.’

Response: Tolerance here primarily relates to SAEs, which this study did not have. This line has been added to the text.

Time passes by quickly and the volume of information regarding quetiapine and its off label uses has been rapidly mounting, especially since 2006 onward. From the time this protocol was initially written to the time the actual study was completed (around 3 years) off label data were either in abstract form or were in preliminary reports. Therefore, hard data as to what might be an ‘adequate’ dose was a matter of some debate.

A second, somewhat difficult point to make in a manuscript is that many of these patients had had at least 3 (some more, as we could not fully document them) courses of drug therapy. Some (many?) patients (and this is my opinion) were simply weary about another ‘drug trial’. As the dose level was flexible and was open for discussion with the patient, the overall doses were on the moderate side.

Third, again, this study was not about achieving maximum effect but a detectable one. Furthermore, the same logic applied to question the possible ‘solo’ effectiveness of CBT in this study must also be consistently applied to that of the ‘antidepressant’ or ‘drug’ effect of quetiapine. This study was not designed to assess the antidepressant efficacy of quetiapine but rather, to assess whether combined CBT and quetiapine were more effective than CBT and placebo in TRD using as a measure a detectable (albeit not maximal) effect.

Query: ‘I wonder how “CBT significantly . . . resulted in clinical improvement” (bottom p. 11) jibes with “no significant improvement was observed in the CBT+placebo group.”’

Response: Quite right. The statement referred to the combined CBT group and these references have been either removed or substantially downgraded in the revised text.

Query: Would a Fisher, rather than a standard Pearson, be more appropriate?..?

Response: An interesting point. The answer here is yes and no and it really depends on
how one interprets the data. As it is stated in the text, one patient was withdrawn from the CBT group due to an erroneous ECG report (otherwise known as Murphy’s law). In fact, there were no actual ‘drop outs’ (a patient or PI initiated event due to an actual SAE, clinical non response or clinical deterioration or simple withdrawal of consent) from the CBT group. The patient requested to remain on study. Obviously, opening the blind precluded this. Hence, this data (survival) is a bit difficult to analyze statistically (hence your query). Fisher (a bit more complicated) or Yates are basically corrections that can be used when one of the cells have few occurrences and would not compensate for the underlying fact that the n value that should be there, cannot be. So, after some thought, the answer to this question is that neither uncorrected or corrected are really ideal here.

I have solved this problem in 2 ways. The first is to simply ‘note’ the differences in survival in a naturalistic fashion without comment. The second (which I should have done in the first place) was to use strictly parametric data and parametric analyses if at all possible. As such, instead, I have calculated, for each patient, the number of CBT sessions given and assessed whether the means differ between groups (ANOVA). This solves the problem of the withdrawn patient, who is now counted up to the time of the withdrawal. It also permits me to eliminate the phrase in this paragraph about the withdrawal, which, upon re-reading, appeared to be a bit ‘whiny’.

Query; The initial sentence of the DISCUSSION is not supported by the results.

Response; Again, I do not entirely agree with the reviewer on this point. However, the opening phrase (and first paragraph) have been revised to better reflect the RESULTS section.

Query; Reference #31 is used as a gateway to another reference, better cite the original.

Response; Quite right, although the principal author of both #31 and the book chapter referenced by #31 are the same I agree that this is not as precise as it should be and it has been changed. Quite a sharp observation!

Query; In the DISCUSSION section, the paragraph restating the general results of the study (prior to the discussion on quetiapine) is confusing.

Response; Agree. In any case, most of the paragraph restates what is now (hopefully) clearer in the revised manuscript. I have eliminated most all of it. Another reason is that I have shied away as much as possible from using the term ‘CBT alone’ in the manuscript given that, first, it was never given alone but rather with placebo and second, there is a recent publication (in BMC Psychiatry) about the possible influence of ‘placebo’ pills on the effectiveness of CBT in panic disorder.

Query; In the DISCUSSION section, the section regarding interpreting the usefulness of quetiapine should be more voluminous (perhaps less speculative?) by the inclusion of subsets of the HRSD items, such as anxiety, depression and sleep.

Response; Generally I agree with the comment and I have actually looked at both the
HRSD and also the HADS (which is evenly divided between anxiety and depression sections). As to the query about sleep improvement the answer is no. As to the other queries the answer may be more towards the anxiety subscales. That being said, the n values are small and this discussion would essentially become speculative, so I have decided not to include it. Furthermore, such a discussion would most likely be complicated by the obvious fact that CBT is quite effective in the treatment of anxiety disorders and again, would be speculative as to ‘which’ treatment is really effective.

In any case, if this manuscript is accepted then the avid reader will have access to this document, your query and my response so that my preliminary analyses can be reviewed ‘off the record’.

Query: Better document the prior treatments in table 1.

Response: As stated above, a paragraph (second) has been added to the METHODS.

Dr A Khan;

Query: ‘The authors need to address how they are wording or interpreting their results in the abstract and discussion. The statement that cognitive behavioral therapy has a role in depressed patients who are relatively treatment resistant is somewhat misleading. First and foremost, the changes seen in the CBT group could be simply due to passage of time, or due to placebo effects. Only 5 of 11 patients completed this treatment arm and the symptom reduction in this group was small compared to the quetiapine group. In this regard, it could be misinterpreted by some that CBT is sufficient for somewhat treatment resistant depressed patients. The authors need to clearly define what they consider the ‘role’ of CBT in TRD patients.’

Response:

I have addressed this point, which is related to several of those made by Dr Stewart, in the following manner.

(1) The title of the manuscript has been changed to better reflect the methodology used. It is now entitled « The co-administration of quetiapine to cognitive-behavior therapy in treatment refractory depression; a preliminary placebo controlled trial ». The preliminary nature of this study is further highlighted as when I ‘re read’ the methods section, this was really not that clear. In fact, this title is now very close to the one I gave this study while submitting the protocol to the two IRBs.

(2) Second, both the results and conclusion sections of the ABSTRACT have been modified to focus on that group that improved the most, the CBT + Q one. It is no longer mentioned that CBT alone may be of benefit in TRD.

(3) In the INTRODUCTION section, the primary aim section (last paragraph) as been rewritten to better reflect the methodology used and to reduce any ambiguity.

(4) Third, the RESULTS section has been modified in several ways. Again, in line with the title, the results of the CBT + quetiapine (vs CBT + Placebo) double label arm now follow the results of the open phase of the study (overall patient descriptions and the open
label trail of lithium carbonate).

This replaces the ‘overall CBT results’ (i.e., the combined CBT groups) that I presented in the first version of the manuscript and that posed a problem for Dr Khan and for Dr Stewart. These latter results are now integrated into a paragraph at the end of the newly termed ‘Combined quetiapine and CBT administration versus CBT and placebo in TRD’ section of the results. I still believe that the ‘open label’ results (lithium addition and the effectiveness of CBT alone) are worth mentioning and describing although I agree that they should not possess the same degree of importance as the double-blind results.

(5) Lastly, the fourth paragraph of the DISCUSSION section has been substantially rewritten and now includes a discussion of the possible effects of time in this study. In addition, most all paragraphs of the discussion have been rewritten to better reflect the methodology and data.

(6) The CONCLUSION section has also been revised for clarity.

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

Yves Chaput, MD, FRCP(C), PhD