Reviewer’s report

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

Version: 3 Date: 24 June 2008

Reviewer: Jonathan W. Stewart

Reviewer’s report:

This is a BIG improvement, but I feel still needs a little work. Despite my many thoughts, below, this is the right thrust.

First, the title and abstract now more appropriately describe what they did. And, the initial sentence of the Discussion accurately states the only conclusion their design allows. Bravo!

Perhaps it is style, but I would have placed the paragraph introducing quetiapine ahead of the one about CBT. Again, because their design cannot address the efficacy of CBT, but can address possible efficacy of quetiapine, why lead with the treatment you cannot address? The manuscript has to introduce what is known about the utility of CBT for TRD. That is not my beef. Rather, it is that CBT is presented, especially in an earlier version of this manuscript as the answer for TRD, when this is not the case and this study does not make a case in that direction. Yes, CBT needs to be introduced to the reader, but not as the main thing the manuscript is about, or, indeed, something the manuscript can say anything definitive about.

More importantly, while they state a study aim their paper can address, they make no comment about why they used CBT, rather than just doing a drug vs. placebo study. Certainly, it would be nice to know whether CBT could help in TRD, but since they designed the study so they cannot address that question, what is CBT doing in it? We are not informed.

They have provided better documentation of prior treatment. However, I quibble with their stating “maximum recommended” doses. At least to me, this means the highest dose stated in the PDR as being safe to use. Apparently, this is not what they meant, as they give ranges of doses they considered to meet this criterion. I would prefer they state unambiguously what they did rather than leaving it to the reader to guess. For example, if accurate, they might state “an adequate trial was judged to have occurred if prior treatment lasted 8 weeks including at least three weeks during which the dose was at least half the dose listed in the PDR as maximal.” It would be nice to know the mean ± s.d. and range for number of prior treatments. They studied too few patients but ideally they would report whether the more highly refractory patients were less likely to benefit. Embedded in the Discussion we find that “some patients were at stage V.” This information and the number at each stage and/or number who previsously received how many
adequate trials belong in the Results.

Unfortunately, I am unfamiliar with the Canadian Pharmaceutical Compendium so cannot comment on what it says. I think the thing to do, then, is to merely state that you required doses at least at the dose recommended as maximal by the CPC. As few non-Canadian readers will be familiar with what the CPC says, it would probably be best to give several examples of what the CPC considers “maximal” for the more common drugs. What I am ignorant of is whether “maximal recommended” means practitioners should not go any higher than that, or is it more something the CPC suggests clinicians shoot for while there is sometimes a higher allowable dose. In any case, let us know what you actually did and try to place that into a context we readers can relate to (i.e., probably most readers of a non-Canadian journal will not know what is in the CPC).

In his comments to me, the author pointed out that the cut-off doses used in his study were equal to or higher than those patients typically responded to in STAR*D. And, there is a similar comment in the text of the manuscript. I do not think this is the way to think about treatment refractoriness. Thus, just because 20 mg of fluoxetine is the commonest dose for people to improve does not mean I think patients who have received 20 mg/d of fluoxetine have had an “adequate trial”. Would Dr. Chaput say to someone unresponsive to 20 mg/d of fluoxetine, “Well, fluoxetine has not worked for you, let’s stop it and move to something else”? I doubt it, or, at least, hope not. At least clinically, Dr. Chaput does not consider 20 mgd of fluoxetine to be an adequate trial. So, the dose most people benefit from seems a poor way to define adequacy.

Statistical analysis still states alludes to patients being “randomized to CBT.” In fact, determination of who received CBT was not by random. Whether patients received quetiapine or placebo is what was randomly determined. Probably a left-over, but still misleading.

There must be a misprint on p. 13 as both significant secondary efficacy measures are listed as being the CGI-S.

Appropriately, they give the mg/d and range of the patients assigned to quetiapine. However, the standard deviation is missing and the number of pills the patients were taking in the placebo group. They also should show, perhaps in parentheses, the number of pills the active group took with the statistical comparison of number of pills each group took. In my experience, patients taking placebo generally take more than those taking active, both because they are less likely to be getting better (at least if the drug is effective) and because they are less likely to have side effects that might prevent increases. Because this study had such a high drop-out rate in its placebo arm, they may have had the opposite effect, that is, the placebo arm took fewer pills because they never had a chance to increase the dose. Whatever, the reasons for any differences, they should show the data.

While Dr. Chaput states in his comments that he include pill counts in the Results, I could not find it. While the pills were presumably identical in
appearance and identical numbers would presumably have been given to patients, what I would like to know is how many pills patients actually took. Dr. Chaput states in comments but not in the manuscript that these were identical for the quetiepine/CBT vs. the placebo/CBT subjects. This seems unlikely given the wide range of doses taken by the patients in the active drug group.

I do not object to the term “notable” as I agree that the high placebo drop-out rate certainly seems notable. However, why report this rate without informing the reader whether the proportions differ? Showing that the times in the study differ does not address whether the proportions differ. Also, does the fact that the placebo/CBT group had significantly less time in the study (i.e., less opportunity to improve) affect your interpretation of the statistics. I.e., was it more time or effective drug that got the quetiepine/CBT people better?

Rates of various side effects are shown, but we are not informed whether any differ between groups.

We are informed how many patients “responded” to lithium, but not how many remitted. Nor are we informed (at least that I could find) how “response” was defined. Table 2 shows % improvement on a variety of ratings, but we are never told how many patients met response or remission criteria. The reader therefore has no sense at all whether the small per cent improvements represent most patients getting a little better or a few achieving remission. Since we strive to achieve remission, it is important to know whether any patients did. Thus, if quetiepine outperformed placebo on continuous measures but no one remitted, that seems less supportive of quetiepine’s use than it would be if some people’s depression completed went away and no ones did on placebo.

While the comments to the reviewer acknowledge the importance of treating to remission, and this is reflected in the Introduction, as best I can tell this is the end of it. If the authors agree this is important, why do they not make this their major end point, or at least report how many subjects reached whatever their definition of remission might be.

The last sentence of the first paragraph of the Discussion accurately raises questions about the utility of substituting quetiepine for unsuccessful antidepressant. However, doesn’t the failure of the placebo/CBT group to change at all also raise questions about the utility of CBT alone for this population? Seems to me, if this is where they want to raise issues about quetiepine’s efficacy as monotherapy, the efficacy of CBT as monotherapy should also be raised at the same time. If nothing else, to the extent that CBT is not doing anything, their argument that the study tells us nothing about quetiepine as monotherapy is undermined.

At least as I understand what they did, they are comparing apples and oranges in the second paragraph of the Discussion. Maybe even apples and hammers. That is, the 30% they refer to in their study is the per cent change in rating scale score. The comparison 73% is the per cent Keller reported to have met his “response” criterion. As best I could tell, they did not report how many of their
subjects met Keller’s “response” criterion. So, on what basis can the authors assert that their rates are “modest” relative to Keller. Perhaps they are, but not based on the information they give us.

They never speculate about the possible efficacy of quetiapine as monotherapy. Nor do they speculate about the implications of the lack of change in the placebo/CBT group for CBT monotherapy for TRD and whether that might inform our thoughts about using quetiapine as monotherapy vs. combining it with CBT.

Finally, Dr. Chaput states in his comments to me that he has mentioned speculation about CBT’s poor showing. He certainly speculates that perhaps longer treatment would have been of benefit. However, he does not speculate that perhaps CBT is ineffective for this population.