Reviewer's report

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

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Reviewer: Jonathan W. Stewart

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These authors randomly assigned 22 outpatients with TRD to quetiapine or placebo, all subjects also receiving CBT, showing increased efficacy in those receiving quetiapine relative to placebo and concluding that combined CBT/quetiapine is superior to CBT/placebo in the treatment of TRD.

Title & Abstract

I still object to their conviction that this study has anything to do with CBT. While not inaccurate, the title is too obscure to indicate that this was really a quetiapine/placebo trial in which all subjects also received CBT. Abstract Results state that 22 patients were “randomized to CBT” which is true but obscures the fact that no patients were randomized to not receive CBT. In fact, the results first indicate how well patients did not CBT and only then give the quetiapine results, as if the main thrust was CBT efficacy and quetiapine only a secondary consideration. Since the study design only allows inferences about quetiapine, this continues to seem backwards to me. And, while I cannot quibble with their Abstract’s Conclusion, I wonder if it would be appropriate to raise the question of whether CBT contributed anything to the equation, especially since the CBT-placebo group’s ratings did not budge.

Introduction

Certainly they are more or less correct in their description of response rates, perhaps erring (if they err) on the side of being too generous. However, today we seem more interested in remission than in partial benefit, so I wonder whether they might better address remission than response in the Introduction. The advantage of leading off with remission would be it would paint a darker picture more worthy of the type of investigation they did. Thus, their discourse suggests that 85% of depressed patients do pretty well and “only” 15% require our thinking caps as to what else to try with them. Instead, I think at least 50% need our thinking caps (e.g., STAR*D got only 52% remitted after 4 treatments in ITT analysis, John Rush’s more optimistic but theoretical figure of 67% notwithstanding.

Second paragraph continues this “CBT is effective” theme. Again, what they say is probably pretty accurate and a rationale for using CBT, but since the study cannot address whether CBT is doing anything, why place it so prominently?

Methods
Not clear how “maximum recommended dose” could result in patients receiving different doses, as indicated by a standard deviation for all except mirtazepine. I suspect they actually used some criterion other than that stated. Also, they indicate a required time on drug but not whether they required more than a single dose of the “maximum recommended dose” (or whatever their actual criterion for dose was), but not how they handled someone who took minimal dose for 55 days and maximal dose once.

Bipolar is not mentioned as an exclusion. Does that mean bipolars were included?

Text indicates patients had to have lithium level between .6 and .9 by day 7. Does that mean patients with lower or higher lithium levels were dropped? Or, was their lithium dose manipulated to get them within this window? If the latter, was their time prior to determining eligibility for randomization extended?

Results

Middle p. 12, “One . . .” should be “Of . . .”

“A notable between group difference was study completion . . .” Really? 10/11 vs. 5/11 yields a $p = .06$ (by Fisher and by Chi Square).

Average dose of quetiapine is given, but not of placebo. Since dose of quetiapine was low relative to possible maximum dose, one wonders whether placebo-treated patients ended up on more pills and whether this might have “broken the blind”. In any case, pills/d should be reported for both conditions.

Again, it is not inaccurate to report combined improvement rates across treatments. However, isn’t this misleading in suggesting CBT might have been beneficial, when it seems (based on the CBT+placebo condition) that CBT had no appreciable effect? I wonder if more is gained than lost by deleting this paragraph, invested though the authors seem to be to it.

Discussion

Here they go again! The second sentence of the Discussion suggests the results are compatible with efficacy for CBT for TRD. I fail to see how lack of demonstration of significant change in the CBT+placebo group is compatible with efficacy. It was only the CBT+quetiapine condition that demonstrated either presumptive (pre-post differences) or actual (between group) efficacy. The CBT+placebo group did neither. The data are most compatible with quetiapine being effective in treating some patients with TRD. Whether CBT added something to the demonstrated efficacy of quetiapine or was just along for the ride cannot be answered but certainly does not seem “compatible with” CBT’s efficacy. So, why make that the first definitive statement of the Discussion?

Not sure Keller is the most appropriate comparison group, as my recollection is that study was not in prospectively demonstrated TRD. In any case, Keller used CBASP, not CBT, as these authors assert.
“The lower response rate . . .” Relative to what? I suppose they mean relative to Keller, but that is probably not an appropriate comparison in any case, as already noted.

Again, “The results . . . suggest that a combination . . . approach may be superior to either treatment alone.” No! Again, misleadingly suggesting CBT is doing anything. They only showed that quetiapine+CBT does better than placebo+CBT, they did not give anyone quetiapine without CBT so cannot comment on this comparison. But they ought to mention that the results are compatible with all the demonstrated benefits accruing to quetiapine alone, but it would take a quetiapine+CBT vs. quetiapine alone comparison to assess this possibility.

Tables
Show mean # prior treatments but not # of adequate treatments.

I’d leave out the “All patients” column and substitute the statistics for between group comparisons.