Reviewer's report

Title: Introducing a new Concept to assess the Efficacy of psychopharmacological and psychotherapeutic Interventions in Patients with Major Depression

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Reviewer: Jonathan W. Stewart

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There are many reasons to doubt the generalizability of RCT’s to clinical practice. These authors propose a remedy by recommending a study that randomizes patients to typical RCT conditions vs. several alternatives including one that mimics clinical treatment. The beauty of their proposal is it directly compares a typical RCT to studies having various degrees of deviation from a typical RCT potentially allowing a determinations of how closely each iteration comes to what is seen in general practice. Thereby, the proposed randomization of patients to various trial designs will allow clinicians to judge what they might expect in their clinical practices based on the findings of an RTC.

1) My first problem is they are too wordy and convoluted, undermining clarity. The manuscript needs a thorough and ruthless English-speaking editor.

2) Their message is simple and straightforward. Why obfuscate? They should limit their comments to the problem generalizing from RTC’s to clinical practice and their proposed remedy. In discussing their proposal, they need to mention its negatives, including requiring a huge sample size and risking being unable to reach conclusions due to differential attrition. They should omit irrelevancies, such as psychotherapy and how to maximize placebo effects.

Substantive issues:

3) If it is “difficult for the placebo effect . . . to take place in these trials” (i.e., RTC’s), how do they explain that alarming increase in placebo response rates over the recent years? They acknowledge the recent increase in RTC placebo response rates a page or two later, so I either misunderstand their point here or their assertions are inconsistent.

4) How does limiting RCT’s to arbitrary durations, such as 8 weeks, limit inferences? 8 weeks certainly rarely mimics clinical practice, but should RCT’s mimic clinical practice on this one, or should clinical practice mimic RCT’s?

5) They assert that clinical practice treats more severely ill patients than do RCT’s. This does not jibe with RCT’s having increasing requirements for minimal severity while in practice patients below these limits receive these medications. Certainly, the exclusion of suicidal and psychotic patients may equate to
excluding the more severely ill, so the main point is not so much a severity one as one of how broad the population is that is treated with these agents. But, this broadness of allowed population is inherent in clinical practice viz a viz RCT. Unless one has no entry criteria, one cannot mimic a clinician’s choice of to whom to give a given medication, since someone somewhere will use my favorite antidepressant for whoever walks in the door. But, without entry criteria, it seems difficult to draw any kind of logical inferences beyond “this works/does not work for whoever walks in the door.” And, the likelihood of such an “all comers” study demonstrating efficacy seems slim unless the sample size is huge, while who would you generalize it to even if successful? As a “whoever walks in the door” study would have to be generalized to “whoever walks in the door”, how is that an improvement over what we have now?

6) So, their BACKGROUND section needs to be stated more succinctly and more clearly. It seems to me they make two interlocking points. First, RTC’s do not mimic clinical practice because they X, Y and Z. Second, drugs marketed due to RTC demonstrations of efficacy are used in a much broader population of subjects than allowed into RTC’s. We need RTC’s to more closely mimic clinical practice both in terms of who gets treated and how the treatment is conducted.

DISCUSSION

7) I do not follow “1)”. In any case, I doubt recommendationis 1) and 2) are followed in clinical practice so I am unsure how they help the generalization from RTC’s to clinical practice.

8) “3)” makes a lot of humanitarian sense and ought to be done in all studies. However, at least in the US, the FDA has rules about exposing patients to safety risks prior to efficacy having been at least presumptively demonstrated. That is, I do not see how the FDA would allow use beyond a short-term study of an experimental agent in the participants in the initial efficacy studies. I doubt the FDA would alter its rules on this one, but I suppose these authors could try. Short of that, I see their proposed study a Phase IV trial rather than premarketing.

9) I am unclear how presenting positive expectations of placebo effects attracts “patients more representative of clinical practice”. Since placebos are not used (or, at least, are not labeled as such) in clinical practice, the presentation of positive expectations of placebo effects is also not used in clinical practice. So, how is it that presenting positive expectations of placebo effects attracts “patients more representative of clinical practice”?

10) Informed consent is also not a tool used in clinical practice. Are they recommending its use? Else, how is the informed consent process helpful in mimicking clinical practice?

11) I’d delete the section on psychotherapy. If retained, they need to acknowledge that control conditions besides “wait lists” have been used, for example, supportive psychotherapy or an exercise program in order to control for attention and time, differences demonstrating something “specific” about the experimental condition beyond that the patient is “doing something” or “receiving
a kind person’s attention”.

12) Indeed, my impression is that “doing something” alternatives have largely supplanted “wait lists” in psychotherapy research. In any case, this section gets in the way without helping.

13) While the four studies they present have intuitive merit, such studies suffer from attrition. That is, I may initially agree hoping I will be assigned to Study #4, then be disappointed to be assigned to Study #1 and not agree to continue. Should sufficient numbers not agree to their assigned study, that would invalidate comparisons across studies. The only conclusion would be “there is differential acceptability” but I submit that is not a very interesting conclusion. They indeed state that one of their intended analyses would be to determine whether there was differential nonacceptance but they do not indicate whether differential nonacceptance would affect other between study comparisons, e.g., of response/remission rates.

SUMMARY

14) “Modifying the meaning of what a placebo constitutes . . . seems essential”. Perhaps, but I do not see that they have demonstrated this.

15) It seems to me that if they can avoid differential non-acceptance, then their study design (i.e., randomizing patients to one of several study designs) is both novel and will allow an estimate of the relationship, if any, between the usual RTC (Study #1) and usual clinical practice (Study #4). That is, their design promises to tell us what the generalizability of RTC’s might be.

16) I wonder, though, what the sample size would have to be to have reasonable power. They do not address power/sample size. I suspect they would need a huge sample to be able to detect between study differences and/or suggest that failure to demonstrate differences is more likely due to lack of difference than lack of the power to detect.

Quality of written English: Not suitable for publication unless extensively edited

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

Declaration of competing interests:

I do not see how any organization could gain (or lose) financially from publication of the manuscript except or unless they use it to design a study using the ideas these authors present.

I do not own any patents and am unaware of any patents relating to the content of this manuscript; therefore, I am unaware of whether any organization with which I have done business holds or has applied for patents relating to the content of this manuscript.
I am unaware of any competing financial or nonfinancial interests. Thus, to the best of my knowledge, I have no competing interests, financial or otherwise.