Author's response to reviews

Title: A double-blind, randomized, placebo-controlled study assessing the efficacy and tolerability of desvenlafaxine 10 and 50 mg/d in adult outpatients with major depressive disorder

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Author's response to reviews: see over
Reviewer comments

Reviewer 1

Good design and carried out clinical study, with a negative results, which are as important as positive results sometimes.

However, as stated in the manuscript, a companion study comparing low-dose desvenlafaxine (25 mg/day) and desvenlafaxine (50 mg/day) with placebo did support the clinical superiority of desvenlafaxine 50 mg/day over placebo, and found no significant improvement with 25 mg/day in either observer- or patient-rated measures [13]. The data from the companion study in concert with the findings obtained in the current study suggest that desvenlafaxine is not effective at doses lower than 50 mg/day. To strengthen the clinical impact, it will be much desirable to publish these two trials together as one report.

The paper reporting the trial of desvenlafaxine 25 mg/d and desvenlafaxine 50 mg/d vs placebo is already in press and therefore could not be submitted with the current manuscript. The citation for that paper has been updated in the manuscript to “in press.”

Reviewer 2

Thank you for inviting me to review this article. Overall, this is a very professionally written article, reflecting a generally well-designed clinical trial. Please find my comments and suggestions below.

Major Compulsory Revisions: None

Minor Essential Revisions:

1. In the inclusion criteria, I would be interested to know how the DSM-IV diagnosis of MDD was established (i.e. through clinical interview, checklist, SCID).

The diagnosis of MDD was confirmed through an investigator’s psychiatric clinical interview. We have added this information to the Methods (p5).

2. The authors specify in Figure 1 that 3 individuals were excluded for concomitant medication use. I would like to know what medications were considered for exclusion criteria, and if patients were allowed to use particular types of medications (i.e. benzodiazepines or hypnotics) during the trial period.

We have added the list of prohibited treatments and exceptions to the Methods section (p5-6). As now stated in the text, the sedative hypnotics zolpidem and zaleplon were permitted for sleep, during the first 14 days after randomization only.

3. Similarly, 33 individuals were excluded based on comorbid conditions. I would like to know what psychiatric disorders were used as exclusion criteria and which were not.
The exclusions have been expanded to include more specific information regarding comorbid conditions (p5).

Discretionary Revisions:

1. It may be worth mentioning in the final paragraph of the background section that this study was not designed to compare between the doses of desvenlafaxine used. This is mentioned in the conclusions, but given the number of comparisons made between the treatment groups in the results section, it would benefit the reader to have it pointed out earlier.

We have added the information that the study was designed to test each desvenlafaxine dose group vs placebo to both the Background (p3-4), as suggested, and to the Statistical Analysis section (p8).

2. Were patients with uncontrolled hypertension excluded? If so, specifically mentioning this would be beneficial given concerns with other SNRIs.

Patients with uncontrolled hypertension were excluded from the study, and this information has been added with the detailed exclusions as described above (p5).

3. Were any measures taken at the follow-up visit that occurred 7 to 14 days after the end of the trial period? If not, this may represent a limitation of the trial as separation from placebo may have occurred outside of the 8 week trial period.

No efficacy evaluations were made at the follow-up visits; only safety assessments were collected at those time points. We have added this information to the Methods section (p4 and p7). We agree that it is possible that a separation from placebo might be observed with treatment duration longer than 8 weeks, but because the follow-up visits were scheduled 7 and 14 after the last dose of study drug was administered, separation from placebo at follow-up was unlikely. A longer on-therapy period would be necessary to address that issue.

4. In the conclusions, the authors note that a high placebo response rate is associated with failure to separate from placebo in clinical trials. I think that it is notable that the authors attempted to control for this by excluding individuals with a large placebo response at baseline, and still had a large placebo response during the trial period.

We agree that it should be noted that the magnitude of the placebo response in this trials was large (a 36% decrease from baseline in HAM-D_{17} scores) despite the fact that the run-in was used. The run-in period does appear to have reduced the placebo response compared with previous desvenlafaxine trials, but it was nonetheless greater than the 30% or greater reduction associated with trial failure. We have expanded the Discussion to include this point (p13).