Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial

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Response to Queries from Reviewers (received January January 22, 2001)
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Comments from Reviewer #216 and #87. (Comments are summarized; Responses in *Italics*)

REVIEWER #216

Comment #1. Methods: On page 9, paragraph 2, how long were the subjects allowed to "continue treatment at the same dose". Was the blind broken during the continued treatment phase?

Response to Reviewers: Patients who stayed on therapy beyond the 8-week study period continued to receive blinded medication for a total of 6 months. The manuscript has been revised to reflect this clarification. Please see page 9.

Comment #2. Results. Where are the results regarding the mean CGI improvement scores? They should be included in Table 2. They are only mentioned on page 14, first paragraph.

Response to Reviewers: The Reviewer is correct in noting that the mean CGI improvement scores are mentioned in the text. However, the mean CGI scores at week 8 endpoint are indeed found in Table 2 – near the bottom between the K-SADS-L 9-Item Depression Subscore and the HAM-D total score.

REVIEWER #87

Comment #1. While the discussion regarding the high placebo response rate is improved, it is still not adequate. The fact that approximately 50% of adolescents who supposedly had been depressed for one year prior to entering the study improved in the placebo arm is one of the most interesting findings of the study. The only point raised that possibly addresses this is that the weekly case management sessions may have been therapeutic. If so, this fact should be expanded since this has significant clinical implications. It seems less than likely that a lack of placebo run in phase should contribute that much to a higher placebo response given the length of time the patients

were reportedly ill prior to entering the study. The authors allude to the fact that the HAM-D scores in this sample were lower than in studies with adults. They also suggest comparisons between HAM-D scores in adults and adolescents may not be valid due to age related variability in the HAM-D. However, there is no reference to this nor is there any clarification about what they mean by this. Is the HAM-D a valid measure in adolescents? Is there something about the course or pattern of illness in adolescent depression that makes it different than adults? The authors note that comorbidity with externalizing disorders might have increased a placebo response rate, yet they do not describe why this might be the case. Moreover, their own data do not support this.

Response to Reviewers: The Reviewer is correct in pointing out the importance of the high placebo response rate in our study. Accordingly, we have revised the Discussion section (page 18) to place more emphasis on the possible role of supportive case management in clinical improvement.

Regarding the Reviewer's concern about the use of the HAM-D and possible age-related variability in adolescents, this is a hugely understudied area. The HAM-D was believed to represent a viable rating instrument at the time the study was undertaken. Moreover, we suspect that there may be age-related differences in the HAM-D, but we are not aware of data supporting this suspicion.

Regarding the effect of externalizing disorders on placebo response. At the suggestion of the Reviewer, we revised the Limitations section (page 19) to mention that we conducted a post-hoc analysis of patients with ADHD in an attempt to tease out possible contributing factors to placebo response. As stated in the manuscript, this subpopulation did not contribute to placebo response.

Comment #2. In the clinical implications section, the fact that half of patients respond to placebo, which may in fact be a therapeutic response to clinical case management, needs to be highlighted. Is paroxetine an acceptable first treatment of choice when half the patients may respond to case management alone? This obviously can be debated given that paroxetine was found to be superior to placebo on some measures, however, the issue does need to be discussed.

Response to Reviewers: The text in the Clinical Implications section (page 20) has been revised as suggested by Reviewer #87. The high placebo response rate has now been highlighted and the text revised. However, other factors (as outlined in the 'Limitations' section), not just the effect of case management, likely contributed to the observed high placebo response rate. We therefore, request that the Limitations and Clinical Implications sections remain as is.

The Reviewer feels that the Clinical Implications section states that paroxetine is the treatment of choice. We do not believe that the text makes this claim. We believe that the SSRIs, as a class, are currently our best choice of therapy for adolescents with major depression for the reasons stated in the manuscript.

Comment #3. How did the authors' determine that most of the adverse events in the paroxetine arm were not due to the medication? It is interesting that this arm had the highest rate of psychiatric adverse events, including emotional lability with suicidal ideation and gestures as well as conduct problems and/or hostility. Seven patients in this arm were hospitalized for these difficulties. These numbers are certainly higher than the rate of these problems found in the other two arms. Treatment with SSRIs has been associated with increased irritability as well as the more controversial reports of increased suicidality. It is not stated how many of the serious psychiatric adverse events in the imipramine or placebo arm required hospitalization. Therefore, it is assumed that only those patients in the paroxetine arm were hospitalized. This is a clinically significant finding and needs to be more adequately discussed.

Response to Reviewers: The causality of adverse events, including serious adverse events, was rated by individual investigators. Only 4 patients in the study (1-paroxetine; 2-imipramine; and 1-placebo) were rated by individual investigators to be definitely related (as compared with unrelated, possibly unrelated, or possibly related) to treatment. The text in the Results (page 16) and Conclusion (page 18) sections has been revised accordingly.

The Reviewer also states that the rate of serious adverse events and subsequent hospitalizations in the paroxetine group is markedly higher than in the imipramine group and that this difference is clinically significant. The Reviewer is also concerned that none of the imipramine or placebo patients with serious adverse events were hospitalized. We did not intend to deceive or not disclose information. In fact, the manuscript clearly states (page 16 first full paragraph) that 3 of the 5 patients in the imipramine arm experienced serious psychiatric adverse events, 2 of whom were hospitalized. None of the placebo patients were hospitalized. We do not believe that, given these small numbers, statements about clinically significant differences are responsible. We therefore wish to retain this portion of the text.