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

Response to *Journal of the American Academy of Child and Adolescent Psychiatry* Reviewers

November 3, 2000

Comments from Journal in journal's cover letter. (Comments are summarized; Responses in *Italics*)

1. Please add a 'Clinical Implications' and a 'Limitations' section to the Discussion section.

Response: A 'Clinical Implications' and a 'Limitations' section has been added to the Discussion section.

2. Restrict tables and figures to no more than 5 manuscript pages, particularly those that list nonsignificant findings.

Response: Tables 3 (Measures of Functioning, General Health, and Behavior) and 4 (Medication Doses) were deleted. Figure 1 (study design algorithm) was deleted.

3. All stylistic changes requested by the journal have been made, including deleting 2 tables and 1 figure.

Comments from Reviewer #1. (Comments are summarized; Responses in *Italics*)

1. Overall. Results do not clearly indicate efficacy for paroxetine; authors need to clearly note this.

Response: The Abstract and Discussion section have been revised so as not to overstate the efficacy of paroxetine.

2. Abstract. Efficacy was not demonstrated for paroxetine. Clearly note that paroxetine was not found superior on 3/7 variables. The authors might hypothesize why these findings were equivocal in the conclusions section of the abstract.

Response: The abstract already clearly states that paroxetine was only superior to placebo for 4 out of 7 variables.

3. Introduction. Authors should state that any references are reviews, not original data.

Response: Although this is a good point, we believe that the statements in the Introduction are cited appropriately. When general concepts are discussed (eg, suicide in adolescents), we believe it is acceptable to cite reputable review articles

by recognized experts. Whenever specific data is discussed, original studies are cited accordingly.

4. Methods. a) A more extensive description of supportive case management is needed. b) the primary outcome measure should be stated. c) A thorough description of the titration scheme should be provided.

Response: a) The description of supportive case management has been expanded as suggested by the Reviewer. b) The primary outcome measure was response, which was defined as HAM-D total score ≤8 or 50% reduction in baseline HAM-D total score. The Methods, Results, and Comment sections have been revised to clearly state this. c) A detailed description of the dose titration scheme was added to the Methods section.

5. Page 10. The 3rd paragraph should read: "If changes in cardiovascular parameters occurred, then dosage reductions were required."

Response: This change was made.

6. Statistical Methods. The rationale for not using the Bonferroni method should be described.

Response: It was not the intent of this study to compare paroxetine with imipramine. Therefore the study wasn't powered to take into account correction factors, such as the Bonferroni method.

7. Adverse Effects. a) It should be noted that paroxetine was "generally" well tolerated. b) It should be noted how the AE severity was defined. c) "Down-titration" was mentioned in Results, but not defined in Methods. d) It is not clear why patients with serious AEs were not withdrawn from the study. e) Standard deviation should be used in Tables 2 and 3.

Response: a) The first sentence in the Adverse Effects section was revised as requested. b) The text on page 14 was revised to state that "...most adverse effects were not serious." Serious AEs were defined as fatal, life-threatening, disabling, or requiring hospitalization. c) A description of down-titration in patients prematurely withdrawing from the study was added to the Methods section. d) Discontinuing patients from the study was a clinical judgment made by the investigators, who also had the option of a dosage reduction. e) We choose not to convert the data in Table 2 to SD because we believe that SE is appropriate when demonstrating variability around the mean.

8. Comment. a) It should be noted that the response to imipramine may have been greater had the study been pharmacokinetically controlled. b) The efficacy of paroxetine should not be overstated, and it should be clearly stated that there was a primary outcome measure. c) The authors state that further studies are needed to determine 'optimal dose'. However, 2 studies (Rey-Sanchez and Findling) demonstrate that 10 mg is the optimal dose in pediatric patients.

Response: a) We disagree with this point. Studies in adolescents have not found a correlation between TCA blood levels and improvement. Thus, we do not believe that dose adjustments guided by imipramine blood levels would have made any difference in the outcome. b) The first paragraph of the Comment section has been revised to mention that a HAM-D total score ≤8 is the primary outcome measure, and that paroxetine did not separate statistically from placebo on 3 of the 7 efficacy variables. c) We disagree that 10 mg has been shown to be the optimal dose. The Rey-Sanchez study was an open-label assessment, and the Findling study was a single-dose pharmacokinetic study. Neither can be expected to determine optimal dose.

Comments From Reviewer #2. (Comments are summarized; Responses in Italics)

1. The authors don't fully explore the causes and implications of the high placebo response rate in the Discussion section.

Response: The high placebo response rate is discussed in greater detail in the new, 'Limitations' section.

2. The relatively high rate of serious adverse effects with paroxetine was not addressed in the discussion.

Response: In this study, adverse effects in general, and serious adverse effects in particular, were measured using rigorous criteria. As such, it is not surprising that the rates of serious adverse effects were relatively high (12% for paroxetine; 5% for imipramine; 2% for placebo). However, for all 3 treatment groups, the serious adverse effects were primarily psychiatric in nature, and in only 4 cases were these considered by the investigator to be related to treatment. The discussion has been revised to reflect causality.

3. The high rate of premature withdrawal was glossed over.

Response: We disagree. The extent of and reasons for discontinuation are fully described in a subsection of the Results section.

4 Given the high placebo response rate, are SSRIs an acceptable first-line therapy for depressed teenagers?

Response: An explanation for why the SSRIs are the current treatment of choice is provided in the new 'Clinical Implications' section.

4. Although it is implied, a stronger statement could be made regarding the lack of indications for tricyclic antidepressants given the lack of efficacy and side effect profile.

Response: This is addressed in the new "Clinical Implications" subsection of the Discussion.

5. The explanation for not conducting a 3-arm study is self-serving.

Response: The reviewers make a valid point. We have expanded the section in the Discussion about the study design. Our initial decision for not conducting a 3-arm study involved many factors and ultimately was based on the pragmatics of recruiting a sufficient number of adolescents for this trial. At the time the study was designed, there had not yet been a positive trial with a TCA or SSRI, and we were satisfied that to test each against placebo would make a meaningful contribution to the literature.

5 In the Discussion section, there is statement that the entry HAMD score was lowered to reflect the severity of the disorder in a pediatric population. What does this mean? Are HAMD scores different in adolescents than in adults?

Response: We believe that HAMD scores may be lower in adolescents than in adults, and the revised Discussion provides an explanation for why.