October 22, 1999

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RE: M3 # 100388, EFFICACY OF PAROXETINE BUT NOT IMIPRAMINE IN THE TREATMENT OF ADOLESCENT MAJOR DEPRESSION: A RANDOMIZED CONTROLLED TRIAL

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JAMA MANUSCRIPT # JOC01839

EFFICACY OF PAROXETINE BUT NOT IMIPRAMINE IN THE TREATMENT OF ADOLESCENT MAJOR DEPRESSION: A RANDOMIZED CONTROLLED TRIAL.

Editor: Richard M. Glass, MD

October 22, 1999

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DATE RECEIVED IN AMA OFFICE: ____________________________
This paper reports on a large double-blind trial of paroxetine and imipramine versus placebo. It analyses the efficacy of paroxetine versus imipramine in the treatment of adolescent major depression in a randomized controlled trial.

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1. The major finding in this study was the high placebo response rate, namely 50%. Infections produced only a 20% higher response rate than placebo, and then only on some but not all of the scales used. The parent and patient self-report scales did not show a difference. The proportion of infections over placebo scores suggests that the authors assessed neither the efficacy of the drug treatments nor the existence of the symptoms of depression. It is not clear how the results of this study should be interpreted. Since the authors did not carry out a detailed analysis of the data, it cannot be concluded that the results of this study provide evidence of the efficacy of paroxetine and imipramine.

2. While the above issues are the most pressing, there are several other methodological issues with this paper that may have compounded the problem. The investigators apparently were permitted to include patients with conduct and oppositional defiant disorder. Since the authors (Fagin et al., 1993) reported that such patients have a high placebo response rate and a low response rate to imipramine.

3. Another contributor to the placebo response rate is the inclusion of patients with a T-score Hamilton Depression Rating Scale score of 12 or less on at least two of the clinical trials of antidepressants. The authors do not state if they chose to include such patients and how many such patients were treated in the study or whether they were equally distributed between the two treatment conditions (placebo vs. active treatment) if these patients were included.

4. Another issue that bears on the magnitude of its double-blind differences is the time course of response. It is common practice to show a plot of response versus time for the various conditions to allow the reader to judge when the active treatment separated from the placebo control condition. The authors provide no information about whether patients separated from placebo only at the end of the study or at several different points in a temporally consistent manner. However, the information is particularly important given the magnitude of the response difference. The reader should address this issue and provide at least two figures showing the time course of response.

5. The wording of the instructions during the drug did not employ any therapeutic drug monitoring on the child to control for substantial interindividual variability in its chronicity. It also involved a forced entry schedule which may have skewed the study conditions such that more patients would have been treated with the drug for the first two weeks and yet required achievement of a dose of 200 mg/day by the end of the study. This dose would be high for many patients. Yet, the authors reported that patients who could tolerate such a dose had to be withdrawn from the study. This strong adverse and improvements in depression levels, both subjective and poorly tolerated. In contrast, patients on paroxetine were spared and maintained for four weeks or in

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parameters in contrast to a tricyclic antidepressant such as imipramine. However, therapeutic drug monitoring has been used for several years in both adults and children to madness adjust the dose of imipramine and other tricyclic antidepressants. In fact, the authors did measure plasma levels of imipramine at weeks 4 and 8 but did not report the results.

6. The high dose of imipramine employed in this study likely also compromised the blind. The authors do not address this issue. However, the anticholinergic adverse effects cited in Table 5 are such that one would expect the authors should have been able to determine who was on imipramine with reasonable certainty.

7. Overgeneralisation (Page 9) is not an ideal way to present the blind of a study. Many patients will open the capsule to see what medication they are taking.

8. The definition of remission and response overlap is this manuscript (Page 10).

9. The blood pressure parameters given at page 11 do not make sense (i.e., systolic blood pressure >140 mm Hg/diastolic blood pressure <15 mm Hg). The authors should clarify.
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GENERAL AND SPECIFIC COMMENTS OF REVIEWER TO AUTHOR

JAMA

MS Number: JCO91339
MS Title: EFFICACY OF PAROXETINE BUT NOT IMIPRAMINE IN THE TREATMENT OF ADOLESCENT MAJOR DEPRESSION: A RANDOMIZED CONTROLLED TRIAL
Author: Keller

The authors describe a multi-site parallel groups randomized study of paroxetine, imipramine, and placebo treatment of adolescent depression. Most indicators of efficacy showed a significant improvement after treatment with paroxetine relative to placebo. There were no significant improvements on imipramine relative to placebo. There was an overall order effect in which ratings of depression were lower on placebo at the end of treatment than at baseline. In addition, more subjects treated with imipramine dropped out due to adverse events, most notably cardiovascular changes.

The strength of the study is that it is the first replication of the efficacy of antidepressants in treatment of adolescent depression and the first report of efficacy of paroxetine. The introduction does an excellent job of discussing the past studies of adolescent depression and in describing the limitations of all but one of those studies. The study is well-powered for demonstrating efficacy of paroxetine, but not for a weaker treatment effect, such as in the treatment with imipramine, due to placebo effect typical of antidepressant trials. The study design is standard for a clinical trial with use of well-standardized diagnostic and outcome measures.

A major weakness of the report is the implication that paroxetine is superior to imipramine on the basis of significant evidence of efficacy for paroxetine relative to placebo, but the absence of a significant difference between imipramine and placebo. If the intent is to compare paroxetine and imipramine, then a significant difference in the response between these two treatments must be demonstrated. Such an analysis appears not to have been planned. If demonstration of lack of efficacy of imipramine is intended, more analysis of the power of the study to show that effect should be provided. Considering the lack of efficacy is likely a lack of power, considering a high placebo response rate, the title should be changed to "Efficacy of Paroxetine but Not Imipramine in the Treatment of Adolescent Major Depression: A Randomized Controlled Trial." If the authors wish to continue to emphasize the lack of efficacy of imipramine, they need to demonstrate greater than 85% power (to adhere to the standard of 5% alpha level for a positive statement - given that the null hypothesis in lack of efficacy is presence of efficacy, the authors would need to design a study to show that imipramine isn't efficacious given 5% power). This is particularly important given the absence of a report of the TCA levels obtained and a relatively low - administered dose. Weight range should be provided in description of the three treatment groups. Given 70 kg subject weight, a dose of 200 mg would be less than 70 kg. Also, the authors should clarify that although up to 300 mg was administered, subjects would have had steady state levels based on 250 mg dose for only 3 weeks and on 200 mg for only 2 weeks. Therefore, the comparison with paroxetine may have been designed for paroxetine to be at a
more optimal does than imipramine, further undermining confidence in an assertion of differential efficacy.

The study provides extremely useful tables in showing adverse events of paroxetine and imipramine in comparison to placebo. In addition to previous studies of TCAs, these data add to the overwhelming evidence of increased cardiovascular events and dropout in treatment with tricyclic antidepressants. It would be easy to conclude that TCAs should no longer be considered first line treatment for adolescent depression and that is implied in discussion of whether subsequent trials of TCAs will be performed. However, there is a major omission from the tables. The serious adverse events should be at the top of any table of adverse events and these do not favor paroxetine. In fact, it is troubling that the authors do not note a significant increase in SAEs after paroxetine (but not IMI) relative to placebo (p < 0.05 by Fisher’s exact test).

More importantly, many have assumed that with fewer cardiovascular side effects, TCAs are safer to prescribe. However, given the high rate of primary care prescription of antidepressants and the readership of JAMA, it is important to emphasize that behavioral side effects in a minority of patients treated with paroxetine may be more serious than with TCAs and that they require excellent provider of psychiatric assessment and management, including access to psychiatric hospitalization. In other words, it is easier to assure quality control for ECO administration and reading them to know that all of the primary care physician prescribing antidepressants have adequate training in monitoring of the psychiatric side effects of SSRIs and other antidepressants.

It is also easier to assume access to ECOs than weekly supportive clinical visits with experts in treatment of adolescent depression. The authors do not sufficiently highlight that the level of psychological treatment provided in this study is much more intense than that covered by almost every health insurance plan and far exceeds the usual time spent between a primary care physician and a depressed patient given continuing pressure from third party payers and ongoing discrimination against psychiatric patients and psychiatric treatment (provided by generalists or psychiatrists).

The protocol does not exclude prior use of imipramine or paroxetine, other than recent use or an adequate trial within 1 month. This may allow inclusion of either past responders or past non-responders. The number of patients treated with IMI or paroxetine in the past should be listed.

It is not clear why 21 authors are given publication credit, but 9 are only acknowledged. Given the contact by the sponsor of the study, apparent conduct of data analysis, and its publication, the reason for the two authors at the sponsor's site being given authorship credit and the professionals not involved should be justified to the journal upon submission. Given concern about the summary of the authors and sufficient input into the analysis and interpretation, the authors should state that all authors were granted full access to the full data set to verify the accuracy of the report, that all authors were in full agreement with the manuscript as submitted, or what mechanisms were provided for resolving disagreements, particularly when they involved discrepancy between views of investigators and the sponsor.

Minor points:
The use of the term adolescent is based only on an age of 12-18. Some of the younger boys may have been prepubertal. Adolescent is defined by post-pubertal status. The Tanner stage of all participants should be included in the description of the subjects.

Throughout, the term effectiveness is sometimes used when efficacy is what was being tested.

p. 2, Results – ‘Improvement in all treatment groups’ should be recorded. p. 5, Results – If a statement is made about increased drop-out from imipramine, an analysis showing this is significant should be provided in the body of the report.

p. 5, Conclusions – ‘optimal doses’ implies a single dose rather than determining the range of optimal doses across adolescents.

p. 6, para 2 – provide the median and range of previous sample sizes of TCAs in adolescent depression.

p. 7, para 1 – ‘Another study, employing a historical…’ is confusing following the previous sentences and is probably best documented by a new paragraph or other indicator of transition.

p. 8, para 1 – The PPVT is not an intelligence test, so it should not be described as an IQ score. It should be described as PPVT standard score of at least 80. It could be further described as an indicator of an aspect of language relatively well correlated with IQ. However, many patients with the higher end of mild mental retardation will have a PPVT of at least 80.

p. 8, para 1 – change ‘pervasive mental disorder’ to ‘pervasive developmental disorder’

p. 9, para 2 – it appears that placebo was not administered during the screening phase, but this should be clarified and a comment should be provided later on the advantages and disadvantages of not having a placebo run-in, given comment on this by several of the authors in other publications about this topic.

p. 11, para 2 – at further evidence of not fully testing efficacy of imipramine, it is not clear why patients with TCA levels greater than 500 were dropped from the study rather than having dosage adjustment. Also, the authors should comment on whether OCP was followed, if patients were not tested for levels 1 week after dosage change or initiation of treatment with TCAs, given that if a subject had a level of > 500 mg/ml at the end of week 4, they likely had increased levels at the end of week 1 or 2. Range of TCA levels at the end of weeks 4 and the end of week 8 should be provided. The number of subjects excluded with levels > 500 mg/ml should be provided.

p. 11, para 2 – it is likely that the authors didn’t exclude nonceptive adolescents, so it is assumed they meant to exclude subjects with diastolic blood pressure > 85 mm Hg.

p. 12, para 3 – Since family history wasn’t described in the methods, it is unknown what the authors mean by positive family history. Presumably, this is any relative, rather than first-degree relatives, but it should be clarified.

p. 13, para 2 – detail the cardiac adverse events leading to premature discontinuation.

p. 13, para 3 – clarify whether LOCF or complete analysis is being described throughout the results and tables describing results.

p. 17, para 2 – description of ‘numerically superior’ is not appropriate and results should be described as superior only when significant. There is a bias in reporting percentage results as numerically superior but failing to emphasize this is also the case for many of the outcome measures with imipramine.

p. 18, para 1 – The authors do not address why comparison to trazadone isn’t possible since it is already available rather than NE specific reuptake blockers.
p. 18, para 2: Descriptive data was inadequate for making comment on doses administered.

Table 3 - There is no mention in the text of the failure to demonstrate efficacy for the quality of life measures indicated in this table.

Figure 2 - There are two bar graphs, but the p values appear to only refer to one of them.
1. From the way this last sentence is worded, it appears as though the treatment (SSRI) is being compared to a comparison (placebo vs. a tricyclic antidepressant). This is clarified later in the manuscript, but at this juncture it is unclear.

2. The wording (likewise on page 7) suggests that the combination of paroxetine and imipramine is being compared to placebo. Again, this is clarified, but only later.

3. How was the dose (20 mg to 40 mg) of paroxetine chosen for a specific patient?

4. The fifth efficacy endpoint, CGI, groups very much improved with much improved. If we can assume that very much improved is better than much improved, then combining these categories is tantamount to throwing away data which can be used to distinguish among different outcomes. This would be an inappropriate dichotomization of what is at least a trinomial endpoint. See Moses, L. E., Emerson, J. D., and Hosseinian, H., 1984, "Analyzing Data from Ordered Categories", New England Journal of Medicine 311: 442-446. Alternatively, patients could be classified as "very much improved", "much improved", or "less than much improved". Then you would use a single comprehensive analysis, such as the Kruskal-Wallis test. See Berger V. W., Ferrant T., and Ivancev A., 1998, "The Kruskal-Wallis Test for Ordered Categorical Data", Biometrics 54, 1541-1550.

5. Significantly greater improvement than what?

6. What is the meaning of lifetime prevalence for an adolescent?

7. Was placebo administered during the screening phase? If so, then were responders to placebo excluded? If so, then this should be made explicit in the interpretation of the results. See "Run-In Periods in Randomized Trials", Peklo-Perez et al., JAMA 1/21/98, 279, 3, 222-225 and "Threats to the Validity of Clinical Trials Employing Enrichment Strategies for Sample Selection", Leber P. D. and Davis, C. S., Controlled Clinical Trials 19, 178-187, 1998.

8. What determined the length (7-14 days) of the screening phase for a patient?

9. It is deceptive to refer to an analysis population based on having at least one post-baseline efficacy evaluation as "intent-to-treat". The true intent-to-treat population consists of all patients randomized, analyzed as they were randomized. See Heijmen, D. F., 1999, "Causal Inference in a Clinical Trial: A Comparative Example", Controlled Clinical Trials 20, 359-370.

10. A sensitivity analysis should be performed, using other imputation methods.

11. Were the ANOVA assumptions checked? What were the results?