Journal of the American Academy of
CHILD & ADOLESCENT PSYCHIATRY

cc: Sally Laden
file

Mina K. Dulcan, M.D.
Editor

Is this Dulcan's note or Keller's

July 27, 2000

Martin B. Keller, M.D.
Dept. of Psychiatry and Human Behavior
Brown University School of Medicine
345 Blackstone Boulevard
Providence, RI 02906

Re: **Manuscript Number: 2000/1310**
Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial

Dear Dr. Keller: Marty

Your manuscript has come back from review, and I enclose copies of the reviewers' comments and suggestions.

If you will revise your manuscript to meet their concerns, we will be happy to consider it further for publication. Please send us four copies of the revised paper, highlighting one copy to indicate where you made changes. A cover letter indicating your response to each of the reviewers' suggestions must accompany the revision. Also, in your discussion section, please highlight the clinical implications of your findings, i.e., in a subsection entitled "Clinical Implications," describe how they should influence diagnosis or treatment. Additionally, please include a subsection entitled "Limitations", where you point out and discuss any weaknesses in study design or execution. Tables and figures should be no more than 5 manuscript pages. Please condense and reduce the number to fit our specifications, especially eliminating those with non-significant findings. Please note that the current limit for articles accepted by the Journal is 6,000 words, including title page, structured abstract, references, tables, and figures. A final decision on your paper will be made after we receive all of the above items.

I look forward to receiving your revised manuscript.

With my best wishes,

Sincerely,

Mina

Mina K. Dulcan, M.D.

Children's Memorial Hospital | 2300 Children's Plaza, #156 | Chicago, Illinois 60614-3394
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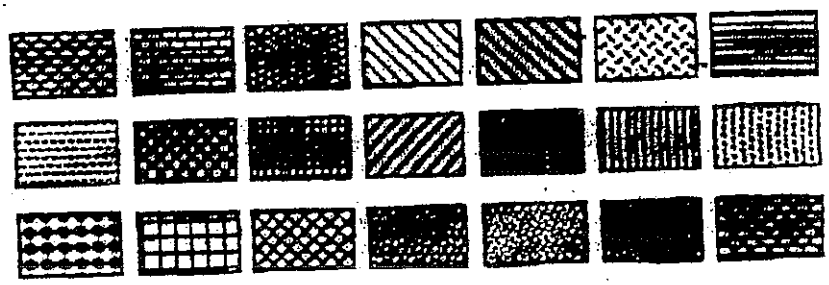

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Achenbach TM, Edelbrock C (1983). *Manual for the Child Behavior Checklist and Revised Child Behavior Profile*. Burlington: University of Vermont, Department of Psychiatry

Achenbach TM, Verhulst FC, Baron GD, Akkerhuis GW (1987). Epidemiological comparisons of Amsterdam and Dutch children, I: behavioral/emotional problems and antecedents reported by parents for ages 4 to 16. *J Am Acad Child Adolesc Psychiatry* 26:317–325

Bell AC (1930). *The Child and His World*. New York: Macmillan. 1975 (If the year of original publication does not coincide with the edition referred to, add the year of publication of the edition used after the publisher's name.)

Tarr LC (1969). Children communicate in small groups. In *Post-Traumatic Stress Disorder in Children*, Eth S, Pynoos RS, eds. Washington, DC: American Psychiatric Press, pp 67–78

Tarr LC (in press). *The Journal to Oz*. New York: Harper & Row

US Department of Health and Human Services (1987). *Report of the Surgeon General's Workshop on Children with HIV Infection and Their Families* (DHHS Publication HRS-D-MC 87-1). Washington, DC: US Government Printing Office

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In preparing research reports, follow the [illegible] format, with separate headed Introduction, Method, Results, and Discussion that describe the problem, how it was studied, the findings, and what they mean. In the *Introduction*, include the purpose of the study, a priori hypotheses, and a succinct and relevant literature review. In the *Method* section, clearly describe the design, with information on sample selection, inclusion/exclusion criteria, method of randomization (if applicable), the determination of sample size (include power calculation), and whether or not the study was "blind" in any way. Discuss the representativeness of the sample selected (research and patients). Complete information about *study sample* composition includes gender, race/ethnicity, and *family* composition, status and educational attainment. Use the current and available *occupational categories*, *four educational attainment categories* (without H.S. diploma, H.S. graduate without college education, some college education, degree from 4-year college or more), and *five racial/ethnicity categories* (e.g., U.S. Bureau of Census). *Specify sampling frame* and study-sampling strategies. Screen the response and treatment variables in the study. In describing data collection, include response rates or follow-up rates and discuss possible sampling bias. Clearly describe all analyses and provide the names of specific statistical tests used. Include the name(s) of the study statistical expert(s) on the manuscript cover sheet. Justify and clearly reference the use of unusual statistical techniques. If multiple comparisons are unavoidable, use an appropriate adjustment to control type I error. State whether tests were one- or two-tailed. In the *Results* section, present summary statistics (such as means and standard deviations) to explain any null results. When reporting significant results, include the statistical test used, the test value, degree(s) of freedom, and the probability level (p value). When possible, report confidence intervals on the main findings. Keep the number of tables to a minimum, generally not more than 5 double-spaced manuscript pages. In the *Discussion* section, consider both statistical and clinical significance. Focus on integrating the findings into what is known, and how these findings advance theory or practice. In a subsection titled *Limitations*, point out and discuss any weaknesses in study design or execution. Include a subsection titled *Clinical Implications* in which relevance for clinical practice or developmental theory is specifically considered.

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JOURNAL OF THE AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

MS: 2000/1310, "Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized Controlled Trial".

This study involved an 8-week multicenter randomized double-blind design with parallel arms, comparing both imipramine and paroxetine to placebo. Paroxetine was superior to placebo on some of the clinician ratings used as outcome measures. There was a high placebo response rate. Imipramine was not superior to placebo, and had a high rate of adverse effects.

This study has multiple strengths, including large sample size, randomized controlled design, and the use of standardized measures addressing multiple domains. Moreover, the study addresses an important area of clinical child psychiatry, the efficacy of antidepressant therapy in depressed youth. The results are clearly presented. Documenting that paroxetine has efficacy in adolescent depression is an important finding.

There are some issues that if addressed would greatly improve the paper. Although the authors devote considerable discussion to the high placebo response rate, this primarily serves to defend the validity of the paroxetine results, rather than truly explore the significance of these findings. Several issues are seemingly ignored, included:

1. The implications of a high placebo response rate given that the average subject was depressed for one year prior to entry into the study.
2. The fact that parent and subject ratings did not differentiate active medication from placebo.
3. The fact that only a few of the clinician ratings differentiated paroxetine from placebo. For example, the total HAM-D scores showed very little difference, either clinically or statistically.

not done

There are several interesting ramifications of these results that are ignored. The authors dismiss the placebo response rate as consistent with findings in adult studies, but that is not accurate. The issue of high placebo response rate in youth is a very consistent finding that has generally been attributed to sampling or severity issues. The field has maintained that the diagnosis of depression in youth is essentially the same as that in adults, yet the treatment literature is strikingly different. Do these findings potentially suggest something about either the method used to diagnose depression, or the validity of the diagnosis itself, in this population? How is it that youth with persistent major depression for a year improve at basically a 50 percent response rate in a placebo arm.

NOT really addressed

REVIEW FORM

Comments to the Author(s) - Brief summary of paper, along with an outline of the strengths and weakness of the work.

MS Number: 2000/1310 Reviewer Number: 216

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

Overall this is an important study due to its large size and its design of SSRI vs. TCA vs. Placebo. However, the results do not clearly demonstrate efficacy for paroxetine. Therefore, the authors need to clearly note this.

ABSTRACT: As mentioned above, efficacy was not demonstrated for paroxetine. It should be clearly noted that paroxetine was not found to be superior to placebo on 3/7 rater-completed measures of antidepressant efficacy in the Results subsection. The authors might hypothesize why these findings were equivocal in the Conclusions subsection.

INTRODUCTION: The points made in the Introduction are good ones. However, the authors should cite that many of the references used are review articles and not original communications of scientific data.

METHODS: Since most of the readership may not be familiar with the supportive care management provided, a more extensive description is indicated. As this was a pharmaceutical industry-sponsored study, it is likely that there was a primary outcome measure that was identified *a priori*. If this is the case, the authors should clearly state what this primary outcome measure was in the METHODS, RESULTS, and COMMENT sections. Since there was a large number of depression outcome measures used and because a Bonferroni correction was not employed, this is a particularly important consideration. As the number of capsules taken are described in the RESULTS section, a thorough description about the schema of how the number of capsules prescribed could vary throughout the study should be noted in order to facilitate the interpretation of these data.

need to specify 1° outcome

The third paragraph on page 10 should read "If changes in cardiovascular parameters occurred, then dosage reductions were required".

As before, considering the large number of outcome measures that were considered, the rationale for not using a Bonferroni correction should be described.

RESULTS: Based on the descriptions, it may be more appropriate to note in the Adverse Effects subsection that paroxetine was "generally" or "usually" well tolerated. In addition, it should be noted how the severity of the AEs was defined/operationalized. What constituted a "mild", versus a "moderate" adverse event? A statement is made about "down titration" on p. 15. There is no mention of this in the Methods section. It is not clear why patients with a serious adverse event completed treatment and were not withdrawn from the protocol. The authors should use Standard Deviations in Tables 2 and 3, as this statistic is more informative and more appropriate.

need to tone down AE claims

not done

Continue on separate sheet if necessary

COMMENT: The fact that this was not a pharmacokinetically controlled study should be considered an important impediment to optimizing the therapeutic repose of IMI (as would be done in clinical practice). This clearly should be noted as IMI did very poorly when compared to placebo.

The authors should clearly note that 3/7 outcome measures did not show paroxetine was superior to placebo without Bonferroni correction. Therefore the authors should not overstate the efficacy of paroxetine. The fact that there was not a single a priori primary outcome measure is quite unusual for an industry sponsored study. If this is the case, this should be clearly noted as a methodological shortcoming. If there was a "primary" outcome measure, the authors should clearly note what that was.

The authors state that "optimal dose range" for paroxetine should be an area of further study. They should note that there are 2 reports that describe 10 mg of paroxetine as optimal for most youths with MDD (Rey-Sanchez et al.1997; Findling et al.1997). It is possible that 10 mg might have been the optimal starting dose for this study and should be considered in the discussion. Were there any open label data available to the authors regarding paroxetine dosing in youth to suggest a 20mg dose was indeed the appropriate starting dose when this study was designed?

PAR001727357

MS: 20000131S, "Efficacy of Paroxetine in the Treatment of Adolescent Major Depressive Disorder: A Placebo-Controlled Trial".

Were they really persistently depressed over that entire year? In clinical settings most "depressed" youth have moods that are more labile and reactive. Is this well reflected in methods using standardized interviews? Is there possible informant bias in the way either parents or youth report depressive symptoms? A more broad based discussion of these issues that challenged existing dogmas would be very interesting and of great benefit to the field.

NOT DONE

There are other issues that need addressed, including:

1. The rate of serious adverse events in the paroxetine arm is somewhat high (11 subjects, presumably out of 93). This is included in the results, but not discussed at all.
2. Similarly, each group had a fairly high rate of not completing the 8-week trial that is somewhat glossed over.
3. Given the high placebo response rate, what algorithm should clinicians follow when treating a depressed teenager. Are SSRI's an acceptable first line treatment if approximately one-half of youth got better with only supportive interventions.
4. Although its implied, a stronger statement could be made regarding the lack of indications for tricyclic antidepressants given the lack of efficacy and side effect profile.
5. In the discussion section, there is statement suggesting that a traditional three arm comparative trial was not done due to the risk of exposing additional subjects to clinical research. This seems rather self-serving, since I suspect the power issues and sample size limitations prevented this from being done, not human subjects concerns.
6. In the discussion section, there is a statement that the entry HAM-D score required was lowered to greater than, or equal to 12 "to reflect the severity of their disorder" in a pediatric population. What does this mean? Is the scale not valid in youth? Are their scores somehow different than adults?