

*Dr. Keller and Mr. McCafferty reply:*

This is in response to Drs. Correll and Pleak's requests for clarification on the study methodology as well as for additional information on the study results.

The criteria for therapeutic response were defined in the report as a final HAM-D score that was 8 or less or a reduction from baseline of 50% or more. Dual criteria were selected for this study because the scores at entry could range from a minimum of 12 (set by protocol) to a maximum of 53 (highest scores for the 17-item HAM-D). Limiting response to either a 50% reduction or a specified cut point would impede patients at the lower end of the ranges from meeting the criterion.

Three nonsymptom measures were included in the study: the Autonomous Functional Checklist (AFT), the Self Perception Profile (SPP), and the Sickness Impact Profile. These scales, which assess a variety of functions and roles associated with teenage life including scholastic and athletic competence, as well as family, social, and recreational activities, have many subscales. These results will be the subject of a separate report. In brief, the largest differences compared with placebo were seen in the parent-rated AFT scores for self-care and family care, although this did not achieve statistical significance. Smaller effects were seen in patient-rated scores of the SPP, which represent perceptions of self-esteem.

Blood drug levels were monitored when patients completed 4 and 8 weeks of study medication. The intent was to ensure that levels for combined imipramine and desmethylimipramine concentration did not exceed 500 ng/mL. To maintain the blind, the samples were drawn from all patients, but only samples from the imipramine-treated patients were analyzed. If the blood levels did not meet the threshold value set by protocol, the data were maintained at the laboratory (Quest Diagnostics). In three cases—all during the 8-week treatment period—the measured levels exceeded 500 ng/mL. In two of these cases, no adverse events were reported. In the third instance, the patient had reported increased heart rate and dyspnea that resolved upon stopping the study medication.

Twenty patients withdrew from the imipramine group during the initial month of treatment and 18 withdrew during the second month. Thus the lack of response in the imipramine group does not appear to be related to high termination rate early in therapy, as approximately 80% of the subjects were treated for at least 4 weeks.

The potential for SSRIs to induce mood disorders is not clear. In the present study, there was a history of behavior problems in several of the subjects that recurred during treatment.

Although weight gain has been reported for both SSRIs and TCAs when given over an extended period of time, significant changes in weight were not observed in this 8-week trial.

We are very much in agreement with Drs. Correll and Pleak that additional studies are required to assess the usefulness of

SSRIs in nonadult depression, including those with recurrent depression and those who failed to respond to therapy. It is anticipated that additional information on the SSRIs will soon be forthcoming as a result of the Food and Drug Administration's pediatric rule. This regulation requires sponsors of a new drug application and any supplemental application—regardless of the indication—to provide information on the use of the medication in nonadults.

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*To the Editor:*

We read the report by Keller et al. (2001) with great interest. We wish, however, to raise some concerns. Although randomized controlled trials are the gold standard for proving efficacy of treatments, studies such as this have some limitations and may have hidden biases. The paper would have been more useful to clinicians seeking to apply the results in their practice if the CONSORT diagram (Begg et al., 1996) had been used to report the numbers of potential subjects at each stage of recruitment, treatment, and evaluation. Ability to generalize to clinical populations would be enhanced by a broader range of severity, less restrictive inclusion criteria, and fewer exclusion criteria. More details on the method of randomization to paroxetine, imipramine, and placebo would be appreciated. Are data available on whether the evaluators who completed the HAM-D remained blind to the subject's treatment? The side effects of imipramine, especially at higher doses, may threaten the blindness and introduce a source of bias in clinician ratings.

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Keller MB, Ryan ND, Strober M et al. (2001), Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry* 40:762-772

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