PAROXETINE IN THE TREATMENT OF ADOLESCENT MAJOR DEPRESSION

To the Editor:

The study by Keller et al. (2001), recently published in the *Journal,* marks a major step toward bridging the gap in the support for pharmacological treatment of juvenile depression, created by disappointing results with tricyclic antidepressants (TCAs) (Geller et al., 1999). This multicenter, 8-week, double-blind, placebo-controlled trial found paroxetine to be superior to placebo in the endpoint Hamilton Rating Scale for Depression (HAM-D) score ≤8 (one of the two primary outcome measures), HAM-D and Schedule for Affective Disorders and Schizophrenia for Adolescents-Lifetime version depressed mood items, and the Clinical Global Improvement score of 1 and 2. In contrast, imipramine did not differ significantly from placebo on any measure. Major strengths of this study are the rigorous design, large sample size (n = 275), and inclusion of imipramine (although the study was underpowered to detect a difference between paroxetine and imipramine). While this study clearly aids clinicians in their evidence-based treatment of depressed adolescents, we would like to address several methodological issues.

First, it remains unclear why Keller et al. defined one of the two primary outcome measures as a HAM-D score of ≤8, instead of the commonly used ≤7. Moreover, the most widely accepted criterion of a 50% reduction in baseline HAM-D score was not reported separately, but collapsed with the HAM-D score of ≤8 (p = .11). Second, while neither paroxetine nor imipramine differed significantly from placebo on either self-rating scales (parent and patient) or nonsymptom measures (functioning, health, and behavior), this negative finding is not detailed in the Results section and the clinical relevance of rating score reductions is not discussed.

Third, although the study involved monthly assessments of blood medication levels, neither mean values for imipramine (documenting adequacy of dosing range) nor correlations between imipramine levels and cardiovascular adverse events or between both active treatments and treatment response were reported. Fourth, although the authors analyzed efficacy data for completer and last observation carried forward (LOCF) samples, the timing of imipramine dropouts was not reported. If, indeed, most imipramine dropouts occurred before week 4, i.e., before the separation between active treatment and placebo started to take place, results would be biased against imipramine, even when using the LOCF method, and imipramine completers ≥1 month should be analyzed instead.

Fifth, although serious adverse effects occurred with paroxetine (n = 11) more often than with imipramine (n = 5) and placebo (n = 2), only one case of severe headache was considered to be related to paroxetine. However, a potential selective serotonin reuptake inhibitor (SSRI)-induced mood disorder (King et al., 1991) is of concern in those 8 cases (4 requiring hospitalization) with "emotional lability (n = 5), "conduct problems or hostility" (n = 2), and "euphoria/expansive mood" (n = 1), particularly if subjects did not have comorbid externalizing conditions before paroxetine treatment. Finally, it is unclear whether "clinically significant increases or decreases in body weight were not observed among any three treatment arms" (Keller et al., 2001, pp. 768–769) simply because weight changes were based on group means, or whether, in fact, fewer than 5% of subjects had significant weight gain or loss. The latter would be inconsistent with findings in adults (Fava, 2000) and adolescents considered prodromal for schizophrenia, where 22% of paroxetine-treated patients experienced significant, yet partially reversible weight gain (Correll, unpublished data).

Although difficult to conduct, more large-scale placebo-controlled studies in children and adolescents are needed to increase the scientific evidence for the usefulness of SSRIs in nonadult depression. Considering the negative results for TCAs, we agree that future studies should include novel antidepressants as comparators for SSRIs instead. Since most patients (77%–81%) in this important study by Keller et al. had their first depressive episode, future studies are required to show effectiveness of SSRIs in the treatment of recurrent and unresponsive adolescent depression.

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Fava M (2000), Weight gain and antidepressants. *J Clin Psychiatry* 61(suppl 11):37–41

Geller B, Reising D, Leonard HL, Riddle MA, Walsh BT (1999), Critical review of tricyclic antidepressant use in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 38:513–516

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

King RA, Riddle MA, Chappell PB et al. (1991), Emergence of self-destructive phenomena in children and adolescents during fluoxetine treatment. *J Am Acad Child Adolesc Psychiatry* 30:179–186

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