ized clinical trial reporting has been described in the CONSORT statement (1); one of its recommendations is to describe the flow of the subjects in the study (number screened, proportion randomly assigned, etc.). Dr. Wagner and colleagues did not report the proportion of subjects who were excluded from the random assignment after the single-blind period. This information is critical because a placebo run-in period might help to "wash out" nonspecific responders, allowing sharper evaluation of treatment-specific effects as shown in some pharmacotherapy studies (2).

An additional concern is the elicitation method used for adverse events at a time when the safety of SSRIs in youth has been called into question (3). The adverse events were: "reported by patients or observed by investigators" (Wagner et al., p. 1080). The reliability of this practice is questionable because some adverse events, even very severe ones, could neither be reported by the patient nor observed by the investigator and would need to be specifically assessed (4).

Finally, it is somewhat surprising that the authors do not compare their results with those of another trial, involving 244 adolescents (13–18-year-olds), that showed no evidence of efficacy of citalopram compared to placebo and a higher level of self-harm (16 [12.9%] of 124 versus nine [7.5%] of 120) in the citalopram group compared to the placebo group (5). Although these data were not available to the public until December 2003, one would expect that the authors, some of whom are employed by the company that produces citalopram in the United States and financed the study, had access to this information.

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TO THE EDITOR: We read with interest the study by Dr. Wagner et al. We have a number of concerns about this study. In the Method section, it is not clear how the patients were recruited. One is also left in the dark about the method of random assignment and if the random assignment list was concealed. The authors also give no indication of how they arrived at the sample size and if a power calculation was done. Given the recent concerns about the risk of suicidal thoughts and behaviors in children treated with SSRIs, this study could have attempted to shed additional light on the subject. The authors called the analysis of data an intent-to-treat analysis, although four patients who were lost to follow-up were excluded. In a true intent-to-treat analysis, all patients are analyzed in the groups to which they were initially assigned, regardless of whether they received the treatment or not. We consider the use of the term "intent-to-treat" in this context misleading.

Dropouts from the study have been accounted for by using the last observation carried forward. Treatment response in depression is frequently followed by a subsequent return to original or baseline values on a scale such that the last observation carried forward may be an unduly optimistic estimate. The classification of dropouts as treatment failures is based on safer assumptions than the last observation carried forward.

Our greatest concern is with the results and conclusions drawn. There is no table showing the results in detail. The authors have only stated that 36% of citalopram-treated patients met the criteria for response, compared to 24% of patients receiving placebo. This response rate, while in itself marginal compared to other studies of antidepressants, does not in itself show that citalopram is better than placebo.

We calculated the absolute benefit increase of using citalopram as 0.12 (95% confidence interval [CI]=–0.015 to 0.255). The relative benefit increase that could be attributed to citalopram was 50% (95% CI=–135% to 6%). The odds ratio, i.e., the odds of improving while taking citalopram compared to placebo was 1.75 (95% CI 0.92 to 3.43). The number needed to treat, i.e., the number of children who need to be treated with citalopram for one additional positive outcome was eight (95% CI=4 to infinity). None of these shows that citalopram is any better than placebo.

We would argue that the authors did not provide sufficient evidence to support their claim that "citalopram produces a statistically and clinically significant reduction in depressive symptoms in children and adolescents" (p. 1082). We are surprised that the most respected psychiatric journal in the world published a study that is misleading to its readers in the extreme.

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Dr. Wagner and Colleagues Reply

TO THE EDITOR: Dr. Mathews and colleagues request further information about the randomized, placebo-controlled trial of citalopram for treatment of depression in children and adolescents. Randomization was on a 1:1 basis and was stratified by age group. The random assignment list was concealed from the investigators, which is fundamental to the claim that

the study was performed under double-blind conditions. The protocol-specified population for all efficacy analyses, defined as the "intent-to-treat" population, included all patients who received at least one dose of double-blind study medication and had at least one postbaseline efficacy assessment. The analyses we presented in the manuscript were not only conventional in nature; they were, in fact, defined a priori. The justification for defining this population for the efficacy analyses is that the primary analysis was the change from baseline, therefore requiring a postbaseline assessment.

Although recently a mixed-model approach has gained some currency for the analysis of efficacy in antidepressant trials, the last-observation-carried-forward method of analysis has always been conventionally considered the most conservative method of analysis. Certainly this was the case when the study protocol was being developed. In escitalopram trials in adult patients, last-observation-carried-forward analyses minimize the treatment effect that is demonstrated by observed-cases analyses of the patients who actually remain in treatment (1, 2). These analyses are considered more conservative than observed-cases analyses for acute treatment antidepressant studies because the onset of antidepressant effect is typically delayed for up to several weeks. Therefore, the last observation of patients who discontinue active treatment prematurely is not likely to capture the full potential antidepressant effect.

Regarding suicidality, it is helpful to note that the manuscript states clearly that no serious adverse events were observed in the trial for citalopram-treated patients. At the time the manuscript was developed, reviewed, and revised, it was not considered necessary to comment further on this topic.

Dr. Martin and colleagues inquire about the value of 2.9, which was calculated as the quotient of the least square mean, divided by the common standard error of the mean for each treatment group. With Cohen's method, the effect size was 0.32.

In response to Dr. Barbe's questions about the methods of this randomized clinical trial for the treatment of depressed children and adolescents, there were 75 subjects who were screened but not randomly assigned. The method for elicitation of adverse events was chosen because it was the accepted standard at the time the study was designed for multicenter, industry-sponsored clinical trials in juvenile depression.

It may be considered premature to compare the results of this trial with unpublished data from the results of a study that has not undergone the peer-review process. Once the investigators involved in the European citalopram adolescent depression study publish the results in a peer-reviewed journal, it will be possible to compare their study population, methods, and results with our study with appropriate scientific rigor.

We believe that the results of our study, which demonstrated a significant difference between citalopram and placebo beginning at week 1, is clinically meaningful, particularly at a time when there have been so few antidepressants shown to have superiority to placebo for depressed children.

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