Adolescents With Depression

To the Editor: The authors of the Treatment for Adolescents With Depression Study (TADS) conclude that " . . . despite calls to restrict access to medications, medical management of MDD [major depressive disorder] with fluoxetine, including careful monitoring for adverse events, should be made widely available, not discouraged."[1] We disagree with this conclusion. Looking at the primary outcome measure (change in the Children's Depression Rating Scale-Revised total score), fluoxetine alone resulted in minimal benefit over placebo: the placebo effects were 86% of the fluoxetine effects (change of 19.4 compared with 22.6 points). At the same time, fluoxetine caused a significantly higher rate of harm-related adverse events, such as suicidal ideation, and physiological effects (diarrhea, insomnia, and sedation) compared with placebo or cognitive-behavioral therapy (CBT) alone, as well as a higher rate of psychiatric adverse events (irritability, mania, and fatigue) compared with placebo.

Our own risk-benefit analysis of these results leads us to conclude that a drug-free treatment like CBT alone, or even a psychological placebo such as exercise, should be offered as the first-line treatment because many adolescents will benefit without incurring the increased risk of psychiatric and nonpsychiatric adverse events.

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1. Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA*. 2004;292:807-820.

To the Editor: While the TADS trial provides valuable data about a significant problem, we differ from the authors in their conclusion that treatment with fluoxetine should be made widely available, and that CBT in combination with fluoxetine should be "readily available as part of comprehensive treatment for depressed adolescents."[1] Because 2 of 3 outcome measures (Clinical Global Impressions [CGI] and Reynolds Adolescent Depression Scale [RADS]) show no significant difference between fluoxetine treatment alone and fluoxetine in combination with CBT, we do not see this study showing an advantage for the addition of CBT in all adolescents with MDD.

The Suicidal Ideation Questionnaire-Junior High School Version showed significantly more improvement with fluoxetine in combination with CBT compared with fluoxetine alone. Although this difference may not apply to attempted or completed suicides, it does lend support for the use of fluoxetine in combination with CBT for adolescents with MDD and suicidal ideation. For the majority of patients who have MDD without suicidal ideation, the addition of expensive and time-consuming psychotherapy does not seem to be justified by this study.

According to the US Census Bureau, there were 29 million individuals between the ages of 12 and 18 years in 2003.[2] Assuming a point prevalence of MDD in adolescents of 5%[3] would translate to about 1.5 million adolescents. We do not believe that resources can be committed for all of these adolescents to receive fluoxetine in combination with CBT. For all adolescents with MDD to receive fluoxetine alone will require primary care physicians to be the prescribers for much of the fluoxetine. Providing CBT to all adolescents with MDD would be even more difficult, given the limited number of qualified therapists, the significant expense, and the need for compliance with a time-consuming treatment. Therefore, it seems most sensible to prioritize CBT (with pharmacotherapy) to adolescents who have MDD with suicidal ideation.

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1. Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA*. 2004;292:807-820.
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Letters Section Editor: Robert M. Golub, MD, Senior Editor.

To the Editor: In interpreting the TADS results,[1] the central issue is the benefit-to-risk ratio, which can be determined by considering the number needed to treat (NNT), the number needed to harm (NNH), and the number needed to prevent.[2] In this study, a categorical positive response was achieved in 71.0% of participants treated with fluoxetine in combination with CBT; in 60.6% with fluoxetine alone; in 43.2% with CBT alone; and in 34.8% with placebo. Based on these outcomes, the NNT is 3.9 for fluoxetine alone compared with placebo and 3.7 for drug vs no drug. I believe that these represent low NNTs (high benefit) that are clinically meaningful.

The TADS Team reported suicide-related adverse events in 6.9% of children taking fluoxetine and in 4.0% of children who did not take fluoxetine; this corresponds to a NNH of 34. Likewise, TADS reported suicide attempts in 6 (2.78%) of 216 adolescents taking fluoxetine and in 1 (0.45%) of 223 adolescents not taking fluoxetine. The corresponding NNH is 43. The NNT is far more salient than either NNH.

There were no completed suicides in the TADS trial. Nevertheless, extrapolating from epidemiological data that indicate 8% of reported suicide attempts overall are lethal,[3] the estimated NNH with an outcome of completed suicide would be 535. Balancing any risk of drug-attributable suicide is the prevention of disease-attributable suicide in patients who receive the drug. Using a conservative lifetime case-fatality rate estimate of 2.2% among outpatients diagnosed as having MDD,[4] and allocating 30% of this risk to the adolescent years,[5] a completed suicide rate of 0.66% would be expected. When the TADS-observed NNT of 3.7 is applied to these estimates, the number needed to prevent 1 suicide is 560. Thus, there is suggestive evidence of equipoise between the therapeutic outcome of preventing suicide and any potential drug-related provocation of suicide among adolescents treated for MDD with fluoxetine. Overall, these estimates of absolute risk support the conclusion that favorable benefit-to-risk ratios exist for treatment with fluoxetine in adolescents with MDD.[1]

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1. Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA*. 2004;292:807-820.
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To the Editor: In their study, the TADS Team reported that the most effective treatment was fluoxetine in combination with CBT.[1] Treatment with CBT alone was less effective than treatment with fluoxetine alone and not significantly more effective than treatment with pill placebo. The TADS Team was surprised by the 43% clinical response rate for CBT alone, which was lower than in some other studies,[2,3] and posited that the lower response rate may have been due to greater severity, chronicity, and comorbidity in the TADS trial participants compared with previous trials.

In one of those earlier studies, we compared CBT with 2 other psychosocial treatments for mostly clinically referred, depressed adolescents.[2] Greater severity was associated with a less robust response to CBT, and it indeed does appear that the TADS participants had more functional impairment and greater chronicity of depression. However, our rates of comorbidity were comparable (58.2% vs 59.5%), and in fact, in our study, comorbid anxiety was a positive prognosticator of response to CBT.[4] This finding was corroborated in another treatment study of adolescent MDD using CBT,[5] which also found that treatment response to CBT is robust, even in the face of comorbidity with disruptive and substance abuse disorders.

Other explanations for the difference in response rates, besides greater severity and chronicity, may have to do with the difference in expectation, content, and format for treatment delivery. Because those who agreed to randomization knew that they might get medication, it is possible that these participants had different expectations about treatment than those who agreed to a study in which all of the options were psychotherapy. There may have been differences in the method of delivery and content of the CBT. With regard to format, in 1 of the 2 previous CBT studies,[2] the delivery was less structured and in the other study[3] CBT was highly structured, but delivered in a group format. With regard to content, both TADS and one of the previous studies[3] focused on teaching multiple skills, whereas the other study focused almost monothematically on cognitive restructuring.[2]

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1. Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA*. 2004;292:807-820.
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In Reply: We appreciate the opportunity to clarify the results of TADS. Drs Antonuccio and Burns interpret our results as showing that fluoxetine offers no significant ben-

efit over placebo, arguing (we believe incorrectly) that exercise is a placebo treatment and is somehow preferable to any of the TADS treatments. Drs Rifkin and Rifkin conclude that for the study population as a whole CBT plus fluoxetine offers little or no advantage over fluoxetine alone. In response, we note that TADS used the rate of improvement and 12-week outcome on the Children's Depression Rating Scale, the rate of improvement and 12-week outcome on the RADS, and percentage of patients much or very much improved on the CGI scale. Fluoxetine in combination with CBT was superior to placebo and to CBT alone on all 5 measures. Combined treatment was superior to fluoxetine on 2 measures. Fluoxetine alone was superior to placebo on 3 measures and to CBT alone on all 5 measures. Additionally, fluoxetine in combination with CBT showed a large effect size and fluoxetine alone showed a moderate effect size on the Children's Depression Rating Scale-Revised and on the CGI, whereas CBT alone was not different from placebo. Thus, we believe that the data show that fluoxetine in combination with CBT is best, fluoxetine alone is effective but not as effective as combined treatment, and that either fluoxetine-containing treatment is superior to CBT alone.

Drs Antonuccio and Burns state that the relatively small risk for adverse events associated with fluoxetine is unacceptable. However, on the Suicidal Ideation Questionnaire, which indexes suicidal ideation rather than MDD, combined treatment proved superior to fluoxetine alone, to CBT alone, and to placebo, but the 2 monotherapies and placebo did not separate. Thus, for suicidal thinking, fluoxetine in combination with CBT was the only treatment that offered benefit, whereas fluoxetine alone did not appear to induce suicidal thinking. On the other hand, the TADS results are consistent with recent Food and Drug Administration findings in identifying an approximately 2-fold increase in risk of self-harm behaviors associated with antidepressant medication. Fortunately, these behaviors are uncommon, occurring in the Food and Drug Administration analyses in approximately 4% of patients treated with an antidepressant and 2% of patients treated with placebo[1]; hence, the absolute risk increase associated with medication is 2%, corresponding to an NNH of 50 patients.

Dr Carroll notes (and we presented at the Food and Drug Administration hearings on antidepressant risk for suicide) that the benefit (NNT) to risk (NNH) ratio strongly favors fluoxetine in combination with CBT and, less robustly, fluoxetine alone. We think Carroll may actually overestimate the population-derived rate of suicide attempts and completed suicide, and thus underestimate the degree of benefit relative to risk. Using Spicer and Miller's[2] definition of attempters as those who make an attempt resulting in an injury, poisoning, or overdose that had to be treated by a physician or nurse, and data from the Youth Risk Behavior Survey,[3] the attempted case rate in the adolescent population is 0.6% in boys and 0.09% in girls. If this is the case, the corresponding case-fatality rates are more than an order of magnitude lower than those cited by Carroll. This implies that the NNH for adolescents would be in the thousands, not hundreds, and, hence, that the risk-to-benefit ratio is not at equipoise as Carroll suggests, but strongly favors including medication management as one component of treatment if the aim is to prevent suicide.

Nonetheless, given the large number of suicide attempts in adolescents each year, any level of increased risk is relevant to the public health, and we believe warrants strong cautionary labeling language. Importantly, the TADS findings suggest that combining CBT with fluoxetine may directly reduce suicidal ideation and, via an unknown mechanism, also reduce the small risk for harm-related adverse events attributable to fluoxetine.

Finally, while we do not disagree with Rifkin and Rifkin when they suggest that CBT should be reserved for adolescents showing risk for suicidality, we believe that TADS provides a potent public health argument for making CBT more widely available for adolescents with MDD. Without a strategy to speed adoption of CBT, adolescents with MDD will not receive the clinically meaningful increase in benefit and reduction in risk conferred by fluoxetine in combination with CBT.

In this context, and considering the points of Drs Bridge and Brent, it remains to be seen if the less severely ill adolescent might do well with CBT alone or if CBT alone will fare better at 36 weeks than it did with acute treatment. Planned analyses from the TADS group should shed further light on the question of which treatment is best and with which set of adolescent clinical characteristics.

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Spontaneous Regression of Cancerous Tumors Detected by Mammography Screening

To the Editor: In their study, Dr Joensuu and colleagues[1] reported that cancerous tumors detected by mammography screening have a lower risk of distant recurrence and better survival than those detected outside of screening, independent of the number of positive axillary lymph nodes, the primary tumor size, age at cancer detection, histological grade, and other biological factors.

In several European countries with nationwide screening programs, the breast cancer rate in the invited age groups is about 50% higher than the background level prior to the introduction of the screening program.[2,3] This difference has so far been explained by a lead-time effect, assuming that