Turning darkness into light
A new landmark study on the treatment of adolescent depression.
Comments on the TADS study

Depression in adolescence is one of the most common causes of both morbidity and mortality. Its point prevalence is between 3 and 8%, with as many as 15% of adolescents having had at least one depressive episode [1]. It is an impairing disorder, with a negative impact on school performance and interpersonal relationships. The sequelae of depression are very serious: academic and employment underachievement, continued interpersonal impairment, an increased risk for tobacco, alcohol, and substance abuse, and a very high likelihood for recurrent depressive episodes. Most concerning is that depression is the single most salient risk factor for both attempted and completed suicide, which in turn is one of the leading causes of death in adolescence. Thus, the detection and treatment of adolescent depression is a public health issue of the first magnitude.

The National Institutes of Mental Health (NIMH), the main source of funding for mental health research in the United States, recognizing the importance of this problem, called for proposals to establish the effectiveness of commonly utilized treatments for adolescent depression. The result was the Treatment of Adolescent Depression Study (TADS), which took 6 years, 17 million dollars, and 13 sites to accomplish the task [7]. As a result of NIMH’s vision and the hard work and meticulous attention to detail of the investigative team, the results are clearly worth the wait, and shed light on recent concerns about the efficacy and safety of selective serotonin reuptake inhibitors (SSRIs) for the treatment of adolescent depression.

The study compared four treatment conditions: Cognitive Behavior Therapy (CBT) plus fluoxetine, fluoxetine alone, CBT alone, and pill placebo. Subjects and investigators were blind as to medication status, whereas independent evaluators were blind to both medication and psychotherapy status. Subjects were mid-adolescents, 55% female, 21% ethnic minority, and with clinically significant disease, namely, with high rates of comorbidity and fairly severe degree of impairment [Children’s Global Assessment Scale of around 50 and Children’s Depression Rating Scale (CDRS-R) of around 60]. Although acute suicidality was an exclusion criterion, nevertheless, according to the self-reported Suicide Ideation Questionnaire, Jr., 29% of subjects had clinically significant ideation upon study entry. Subjects assigned to the fluoxetine condition received six 20–30 min pharmacotherapy sessions over 12 weeks, with a starting dosage of 10 mg, increased to 20 mg at week 2, and an option to increase again to 40 mg at week 8. CBT was a manual-based, skills-focused treatment, which drew in part on previously demonstrated efficacious CBT treatment approaches [2, 6]. In addition, there were two parent-only sessions to provide psychoeducation about depression, and one to three parent-child conjoint sessions to address parent-child relationship issues. The study had two primary outcome measures, the CDRS-R, a continuous measure of depressive severity, and the more global Clinical Global Improvement score at the end of treatment (CGI-I). Two additional secondary, self-report measures were obtained, the Reynolds Adolescent Depression Scale (RADS), and the Suicidal Ideation Questionnaire-Junior High School Version (SIQ-Jr.).
In total, 439 subjects were enrolled, of whom 411 had at least one post-intake rating on the CDRS. Forty-eight subjects withdrew consent prior to week 12, and the investigators terminated another 42 prematurely because they required out-of-protocol treatment according to the text. According to Table 1, 38 withdrew consent, 10 terminated from the study and then dropped out, and 32 were terminated prematurely from the study by investigators, which leaves 10 subjects described in the text unaccounted for on the figure. There were no statistically significant differences among the four groups with regard to baseline characteristics on omnibus tests, although the rate of comorbid dysthymic disorder, a known negative prognosticator for slow and less robust response to the treatment of depression, was nearly three times higher in the CBT-alone group than in the fluoxetine-alone group (15.45% vs. 5.5%).

The results using the CDRS-R, one of the two designated primary outcome variables, were analyzed in two ways, using random effects linear regression to test treatment differences in slope, and comparing endpoint values while covering for the CDRS-R at baseline. With regard to change in slope, the combined treatment (CBT plus fluoxetine) showed the greatest decrement compared to each of the other three treatments. Neither fluoxetine alone nor CBT alone were superior to placebo, although fluoxetine was superior to CBT alone. In comparison of baseline adjusted endpoint scores, the combined treatment was superior to CBT alone and to placebo, but not superior to fluoxetine. Fluoxetine alone was superior to CBT alone. The contrast between fluoxetine alone and placebo was not reported. Using the global Clinical Improvement Score, a higher proportion of those treated with the combined treatment were either “very much improved” or “much improved,” with a similar rank ordering: combination, 71%; fluoxetine, 61%; CBT, 43%; and placebo, 35%. Both the combined treatment and fluoxetine were superior to both CBT alone and to placebo, and there was no statistically significant difference between combination and fluoxetine alone, nor were CBT alone and placebo significantly different from one another. The results of the random regression and adjusted baseline analyses using the RADS were exactly parallel to the analyses using the CDRS-R.

The impact of treatment on suicidal ideation was also examined, with the SIQ-Jr. as the outcome measure. Combined treatment was superior to both monotherapies and to placebo, whereas neither monotherapy was different from the other, or from placebo.

The rate of harm-related events, defined as non-suicidal self-injury, worsening or onset of suicidal ideation, suicide attempt, aggressive ideation, or actual harm to others was compared among the four treatment groups and was 2.2 times higher in the medication than non-medication conditions. Similarly, those treated with fluoxetine were 2.4 times more likely to engage in suicidal thoughts or behavior than those treated with placebo. In the recent FDA-sponsored reclassification and analyses of such events, the rate of suicidality in those treated with medication alone was 4.6 times that of those treated with placebo [10].

One important consideration is that the study was designed prior to the recent concern with treatment impact on suicidality. As investigators have turned to this question, it has become apparent that measuring suicidality and its change over time is more complex than it appears. There is a need for a reexamination of the psychometrics of the scales and definitions that are used. Are suicidal threats more severe than suicidal gestures? What level of suicidal ideation, or change thereof is clinically significant? Is there a subset of adolescents more at risk for harm-related behavior in response to treatment with SSRIs?

The authors conclude that the combination of CBT plus medication was most potent in reducing depression. Combination treatment resulted in a faster rate of improvement than either monotherapy, particularly during the first 6 weeks. While the combination was superior to either monotherapy with regard to the slope of improvement, both adjusted endpoint analyses on the CDRS-R and global improvement on the CGI did not distinguish between the combined treatment and fluoxetine monotherapy. This report could have provided more information about the clinical, as compared to the statistical, significance of the findings. Were there group differences in the proportion of subjects who achieved clinical remission, often defined as a CDRS-R < 28, or who no longer met criteria for major depression on psychiatric interview? While suicidal ideation decreased the most in the combined treatment group, were there group differences in the proportions of subjects whose suicidality changed from above the criteria for clinical concern to below it?

In the Discussion section of the paper, the TADS...