Findings From the Treatment for Adolescents with Depression Study (TADS): What Have We Learned? What Do We Need to Know?

Mark A. Reinecke
Department of Psychiatry and Behavioral Sciences, Northwestern University

John F. Curry
Department of Psychology and Neuroscience, Duke University

John S. March
Division of Neurosciences Medicine, Duke Clinical Research Institute

This introduction to the special section on findings from the Treatment for Adolescents with Depression Study provides a review of the rationale for the study, its design, and principal findings to date. Findings with regard to acute effectiveness of alternative treatments, relapse, recurrence, maintenance of gains, and the effects of treatment on suicidal ideations and suicidal behavior are reviewed. We conclude with a brief discussion of unresolved clinical issues, including treatment resistance, management of partial response, moderators and predictors of long-term response, and mediators of clinical change. The articles of the special section address a range of issues including relations between cognitive factors associated with depression, relations between maladaptive beliefs and treatment response, cognitive mediators of therapeutic improvement, relations between family conflict and treatment response, and the economic costs of adolescent depression.

Major depression during adolescence is an increasingly important clinical and social concern. The disorder is common. A recent meta-analysis of epidemiological studies generated estimated point prevalence rates of adolescent major depression of 5.9% for girls and 4.6% for boys (Costello, Erkanli, & Angold, 2006). The lifetime prevalence rate also is high—approximately 14% of youth between 15 and 18 years of age have experienced a major depressive episode. Although the average age of onset appears to be declining (Reich et al., 1987), rates of suicide among youth have increased during recent years. Between 1990 and 2003, the suicide rate for individuals between 10 and 24 years of age had been trending downward, declining from 9.48 to 6.78 per 100,000 persons. From 2003 to 2004, however, the rate increased from 6.78 to 7.32. Results of an analysis of trends in rates of suicide completed by the Centers for Disease Control and Prevention indicated that, from 2003 to 2004, suicide rates for girls and young women aged 10 to 14 years and 15 to 19 years, and young men between 15 and 19 years of age, "departed upward significantly from otherwise declining trends" (Lubell, Kegler, Crosby, & Karch, 2007,
Depression among youth is associated with significant psychosocial impairment and family burden (Achenbach, Howell, McConaughy, & Stranger, 1995; Fleming, Boyle, & Offord, 1993). It places youth at risk for substance abuse and for repeated episodes of depression during adulthood (Harrington, Rutter, & Frombonne, 1996; Kovacs, Obrosky, Gatsonis, & Richards, 1997; Reinecke & Curry, 2008; Weissman et al., 1999). Early onset depression, then, is a serious and pernicious disorder.

With these concerns in mind, the National Institute of Mental Health funded the Treatment for Adolescents with Depression Study (TADS). TADS, a randomized, placebo-controlled study, examined the short- and long-term effectiveness of three active treatments for youth with major depression: (a) cognitive-behavioral psychotherapy (CBT), (b) medication management with fluoxetine (FLX), and (c) combination of medication management with fluoxetine and CBT (COMB). The fourth condition was a control condition in which participants received medication management with pill placebo (PBO). Participants included 439 youth between 12 and 17 years of age with moderate to severe major depression. Participants were recruited at 13 sites and were demographically representative of youth in the United States (The Treatment for Adolescents with Depression Study [TADS] Team, 2005). Youth were randomly assigned to one of three active treatment arms or pill placebo during the 12-week acute treatment phase of the study. The FLX and PBO conditions were administered under double-blind conditions; the COMB condition was not blinded. At the end of Stage I the blind was broken and non- and partial-responders in the PBO arm were offered their choice of treatment. By design, participants in the PBO arm were not included in analyses after this point. Participants in the CBT, FLX, and COMB arms received 6 weeks of additional treatment during the Stage II continuation phase. At the end of this time, participants entered Stage III, an 18 week maintenance phase in which they continued to receive medication management and/or “booster” CBT sessions every six weeks in their assigned treatment arm. At the end of Stage III, all treatments were discontinued and participants entered Stage IV, an open 52-week follow-up period. The methods of the project and participant characteristics are described in greater detail elsewhere (The TADS Team, 2003, 2005).

The TADS project represents the largest controlled outcome study of youth depression ever conducted. Its primary goal was practical—to provide evidence that might be used to develop guidelines for treating depressed youth. With the completion of the study, it is reasonable to ask if this goal was realized. Has TADS aided the development of guidelines for depressed adolescents? What can be said with confidence about the treatment of depressed adolescents?

TADS—WHAT HAVE WE LEARNED?

The first conclusion one can draw from TADS is that treatment works (The TADS Team, 2004, 2007). Intent-to-treat analyses indicated varying response rates across arms (The TADS Team, 2004). Rates of response during Stage I were 71% for COMB, 61% for FLX, 43% for CBT, and 35% for PBO. The greatest improvement, as indicated by slopes of scores on the Children's Depression Rating Scale—Revised, was observed among youth who had received a combination of fluoxetine and CBT. The two medication arms (COMB and FLX) were more effective in alleviating symptoms of depression than were CBT or PBO during this period. It is worth acknowledging, however, that a substantial number of adolescents continued to manifest significant symptoms of depression at the conclusion of Stage I (Kennard et al., 2006). Twelve weeks of treatment, for many depressed youth, is insufficient. After 36 weeks of treatment, however, rates of response were 86% for combination therapy, 81% for CBT alone, and 81% for fluoxetine alone (The TADS Team, 2007). Given sufficient time, approximately 80% of moderately to severely depressed youth benefit from treatment.

It also appears that medication management with fluoxetine accelerates improvement. Random regression analyses indicated that rates of improvement were greatest for the two medication arms during the acute treatment phase (Kratochvil et al., 2006; The TADS Team, 2004). Analyses of time-to-response indicate that the probability of an early, sustained treatment response was approximately three times greater for youth receiving a combination of CBT and fluoxetine than PBO and two times greater for fluoxetine than PBO (Kratochvil et al., 2006). After 18 weeks of treatment, CBT and FLX demonstrated similar rates of improvement (65% and 69%, respectively), as measured by scores on the clinician-completed Clinical Global Impressions—Improvement scale, indicating that CBT alone can be as efficacious as medication alone. Youth receiving CBT alone tend, as a group, to take longer to improve clinically than those who receive FLX.

Third, the results of TADS indicate that treatment of depression is associated with functional improvement (Vitiello et al., 2006). Scores on three measures of functioning—the Child Global Assessment Scale, Health of the Nations Outcome Scale for Children and Adolescents, and the Pediatric Quality of Life Questionnaire—improved for youth in all four treatment arms during...
the acute treatment phase. Clinical improvement was most apparent for adolescents in the COMB condition. These observations are heartening in that they suggest that treatments of depression can lead to improvements in the quality of a child's life and that these effects may be observed within a relatively brief period. It is worth acknowledging that a substantial number of depressed youth continued to manifest significant functional impairment at the end of 12 weeks of treatment. The proportion of adolescents who continued to manifest functional impairment, as indicated by a score of 70 or below on the Children's Global Assessment Scale (Shaffer et al., 1983), ranged from a low of 65% (among youth who had been in the COMB condition) to a high of 86% (among adolescents who had received CBT alone; Vitiello et al., 2006).

Relapse and recurrence of symptoms are important clinical concerns. The results of TADS indicate that treatment gains for all three active treatment arms were maintained over time, at least through the 36 week follow-up period (Rohde et al., 2008). An examination of 242 adolescents who had received FLX, CBT, or COMB during Stage I indicated that among youth who had not achieved a sustained response during the initial 12 weeks of treatment, between 62% and 80%, depending on treatment arm, achieved a sustained response if they continued with treatment. Moreover, youth who had achieved early sustained response with CBT were more likely than those who had done so with FLX to demonstrate a sustained response through the 36-week maintenance phase. Treatment gains were maintained in all three active treatment arms during the 52-week follow-up period.

Serious questions have been raised during recent years about adolescent suicide and the safety of selective serotonin reuptake inhibitors for treating depression among youth. Although not designed as a test of alternative treatments for suicidal youth, findings from the TADS project may illuminate these issues. Results indicate that treatment for depression reduces the frequency of suicidal thoughts (Emslie et al., 2006; The TADS Team, 2004, 2007; Vitiello et al., 2009). Suicidal ideations improved with treatment, with the greatest improvement observed in youth who had received a combination of CBT and fluoxetine. Moreover, youth who had received one of the two CBT treatments (CBT or COMB) demonstrated fewer suicidal ideations than did adolescents who had received fluoxetine or placebo. Suicidal gestures and attempts, although uncommon, were more common among youth who had received fluoxetine than among those receiving CBT or COMB. Findings suggest that CBT may ameliorate suicidal ideations among youth receiving fluoxetine (March, Silva, Vitiello, & the TADS Team, 2006). Taking risk and benefit into account, the results of TADS indicate that the combination of CBT and medication management with fluoxetine appears to offer the benefit of rapid treatment response, maintenance of gains, and enhanced safety for depressed adolescents.

WHAT DO WE NEED TO KNOW?

The results of TADS are congruent with other research in suggesting that CBT may be efficacious for treating depression among adolescents (for reviews, see Curry, 2001; David-Ferdon & Kaslow, 2008; Fonagy, Target, Cottrell, Phillips, & Kurtz, 2002; Klein, Jacobs, & Reinecke, 2007; Weisz, McCarty, & Valeri, 2006), although in TADS it did not surpass PBO acutely. Taken together, studies indicate that the effect size of individual CBT is moderate, that CBT may have an effect on suicidal ideations and that it may facilitate the maintenance of therapeutic gains. Moreover, the combination of CBT and FLX in TADS attained the highest acute response rate for treatment of moderate to severe adolescent depression. There is, then, reason for optimism with regard to the effectiveness of CBT with moderately depressed youth.

As noted, however, a substantial number of adolescents (approximately 15%) do not demonstrate an adequate response, even after 36 weeks of treatment. Important questions come to mind about how we can best aid treatment resistant youth. What factors contribute to treatment resistance? Might cognitive, social, familial, or biological markers be identified to identify youth who may not benefit from sustained CBT or fluoxetine? Along the same lines, many participants in TADS continued to manifest "low-level" depressive symptomatology or comorbid conditions at the conclusion of treatment. How should we understand partial treatment response? Might moderators or predictors of long-term treatment response be identified? How might residual subclinical symptomatology be addressed? Questions also remain as to how the effectiveness of CBT might be optimized. The time-to-response of CBT in TADS was slower than that of FLX or COMB. How might we understand this, and how might it be remedied? Might it make sense to simplify the CBT protocol and offer a smaller number of interventions—those with the strongest association with positive outcome—to youth in a more intensive manner? Alternatively, it may be preferable to select interventions based on the strengths or vulnerabilities of individual patients—to tailor the intervention such that it is a truly prescriptive psychotherapy. Finally, questions remain as to mechanisms of change in CBT. Does cognitive therapy exert its effect through the modification of dysfunctional attitudes, beliefs, expectations, and attributions
associated with depression, or through other means? Before one can address the issue of mechanism of change, however, it is necessary to have a clearer understanding of specific cognitive concomitants of depression and predictors of risk, and their relation to one another. A range of cognitive factors have been associated with severity of depression, including dysfunctional attitudes, perfectionism, attributional style, cognitive distortions, rational problem solving, and problem-solving motivation. Are these cognitive markers of vulnerability for depression or simple concomitants? Do they predict, moderate, or mediate response to treatment? As important, do they move independently of one another (perhaps indicating alternative cognitive pathways toward depression, or alternative mechanisms of change) or are they closely linked temporally and psychometrically?

Questions have been raised about specific features of the TADS design. Concerns have centered on the lack of a blind for youth receiving a combination of CBT and fluoxetine, the lack of a CBT plus placebo control group, and the lack of a control group after Week 12. As noted elsewhere (March et al., 2006), no single study can address the full spectrum of issues that arise regarding treatment efficacy or effectiveness. Rather, design decisions are made such that the study accomplishes its primary goals while attending to very real financial constraints and competing scientific objectives. It has been noted, for example, that in the absence of a CBT plus PBO condition, the superiority of COMB to FLX during the acute phase cannot be disentangled from expectancy effects. Embedded within this issue are substantive questions about what constitutes a "placebo control" for a psychosocial intervention, the nature and mechanism of placebo effect, and the role of cognitive factors (including expectations of improvement) in facilitating therapeutic change in each of the treatment arms.

Our goals in conducting the TADS project were practical—to provide evidence that would support the development of guidelines for treating depressed adolescents and to elucidate cognitive, social, and biological factors associated with clinical improvement. It is not enough, however, for treatments (either pharmacological or psychosocial) to be efficacious. To have true clinical utility, they must also be cost effective, available, and acceptable to parents and families. What are the social and economic costs of adolescent depression? Which treatments are the most cost effective in the short term and long term? Which costs effect treatment utilization? Are different interventions or programs of care more cost effective for specific patients or groups of patients? How do parents and teenagers understand their treatment alternatives, and how does this influence their decision to pursue care?

We began by suggesting that major depression among youth is a common, serious, and pernicious disorder. If we are to reduce its burden on adolescents, families, and the larger society it will be necessary to attend not only to efficacy but also to the broad range of economic and social factors effecting the availability and use of these treatments.

THE SPECIAL SECTION

In this special section we present the results of several secondary analyses of data from the TADS project. Each of the articles included in the special section addresses one of the issues or questions just outlined. Whereas prior TADS research has focused primarily on clinical outcome, maintenance of gains, suicidality, and safety, the articles included in the special section focus on cognitive concomitants of depression, mediators of change, family relationships of depressed youth, and health economics. The findings presented extend prior research by addressing a range of critical gaps in our understanding of adolescent depression and its treatment.

Four of the articles focus on cognitive factors commonly associated with vulnerability for depression. These include articles examining (a) cognitive distortions among depressed youth (Kingery and colleagues); (b) the factor structure of the Dysfunctional Attitudes Scale (DAS), a widely used measure of depressogenic beliefs (Rogers and colleagues); (c) relations between alternative measures of cognitive concomitants of depression (Ginsburg and colleagues); and (d) relations between perfectionism and treatment outcome (Jacobs and colleagues). As a number of writers have noted, interpersonal factors play an important role in the development and maintenance of depression among adolescents (Spence & Reinecke, 2003) and adults (Gotlib & Hammen, 1992; Joiner, 2002). With this in mind, Feeny and colleagues present a study of relations between family functioning, parent–child conflict, and depression among youth. Finally, Domino and colleagues examine the economic costs and consequences of adolescent depression. Their article serves as foundation for research into the cost effectiveness of evidence-based treatments.

The first article in the special section, a study by Kingery and colleagues of the factor structure and psychometric properties of the Children's Negative Cognitive Error Questionnaire (CNCEQ), addresses important questions regarding the organization of cognitive factors implicated in the onset and maintenance of depression among youth. Whereas a substantial body of research has been published explicating relations between cognitive distortions and mood among
422 participants in the TADS project yielded a two-factor structure of the DAS with depressed adolescents, then, it is possible that dysfunctional attitudes may interact for the onset of major depression. Moreover, it has been consistent with that reported with depressed adults. The results of a confirmatory factor analysis indicated that a four-factor solution including a general factor and three “content area” factors (i.e., social, academic, and athletic) best accounted for the data. Of interest, the results were not supportive of conceptually based models in which subscales are organized according to the type of cognitive distortion (e.g., overgeneralization, magnification, selective abstraction). These findings support the validity of the CNCEQ with depressed adolescents and suggest that clinicians may wish to focus on distressing domains or problem areas (i.e., social, academic, athletic) rather than on the specific types of cognitive distortion displayed in those settings.

A study completed by Rogers and colleagues of the factor structure of the DAS follows in the special section. The DAS is a widely studied measure of dysfunctional attitudes or schema associated with depression. Originally developed as a measure of tacit beliefs associated with depression among adults, the scale yields two factors—“perfectionism” or “performance evaluation” and “approval of others” or “need for approval.” Few studies have been completed, however, examining the factor structure of the scale or its psychometric properties with depressed adolescents. The question addressed in this study centers on whether the factor structure of the DAS, when administered to clinically depressed adolescents, is similar to the factor structure of the DAS reported in adults. This question is clinically and conceptually important in that the possibility exists that dysfunctional attitudes may interact with stressful life events in placing individuals at risk for the onset of major depression. Moreover, it has been proposed that depressogenic beliefs may serve as a useful target of clinical intervention. The results of a confirmatory factor analysis of the DAS completed with 422 participants in the TADS project yielded a two-factor solution, with factors incorporating items related to perfectionism and need for social approval. The factor structure of the DAS with depressed adolescents, then, is consistent with that reported with depressed adults. Although these findings indicate that it is possible to assess depressogenic beliefs in depressed youth, further research will be necessary to determine if the factors identified—perfectionism and need for social approval—are associated with vulnerability of depression, clinical course, or treatment response.

The third article included in the special section addresses the question of relations between cognitive factors associated with vulnerability for depression among youth. A range of factors, including attributional style, dysfunctional attitudes, and maladaptive self-cognitions, have been postulated to place youth at risk for depression (Jacobs, Reinecke, Gollan, & Kane, 2008). Few studies, however, have examined relations between alternative measures of cognitive predictors or concomitants of depression. It is unclear whether these alternative cognitive constructs, and their associated measures, reflect unique constructs associated with depression or are tapping overlapping or higher order cognitive constructs. In a study completed by Ginsburg and colleagues, relations between five self-report measures of cognitive factors associated with depression were examined in a study of 390 participants in the TADS project. The results of a principal components analysis yielded a four-factor solution. The identified factors were labeled “Cognitive distortions and maladaptive beliefs,” “Cognitive avoidance,” “Hopelessness,” and “Solution-focused thinking.” These factors were consistent for both boys and girls, and for younger and older adolescents. Scores on each of these factors were positively associated with severity of depression, and scores on three of the four factors predicted or moderated acute treatment response. The identified factors appear to be congruent with several contemporary models of depression, including those proposed by Beck, Compas, Nolen-Hoeksema, Hankin, and D'Zurilla. The possibility exists, as such, that several semi-independent cognitive concomitants of adolescent depression may exist and that these factors may be associated with treatment response.

Relations between maladaptive beliefs and treatment response were examined in greater detail in a study completed by Jacobs and colleagues. Perfectionism, a set of beliefs incorporating high personal standards, self-doubt, pursuit of achievement-oriented goals, need for approval, and excessive self-criticism, has been associated with severity of depression and suicidality in adolescents and adults and with treatment response in adults. Relations between perfectionism and treatment response among depressed adolescents, however, has received little study. In a study of 439 adolescents enrolled in the TADS project, Jacobs and colleagues found that perfectionism was significantly correlated with both severity of depression and frequency of suicidal ideations. Moreover, pretreatment perfectionism predicted (but did not moderate) acute treatment response for both level of depression and suicidal ideations. Youth reporting higher baseline levels perfectionism were found to respond more poorly in all
Treatment conditions. Of interest, clinical improvement in all treatment arms was mediated by change in perfectionism over the first 12 weeks of treatment. This study is significant, then, in that it speaks directly to the paucity of research on cognitive predictors, moderators, and mediators of clinical change. Although the results of their mediation analysis are intriguing, further research is needed to determine if perfectionism also serves as a mechanism of clinical improvement.

The fifth article in the special section, a study by Feeny and colleagues, examined associations between parent–child conflict, severity of depression, and acute treatment response in a sample of 439 depressed youth. Depression occurs in a social context. Studies indicate that family conflict is associated with vulnerability for depression, maintenance of depressive episodes, and severity of depression among youth. Relatively few studies have been completed, however, examining associations between family conflict and treatment response. As noted, research indicates that not all depressed youth benefit from treatment. Fully 15% of depressed youth demonstrate an inadequate treatment response. Factors associated with poor treatment response, however, are not well understood. This study, as such, addresses the need for information on familial and social factors associated with treatment response. The results of this study indicate that adolescents with mothers who reported less parent–child conflict were more likely to benefit from treatment than were adolescents whose mothers reported more conflict. Of interest, none of the measures of family functioning or conflict was associated with severity of adolescent depression, as reported by an independent evaluator. Four family functioning variables—adolescent’s values and norms, family communication, family involvement, and family control—were found to moderate acute treatment response. From a clinical perspective, these findings are potentially important in that they suggest that depressed adolescents’ perceptions of family conflict and functioning during an initial evaluation may be a useful predictor of initial treatment response. The findings are important conceptually in that they broaden our understanding of moderators and predictors of clinical outcome. They direct our attention not to characteristics of the depressed adolescent or to biological markers of treatment response but to characteristics of the adolescent’s social environment.

The sixth and final article in the special section is a study by Domino and colleagues of the economic costs and consequences of adolescent depression. Decisions regarding the dissemination of evidence-based treatments must be based, at least in part, on research regarding their cost effectiveness and their acceptability to parents and families. However, little research has been conducted regarding service utilization, costs, and familial burdens associated with adolescent depression. This study was designed to answer the question, What are the social and economic costs of adolescent depression? To address this question, the authors examined the types of clinical, medical, and social services used by families of depressed youth during the 3 months prior to their enrollment in the TADS project and estimated their costs. Results indicated that approximately 70% of depressed youth received clinical services during this period. In the TADS sample, 21% reported having participated in one or more outpatient mental health visits during this time. Approximately 40% of youth used general health services from a medical provider. These rates of service use are substantially higher than those reported in the general adolescent population. The average participant had $281 in treatment-related costs. Most of the costs of depression were borne by families. Consistent with prior research, ethnic differences in service use and costs were observed. It is worth noting that the results obtained may not generalize to all depressed youth, as extremely depressed or suicidal youth (who might require hospitalization) were excluded from the TADS sample. The results may, as a result, underestimate costs and service utilization of depressed adolescents. These findings are important in that they suggest that adolescent depression can have important economic implications for families. A majority of depressed youth contacted medical professionals, but did not receive treatment for their depression, during the months prior to their entry in the study. There may, then, be opportunities for screening or early intervention in primary care settings.

CONCLUDING COMMENTS

Our understanding of adolescent depression and its treatment has grown dramatically over the past 10 years. A meta-analysis of CBT with depressed youth completed in 1998 included data from six randomized controlled trials (Reinecke, Ryan, & DuBois, 1998), whereas a similar meta-analysis completed a decade later included 31 controlled CBT studies (Weisz, McCarty, & Valeri, 2006). The TADS is the largest randomized controlled trial of alternative treatments for depressed youth ever completed. Although well designed and carefully executed, the results obtained were not beyond controversy. As is so often the case with good science, the results obtained not only answered questions, they raised a range of important issues. Findings from the TADS and other research indicate that we can have some confidence in the efficacy of available treatments for depressed adolescents. That said, important gaps in the literature remain. The articles included in this special section represent a first
attempt to address many of these lapses. They are, however, only a first step. It is our hope that these articles will stimulate clinicians and investigators to address a broader range of questions surrounding vulnerability for depression among youth, treatment effectiveness, and mechanisms of clinical improvement. Findings published to date, including results from the TADS project, indicate that our treatments do some good (at least for some patients). We need, however, to do better.

REFERENCES


