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Onset of Alcohol or Substance Use Disorders Following Treatment for Adolescent Depression

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Abstract

Objective—This study tested whether positive response to short-term treatment for adolescent major depressive disorder (MDD) would have the secondary benefit of preventing subsequent alcohol or substance use disorders.

Method—We followed for five years 192 adolescents (56.2% female; 20.8% minority) who had participated in the Treatment for Adolescents with Depression Study (TADS), and had no prior diagnoses of alcohol or substance use disorders. TADS initial treatments were cognitive behavior therapy (CBT), fluoxetine (FLX), the combination of CBT and FLX (COMB), or clinical management with pill placebo (PBO). We used both the original TADS treatment response rating and a more restrictive symptom count rating. During follow-up, diagnostic interviews were completed at six or 12 month intervals to assess onset of alcohol (AUD) or substance use disorders (SUD), MDD recovery and recurrence.

Results—Achieving a positive response to MDD treatment was unrelated to subsequent AUD, but predicted lower rate of subsequent SUD, regardless of the measure of positive response (11.65% versus 24.72%; or 10.0% versus 24.5%, respectively). Type of initial MDD treatment was not related to either outcome. Prior to depression treatment, greater involvement with alcohol or drugs predicted later alcohol or substance use disorders, as did older age (for AUD) and more comorbid disorders (for SUD). Among those with recurrent MDD and AUD, AUD preceded MDD recurrence in 24 of 25 cases.

Conclusion—Effective short-term adolescent depression treatment significantly reduces the rate of subsequent substance use, but not alcohol use, disorders. Alcohol or drug use should be assessed prior to adolescent MDD treatment and monitored even after MDD recovery.

Keywords

adolescents; major depression; alcohol use disorders; substance use disorders

Alcohol or other substance use disorders (AOSUDs), including psychoactive substance abuse or dependence, are among the most common adolescent psychiatric disorders. Point prevalence rates are approximately 2–3%, with lifetime prevalence rates reaching 12.2% by age 16 (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Lewinsohn, Hops, Roberts, Seeley & Andrews, 1993). AOSUDs increase over the adolescent age range (Costello et al., 2003), frequently follow a chronic or relapsing course (Kaminer, Burleson, & Burke, 2008) and are associated with multiple negative correlates or outcomes, including criminal justice involvement, high-risk sexual behavior, and suicide attempts (Tims et al., 2002; Wu et al., 2004). Because of their prevalence and negative functional impact, it is critical to prevent development of these disorders in vulnerable adolescents.

Adolescents with AOSUDs frequently have other disorders, such as conduct disorder or depression. Such disorders may develop earlier than, and constitute risk factors for subsequent alcohol or drug disorders (Armstrong & Costello, 2002). Therefore, to the extent that treatments for these earlier disorders are effective, they might also mitigate the risk for development of subsequent AOSUDs (Kendall & Kessler, 2002). In the present study we investigate whether effective treatment for adolescent major depressive disorder (MDD) exerts such a secondary benefit (Glantz et al., 2008), by investigating subsequent onset of AOSUDs among participants in the multi-site Treatment for Adolescents with Depression Study (TADS Team, 2004).

Depressive symptoms in adolescence have been associated with subsequent increases in alcohol or drug use, or related problems in several studies. However, studies vary in whether their focus is on alcohol or other substances, and findings are not entirely consistent, appearing to vary by gender and age. In longitudinal studies including both genders, Stice, Barrera, & Chassin (1998) found that depressed and anxious symptoms during adolescence predicted alcohol-related problems one year later, and Chen, Anthony and Crum (1999) found that childhood or early adolescent depressive symptoms predicted early to mid-adolescent alcohol-related problems. In the Dunedin longitudinal study, Henry et al. (1993) found that early adolescent depressive symptoms predicted mid-adolescent drug problems (multiple substance use), but only for boys. Similarly, in the Great Smokey Mountain Study, the effects of depression on substance use were stronger for boys than for girls: Boys with depressive symptoms reported them prior to the onset of cannabis use, abuse or dependence (Costello, Erkanli, Federman, & Angold, 1999). Finally, Marmorstein (2009) found that depressive symptoms in early adolescent males, but not females, predicted faster growth in alcohol-related problems through adolescence.

Two studies that failed to find a link between adolescent depressive symptoms and subsequent alcohol or drug problems measured late adolescent or early adult outcomes. Chassin, Pitts, DeLucia, and Todd (1999) found no effect of internalizing symptoms during adolescence on young adult alcohol use disorders in a high-risk sample; and in the Dunedin study, depressive symptoms at age 15 did not predict increased cannabis use at age 18 (McGee, Williams, Poulton, & Moffitt, 2000).

Even in single gender longitudinal studies there is variability in the link between depression and subsequent alcohol versus drug outcomes. Two recent reports from a study of adolescent girls (Measelle, Stice & Hogansen, 2006; Measelle, Stice & Springer, 2006) indicated that negative emotionality predicted onset of alcohol or substance abuse, whereas depressive symptoms predicted worsening in substance abuse. Taken together, these findings suggest that the link between depressive symptoms and subsequent alcohol or substance use, problems or disorders may vary by age, gender, and whether alcohol or other substance-related outcomes are assessed.

Compared to depressive symptoms, fewer studies have investigated the potential link between diagnosed adolescent depressive disorders and subsequent alcohol or other substance-related problems. A large prospective study of Finnish twins concluded that depressive disorders at age 14 predicted more frequent drug and alcohol use, and recurrent intoxication by age 17.5 years (Sihvola et al., 2008). Rohde, Lewinsohn, and Seeley (1996) found that among adolescents with both depressive and alcohol disorders, there was not a consistent temporal pattern of onset, but depression occurred first in a substantial number of cases (58%). On the other hand, some studies have found that adolescent depressive disorders do not predict subsequent AOSUDs, or that earlier drug or alcohol use predicts depressive disorders (Brook, Cohen, & Brook, 1998; Brook, Brook, Zhang, Cohen, & Whiteman, 2002).

Two considerations may clarify the nature of the link between adolescent depressive disorders and AOSUDs. First, any linkage may be bidirectional (Costello et al., 1999; Swendsen & Merikangas, 2000). If so, a test of the potential secondary preventive benefits of effective depression treatment on subsequent AOSUDs should be conducted with a depressed sample free of pre-existing AOSUD. Second, the link between depressive disorders and subsequent AOSUDs may be indirect, i.e., attributable to other factors. Fergusson and Woodward (2002) found that adolescents who developed MDD between ages 14 and 16 were significantly more likely than those who did not, to develop both recurrent MDD and an alcohol use disorder (AUD) by age 21. However, whereas the link between initial and subsequent MDD episodes was direct, the link between adolescent MDD and subsequent AUD was attributable to other factors, including early drinking and peer influence. Thus, any elevated risk of AOSUD associated with adolescent MDD may be small or non-significant when assessed in the context of other factors (Measelle, Stice, & Springer, 2006). Therefore, when testing whether effective treatment of adolescent MDD has a secondary benefit of preventing subsequent AOSUD, it is important to include additional predictors of AOSUD that were present before treatment.

Taking these two considerations into account, in this study we investigated the preventive effects of successful depression treatment on subsequent alcohol use disorders (AUD) or other substance use disorders (SUD) in a sample with no pre-existing AUD or SUD. We investigated AUD and SUD separately for several reasons. First, as noted above, previous studies have found variable results, depending on whether alcohol or other substance-related problems were assessed. Second, the trajectories of AUD and SUD differ across the age range under investigation. AUD is slightly more prevalent than SUD in early adolescence (Chassin, Ritter, Trim & King, 2003), but becomes much more prevalent by age 20 (Cohen

et al., 1993), and has a substantially higher lifetime prevalence among adults (Kessler et al., 2005). Third, among adolescent psychiatric patients the correlates of alcohol abuse and of other substance abuse are not identical (Becker & Guilo, 2006), and among college students alcohol abuse is associated with major depression, but other substance abuse is associated both with major depression and with other comorbid diagnoses (Deykin, Levy, & Wells, 1987).

We took into account several possible additional predictors of AUD and SUD evident before depression treatment, to assure that any secondary benefit of successful depression treatment on subsequent AUD or SUD could not be accounted for by these other predictors. The potential predictors included demographic variables (age, gender, and ethnicity), comorbid disorders, and pre-treatment use of alcohol or drugs. Demographic variables are important to consider, not only because previous studies have found age and gender differences in the linkage between depression and substance abuse, but also because alcohol and drug use are more prevalent in older adolescents, in males, and vary by ethnic group (SAMHSA, 2010). We included comorbid disorders because a large percentage of adolescents with MDD present with additional comorbid disorders (Kovacs, 1996), and the comorbid disorders, such as anxiety or disruptive behavior disorders, may be the source of risk for subsequent AUD or SUD (Armstrong & Costello, 2002). Lastly, use of alcohol or drugs prior to treatment for MDD must be considered. Costello, Erkanli, Federman, and Angold (1999) found that first alcohol use preceded diagnosed AUD by approximately six years, with a comparable period of about three years between first cannabis use and a diagnosable SUD. It may be that depressed adolescents who are already involved in alcohol or drug use at the time of depression treatment have greater risk for subsequent AUD or SUD than those who are not.

Finally, we took into account the course of MDD following treatment, because this may influence development of AUD or SUD. The great majority of treated adolescents recover from their index MDD episode within one to two years but rates of recurrent MDD across community and clinical samples range from 40% to 70% (Birmaher et al., 2000). In a previous report, we found that 88.3% of TADS adolescents recovered within two years (96.4% within five years), but that 46.6% of recovered adolescents experienced recurrent MDD within five years (Curry et al., 2010). Chronic or recurrent depression may increase the risk of alcohol or substance use disorders. Among adults treated for alcohol or drug dependence, an earlier lifetime history of MDD lowered the likelihood of successful drug or alcohol treatment, and MDD during a period of sustained alcohol or drug abstinence increased the risk of relapse (Hasin et al., 2002). In adolescents, depression is associated with more severe SUD and higher risk for SUD relapse (McCarthy, Tomlinson, Anderson, Marlatt, & Brown, 2005; Riggs, Baker, Mikulich, Young, & Crowley, 1995); in turn, alcohol or substance abuse is associated with longer episodes of depression in girls (King et al., 1996). None of these findings directly demonstrate that chronic or recurrent MDD raises the risk of AUD or SUD onset, but they suggest that persistent/ongoing MDD complicates efforts to avoid or achieve sustained remission from alcohol or other substance use disorders. In the present study we explored whether chronic or recurrent MDD among treated adolescents increased the risk of AUD or SUD onset.

In summary, we tested the hypothesis that, among depressed adolescents with no history of AUD or SUD, effective depression treatment would have the secondary benefit of preventing subsequent AUD or SUD. As noted by Kendall and Kessler (2002), it is not possible to compare treated versus untreated depressed adolescents, because withholding treatment would be unethical. However, it is possible to compare more effective versus less effective treatment of MDD. Indeed, Kendall, Safford, Flannery-Schroeder, and Webb (2004) showed that effective treatment of youth anxiety disorders lowered risk of

subsequent substance use problems. Thus, we compared onset of AUD and SUD among TADS adolescents who successfully responded to acute depression treatment compared to non-responders.

We supplemented our primary analyses with secondary analyses to investigate whether the receipt of a specific type of acute depression treatment or the achievement of response to a specific acute treatment was associated with lower risk for subsequent AUD or SUD. In TADS, the combination of fluoxetine and cognitive behavior therapy (COMB) led to the highest rate of positive short-term treatment response and fluoxetine alone (FLX) led to a greater rate of short-term response than did cognitive behavior therapy (CBT) (TADS Team, 2004). On the other hand, CBT, alone or as part of COMB, was a skills-based intervention and included some skills that are also embedded in effective substance abuse prevention programs (e.g., goal-setting, problem-solving, social skills; Lochman & Wells, 2002). We had an insufficient basis in prior research to justify *a priori* hypotheses for these analyses, but it was possible that faster response, through COMB or FLX, or skills acquisition, through COMB or CBT, might be associated with more favorable subsequent AUD or SUD outcomes.

Method

Relation of TADS to the present study

TADS compared cognitive behavior therapy (CBT), fluoxetine (FLX), and their combination (COMB) to one another over the course of short-term (12 weeks), continuation (6 weeks), and maintenance (18 weeks) stages of treatment. During the first stage, the three active treatments were also compared to clinical management with a pill placebo (PBO). At week 12 the medication blind was broken and PBO non-responders were offered their TADS treatment of choice. After all three treatment stages (Week 36), adolescents were followed openly for one year (TADS Team, 2009).

The present study, Survey of Outcomes Following Treatment for Adolescent Depression (SOFTAD), was an open follow-up extending an additional three and one-half years. The total TADS-SOFTAD time period spanned 63 months (21 months of TADS and 42 months of SOFTAD), with diagnostic interviews administered at baseline and then at the following months after baseline: three, nine, 15, 21 (end of TADS), 27, 33, 39, 51, 63.

The design, sample characteristics, and outcomes of TADS have been described in previous publications (TADS Team, 2004; 2007; 2009). TADS participants were 439 adolescents from 13 sites with moderate to severe, non-psychotic MDD. At the end of short-term treatment, positive response was defined as an independent evaluator rating of 1 (very much improved) or 2 (much improved), on the seven-point Clinical Global Impressions – Improvement scale (CGI-I; Guy, 1976). Adolescents rated with a score of 3 (minimally improved) or higher (no change or worsening) were categorized as non-responders.

Participants in SOFTAD were recruited from all 439 adolescents in TADS, regardless of compliance with treatment or assessments, treatment response, or time since TADS baseline, provided this was no greater than 63 months. TADS recruitment began in spring, 2000 and ended in summer, 2003. SOFTAD recruitment and assessments began in spring, 2004 and concluded in winter, 2008. Recruitment involved: 1) re-contacting TADS early completers and dropouts; and 2) after spring, 2004, asking adolescents and parents completing TADS to participate in SOFTAD. Written informed consent and, for minors, assent, were obtained. The Duke University Health System IRB and each site IRB approved this study.

The initial SOFTAD assessment optimally occurred 27 months after TADS baseline. SOFTAD participants who were enrolled at that juncture could complete seven assessments at six month intervals, of which five included the diagnostic interviews that were used in the present analyses. Some participants, however, were not recruited until after 27 months and their SOFTAD enrollment visit was the assessment that corresponded to their point of entry.

Sample Description

The total SOFTAD sample included 196 adolescents, recruited at 12 of the 13 TADS sites. Four SOFTAD subjects were excluded from the present study because of AUD or SUD diagnosed at or before the end of TADS short-term treatment (week 12). Thus, the sample for the present study consisted of 192 adolescents (84 males and 108 females; 43.7% of the 439 youths randomized to TADS treatments), with an average age at entry into TADS of 14.9 years ($SD = 1.5$ years). Their age at the end of SOFTAD ranged from 17 to 23 years with a mean of 20.1 years ($SD = 1.5$ years). Table 1 includes demographic and clinical characteristics of the present sample at the time they entered TADS. The sample was 79% Caucasian, 9% Latino, 8% African-American, and 4% other ethnicity. Ninety percent of the sample had been in their first episode of MDD at entry into TADS. At intake into TADS, they had been moderately to severely depressed, as indicated on the Children's Depression Rating Scale-Revised (CDRS-R; Poznanski & Mokros, 1996; sample raw score $M = 59.4$, $SD = 10.3$). Functional impairment was also in the moderate range on the 100-point Children's Global Assessment Scale (CGAS; Shaffer et al., 1983; sample $M = 50.3$, $SD = 7.8$). Forty-one of these adolescents (21%) had a comorbid disruptive behavior disorder and 44 (23%) had a comorbid anxiety disorder.

The participants' point of entry into SOFTAD, in months since TADS baseline, was as follows: Month 27 (33%); Month 33 (22%); Month 39 (14%); Month 45 (11%); Month 51 (10%); Month 57 (8%); and Month 63 (2%). Of seven possible SOFTAD assessments, the modal number of completed assessments was 5, with a mean of 3.5 ($SD = 1.5$).

Criterion Measures

Diagnoses—To establish diagnoses, including those of AUD and SUD, the Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present and Lifetime Version (K-SADS-P/L; Kaufman et al., 1997) was administered at five of the seven SOFTAD assessment points. (The Month 45 and Month 57 assessment points included only self-report scales.) The K-SADS-P/L had been used in TADS, and thus was familiar to all participants. It was used to assess mood, anxiety, disruptive behavior, eating, substance use, psychotic, and tic disorders, using DSM-IV criteria (American Psychiatric Association, 2000). This interview has high concurrent validity, inter-rater and test-retest reliability (Kaufman et al., 1997; TADS Team, 2004). At each K-SADS-P/L administration, inquiry was made about symptoms and episodes of any disorder since the last TADS or SOFTAD assessment that the participant had completed, and also about current symptoms of MDD, AUD or SUD. The K-SADS-P/L is typically administered to both the adolescent and a parent. Interview administration was adapted for SOFTAD, as participants were transitioning into young adulthood: the participant was always interviewed; the parent was interviewed if the participant was still living at home. This modification is consistent with other adaptations of the K-SADS for circumstances in which parental involvement is not feasible (Lewinsohn et al., 1993)

The K-SADS-P/L includes an initial screen interview, with supplements for each disorder. The supplements are administered only if the screen indicates the possibility of the disorder. For AUD, the screen interview includes questions about quantity (three or more drinks in a day) and frequency of drinking (three or more days a week), and about whether significant

others have expressed concern about the participant's drinking. If any item is answered positively, the supplement is administered. For SUD, the screen includes a list of possible drugs of abuse (cannabis, stimulants, anxiolytics, sedatives, cocaine, opioids, phencyclidine, hallucinogens, solvents, inhalants, ecstasy, and prescription drugs), and the participant is asked if he or she has used any of these in the past six months. If non-prescribed use has occurred more than once a month, the supplement is administered. Supplement questions are anchored to DSMIV (American Psychiatric Association, 2000) symptoms of abuse or dependence.

Episodes of MDD, AUD or SUD—When the K-SADS-P/L indicated that the participant met criteria for MDD, AUD, or SUD (other than nicotine), at any point since the last interview, the interviewer inquired about onset and, if relevant, offset of the episode. Onset was estimated as the month when the adolescent met all criteria for a disorder episode. Offset was estimated as the month when the adolescent had no remaining clinically significant symptoms of the disorder.

In a previous report (Curry et al., 2011), we focused on recovery from the TADS index episode of MDD and on recurrent MDD. Recurrent MDD was defined as a new episode following at least eight weeks of no MDD symptoms. In this study, we focused on the emergence of episodes of AUD or SUD after short-term depression treatment, defined as those diagnosed after the TADS Week 12 interview. We also investigated the association between recurrent episodes of MDD and the onset of AUD or SUD.

Interviewer training and monitoring—SOFTAD evaluators met the same criteria as those of TADS evaluators (masters or doctoral degree in a mental health profession with previous experience administering research diagnostic interviews). Evaluators completed these steps for certification: 1) a videoconference training session; 2) a knowledge test passed with 80% correct answers; 3) rating a videotaped standard patient interview provided by the coordinating center, with 80% agreement on the full MDD, AUD and SUD DSM-IV criterion sets, agreement on these diagnoses, and agreement on other classes of disorders (e.g., anxiety disorder); 4) completion and rating of an audiotaped site-based interview with an adolescent, subsequently rated at the coordinating center with acceptable reliability, using the same criteria as in step 3.

Following certification, evaluators participated in monthly conference calls to review interviews. Each evaluator was required during their second and third year in the project to reliably rate a patient interview provided by the coordinating center. On these re-certification interviews, ($n = 24$), there was complete agreement between evaluators and coordinating center raters on diagnosis of MDD “since the last interview” ($k = 1.00$), 96% agreement on “current” MDD ($k = .92$); and 91% of evaluator ratings for each time frame exceeded the 80% agreement level on DSM-IV diagnostic criteria sets. For AUD, there was complete agreement for the diagnosis both “since the last interview” and “current episode” ($k = 1.00$). On the DSM-IV criteria sets, 92% of ratings for “since last interview” and 90% for “current episode” exceeded 80% agreement. For SUD, there was 92% agreement on the diagnosis at each time frame ($k = .82$). For each time frame, 83% of evaluator ratings exceeded the 80% agreement level on the DSM-IV criteria sets.

TADS Baseline Measures

For purposes of sample description or as potential predictors of subsequent AUD or SUD, the following variables were assessed at TADS baseline:

Age, Race/Ethnicity, Gender, Family Income, and Referral Source—Age in years, gender, and race/ethnicity (Caucasian, African American, Latino, Asian, or other) were reported by participants at TADS study entry. Race/ethnicity was dichotomized as majority (Non-Latino White) or minority because of limited sample sizes. Parents reported annual family income and whether they had been referred from a clinic or were responding to a study advertisement.

Duration of Index Major Depressive Episode—An independent evaluator completed a KSADS-P/L interview and estimated the date of onset and duration in weeks of the index episode of MDD at the point of entry into TADS.

Children's Depression Rating Scale-Revised (CDRS-R)—The CDRS-R is a 17-item symptom interview completed by the independent evaluator with reference to the past week, which yields an overall severity score. It has high internal consistency ($\alpha = .85$) and test-retest (Poznanski & Mokros, 1996), and inter-rater reliability ($ICC = .95$; TADS Team, 2004).

Reynolds Adolescent Depression Scale (RADS)—Adolescents completed the RADS, a 30-item scale pertaining to the past week, to assess self-reported depression severity. The RADS has high internal consistency ($\alpha = .92$) and test-retest reliability ($r = .80$) (Reynolds, 1987a).

Suicidal Ideation Questionnaire-Jr. High Version (SIQ-Jr)—The 15-item SIQ-Jr was completed by adolescents to assess severity of suicidal ideation. The SIQ-Jr has high internal consistency ($\alpha = .91$) and test-retest reliability ($r = .89$) (Reynolds, 1987b).

Children's Global Assessment Scale (CGAS)—The independent evaluator assigned a rating of general functioning for the past week on the 100-point Children's Global Assessment Scale. This scale has good reliability and validity (Shaffer et al., 1983).

Comorbidity—In addition to MDD, the K-SADS-P/L yielded baseline diagnoses of current dysthymia, any anxiety, disruptive behavior, alcohol or substance use, eating, or tic disorder, and total number of comorbid disorders. The disruptive behavior disorders included conduct disorder, oppositional defiant disorder and attention-deficit/hyperactivity disorder. The anxiety disorders included general anxiety disorder, separation anxiety disorder, social phobia, post-traumatic stress disorder, panic disorder, and agoraphobia.

Personal Experience Screening Questionnaire (PESQ)—Adolescents completed the PESQ, which includes a well standardized 18-item Problem Severity score that measures the extent to which the adolescent is psychologically and behaviorally involved with alcohol or other drugs. Scores range from 18 to 72. Internal consistency reliability (.90 to .95) and validity have been established with normal, delinquent, and substance abusing adolescents (Winters, 1991).

TADS Short-Term Depression Treatment Response

In the TADS project, positive short-term treatment response at Week 12 was defined as a rating by an independent evaluator of 1 (very much improved) or 2 (much improved) on the 7-point Clinical Global Impressions-Improvement scale (*CGI-I*; Guy, 1976). Non-response was defined as ratings of three (minimally improved) or higher. We compared TADS responders to non-responders using this definition.

To facilitate comparison with other depression treatment studies, we supplemented the above definition of short-term treatment response with a second, more stringent definition used in similar studies, e.g. the Treatment of Resistant Depression in Adolescents study (TORDIA; Brent et al., 2008). This second definition of response required both a CGI-I of 1 or 2 and a 50% reduction in CDRS-R raw score. We designated those adolescents who met this definition as symptom count responders (SCR).

Course of MDD

MDD Recovery, Recurrence, and Persistence—Recovery from the index episode of MDD was defined as absence of any MDD symptoms for a period of at least eight weeks. Recurrence of MDD was defined as a new episode following recovery. Chronic or persistent MDD was defined as an index episode from which the adolescent never recovered over the entire TADS-SOFTAD period.

Frequency of Alcohol or Marijuana Use

To determine whether participants with diagnoses of AUD or SUD during SOFTAD were using alcohol or drugs more frequently than other participants, all participants completed 7-point frequency ratings at each SOFTAD assessment point. Each rating indicated frequency of use of alcohol, marijuana, or hard drugs over the past month, with the following intervals: none; one to two times; three to five times; six to nine times; 10–19 times; 20–39 times; or over 40 times.

Statistical Analysis

Non-directional hypotheses were tested and the level of significance was set a 0.05 for each two-tailed test. Due to the exploratory nature of the study, the alpha was not adjusted for multiple tests.

First, we compared the demographic and clinical characteristics of the TADS participants who were included in the present study ($N=192$) to those who were not ($N=247$) using General Linear Models (GLM) for continuous measures and Chi-Square tests for binary outcomes. Alternatively, a Wilcoxon Two-Sample Test or Fisher's Exact Test was used when the assumptions of the corresponding parametric test were not met.

As a check on the validity of AUD and SUD diagnoses, we compared participants with AUD to those without AUD on maximum reported frequency of past month alcohol use, using a non-parametric median test. Similarly, we compared SUD to non-SUD participants on highest reported past month frequency of their drug of abuse (cannabis or hard drugs).

The primary outcomes were rates of AUD and SUD for the 192 participants in the present study. Potential predictors of AUD or SUD were grouped in two clusters: (1) short-term treatment response variables; and (2) pre-randomization baseline variables. Within the first cluster were the two definitions of treatment response, TADS response and symptom count response. Individual bivariate logistic regressions were conducted on each of these separately. In the second cluster, individual bivariate logistic regressions were conducted on each candidate predictor and measures that were significant at the 0.10 level were included in a subsequent multivariable logistic regression. We selected this inclusion criterion because it is sometimes possible for an explanatory variable that had a tendency to influence the outcome in bivariate models ($p < .10$) to become a statistically significant predictor of the outcome ($p < .05$) when evaluated in the multivariable context. Thus, we selected a liberal 0.10 significant level as inclusion criterion for multivariable model to avoid premature elimination of potentially significant predictors (Jaccard, Guilamo-Ramos, Johansson, & Bouris, 2006). Next, multivariable logistic regression analysis was conducted

and a stepwise variable selection approach was applied to derive the most parsimonious baseline variables prediction model. For the stepwise procedure, an entry criterion of 0.10 and retention criterion 0.05 was specified. The resulting multivariable model only included those variables that were significant at the 0.05 after taking into account the relative contribution of the other predictor variables. Each step of multivariable regression analysis was checked for multicollinearity and violation of model assumptions.

Following these analyses, each of the two Week 12 treatment response measures, if individually significant, was added in separate final multivariable models to evaluate the effects of acute treatment response after controlling for other (baseline) predictors in the model.

Secondary exploratory analyses were conducted to determine if assignment to, or response to, any of the four initial TADS treatments were predictive of subsequent AUD or SUD. We compared rates of subsequent AUD or SUD across the four treatment conditions using Chi Square. Exploratory logistic regression analyses were then conducted with potential predictors of AUD or SUD that included initial treatment assignment, treatment response, and the interactions of treatment assignment with response. Separate analyses were conducted using each of the two definitions of response.

Finally, logistic regression was employed to examine the association between MDD course (ordered as: 0=recovery with no recurrence; 1=recovery with one or more recurrences; 2 = persistent depression) and the development of AUD or SUD. Among those who experienced MDD recurrence following recovery, we then described the relation between timing of the recurrence and onset of the AUD or SUD.

Results

Preliminary Analyses

Comparing TADS subjects who did not participate in SOFTAD and the four SOFTAD participants excluded from the present study because of prior AUD or SUD, to the current study participants, we found that participants and non-participants did not differ on percentages randomized to the four TADS treatment conditions ($X^2(3, N = 439) = 1.70, p = 0.64$). The percent of current study participants who had been randomized to each short-term treatment condition was COMB=25%, FLX=24%, CBT= 28%, and PBO= 23%.

Table 1 includes comparisons of participants and non-participants on variables related to our hypotheses and on demographic and clinical variables at TADS baseline. There were no differences in percentage of TADS treatment responders (53.6% versus 51.0%, $X^2(1, N = 439) = 0.30, p = 0.58$), or percentages of symptom count responders (47% versus 44.5%, $X^2(1, N = 439) = 0.24, p = 0.62$). The only significant demographic differences were that study participants were somewhat younger than non-participants ($M = 14.3, SD = 1.5$ versus $M = 14.8, SD = 1.6, F(1, 437) = 9.22, p = .0025$) and included a smaller percentage of minority adolescents (21.4% versus 30.0%, $X^2(1, N = 439) = 4.14, p = .04$). The significant baseline clinical differences were that study participants were more likely than non-participants to have entered TADS during their initial episode of MDD (90.5% versus 82.5%; $X^2(1, N = 429) = 5.59, p = .02$) and had fewer total comorbid disorders (Median = 0 versus 1; $z = -2.51, p = .012$). Participants' involvement with alcohol or drugs at baseline was also significantly lower than that of non-participants (PESQ Problem Severity $M = 21.2, SD = 6.0$ versus $M = 23.0, SD = 7.7; F(1, 422) = 6.81, p = .009$).

Rates of Subsequent AUD and SUD

Of the 192 participants, 49 (25.5%) developed an AUD or SUD during the 60 months following short-term depression treatment. As shown in Table 2, 37 (19.3%) developed an AUD and 34 (17.7%) developed an SUD. These rates are not significantly different from each other (McNemar test $p = 0.70$). Twenty-two adolescents (11.5%) developed both disorders. The mean onset age of AUD was 18.0 years ($SD = 1.7$) and for SUD, 17.4 years ($SD = 1.7$). As indicated in Table 2, one-third of those with initial SUD-only went on to develop AUD as well, whereas none of those with initial AUD-only proceeded to also develop SUD during the follow-up period. Perhaps related to the slightly older age of onset of AUD compared to SUD in this sample, initial diagnoses of AUD were about equally likely to be made in K-SADS interviews with only the adolescent (20 of 37 or 54.0%) or with the adolescent and a parent (17 of 37 or 45.9%), whereas initial diagnoses of SUD were more likely to be made in K-SADS interviews with the adolescent and a parent (22 of 34 or 64.7%) than in interviews with the adolescent alone (12 of 34 or 35.3%). Those who developed AUD did not differ from those who did not, on their average month of initial SOFTAD assessment ($t(190) = 1.35, p = .178$). Similarly, those who developed SUD did not differ from those who did not, on this measure ($t(190) = 1.15, p = .251$).

Among the illicit drugs of abuse, marijuana was the most prevalent drug of abuse, accounting for 26 of the 34 SUD diagnoses. Cocaine, opiates, hallucinogens, other drugs or polydrug use accounted for the other diagnoses. As a verification of diagnoses, the median peak score for participants with an AUD on past month drinking frequency was 6–9 times versus a median of 1–2 times for those without AUD ($z = 4.64, p < .0001$). The median peak score for those with an SUD on past month drug use frequency was 10–19 times per month versus a median of no use for those without SUD ($z = 5.35, p < .0001$).

Treatment Response Analysis

Using logistic regression analysis, we tested whether response to short-term depression treatment reduced the probability of developing either AUD or SUD, using both the TADS response and the symptom count response measures. For AUD, the hypothesis was not confirmed using either definition of response. Among 103 TADS treatment responders, 18 (17.5%) developed AUD; among 89 non-responders, 19 (21.4%) developed AUD ($X^2(1, N = 192) = .46, OR = 1.28 [0.62–2.63], p = .498$). Among 90 symptom count responders, 17 (18.9%) developed AUD; among 102 non-symptom count responders, 20 (19.6%) developed AUD ($X^2(1, N = 192) = .02, OR = 1.05 [0.51–2.15], p = .899$).

We explored whether randomized treatment assignment, or response to a specific treatment reduced the probability of developing AUD. Across the four randomized treatment arms, rates of subsequent AUD were 20.8% (COMB), 14.9% (FLX), 20.8% (CBT), and 20.5% (PBO) ($X^2(3, N = 192) = 0.76, p = .86$). Neither this overall comparison, nor a post-hoc comparison of FLX (which had the lowest rate) to the other three treatments indicated significant differences between treatments in reducing the probability of developing AUD. For the comparison of FLX to other treatments, the percentages developing subsequent AUD were 14.9% and 20.7%, respectively ($X^2(1, N = 192) = 0.76, p = .384$). An exploratory logistic regression analysis including treatment assignment, treatment response and the interactions of treatment assignment and treatment response as predictors of AUD was not significant, regardless of whether the more global TADS measure of response, or the more restrictive symptom count response was used in the analysis. For the full model using the TADS response measure, $X^2(7, N = 192) = 2.92, p = .892$. With the symptom count response measure, $X^2(7, N = 192) = 3.065, p = .879$.

For SUD, the hypothesis was confirmed: response to MDD treatment reduced the probability of subsequent SUD. This finding occurred with both measures of response. Twelve of 103 TADS treatment responders (11.6%) developed an SUD versus 22 of 89 non-responders (24.7%) ($X^2(1, N = 192) = 5.38, OR = 2.49 [1.15-5.38], p = .02$). Nine of 90 symptom count responders (10%) versus 25 of 102 non-symptom count responders (24.5%) developed an SUD ($X^2(1, N = 192) = 6.52, OR = 2.92 [1.28-6.66], p = .011$).

Exploratory analyses showed no significant differences in rates of subsequent SUD across the four TADS treatment conditions, with SUD rates of 14.6% (COMB), 17.0% (FLX), 20.8% (CBT), and 18.2% (PBO) ($X^2(3, N = 192) = 0.68, p = .88$). Neither this overall comparison, nor a post-hoc comparison of COMB (which had the lowest rate) to the other three treatments indicated significant differences between treatments in reducing the probability of developing SUD. For the comparison of COMB to other treatments, the percentages developing subsequent SUD were 14.6% and 18.8.7%, respectively ($X^2(1, N = 192) = 0.43, p = .514$). When the four assigned treatments, treatment response, and the interactions between assigned treatments and response were entered into exploratory logistic regression analyses, the predictive models showed trends toward statistical significance, using either measure of response (with TADS response, $X^2(7, N = 192) = 12.11, p = .097$); with symptom count response, $X^2(7, N = 192) = 12.23, p = .093$). However, since neither model attained statistical significance, further analyses were not warranted.

Baseline Predictors Analysis

To evaluate the effects of MDD treatment on AUD and SUD in the context of possible significant baseline predictors, we next tested whether TADS baseline demographic and clinical variables predicted subsequent AUD or SUD. Because of skewed distributions, index episode duration, and number of comorbid disorders were natural log transformed. Results are depicted in Table 3.

For subsequent AUD, older age ($X^2(1, N = 192) = 8.81, OR = 1.49 [1.14-1.93], p = .003$) and higher alcohol or drug involvement ($X^2(1, N = 185) = 11.93, OR = 1.11 [1.05-1.18], p < .001$) were significant individual predictors. Those who developed AUD averaged 15.0 years of age at baseline ($SD = 1.4$ years), versus 14.1 years ($SD = 1.5$ years) for other participants. Adolescents who developed AUD had mean baseline PESQ scores of 24.8 ($SD = 8.2$), whereas those who did not averaged 20.3 ($SD = 4.9$).

There was a trend for males to have lower risk for subsequent AUD than females. Among 84 males, 11 (13.1%) developed AUD whereas 26 of 108 females (24.1%) did so ($X^2(1, N = 192) = 3.56, OR = 0.48 [0.22-1.03], p = .059$). There was also a trend for youths with longer episodes of MDD prior to TADS treatment to be more likely to develop later AUD ($X^2(1, N = 192) = 3.05, OR = 1.37 [0.96-1.95], p = .081$).

When baseline PESQ score, MDD episode duration, age, and gender were entered into a stepwise model, older age ($X^2(1, N = 185) = 5.13, OR = 1.37 [1.04-1.81], p = 0.024$) and higher PESQ score ($X^2(1, N = 185) = 9.16, OR = 1.10 [1.03-1.16], p = 0.002$) were retained as significant predictors of subsequent AUD. No further multivariable model was tested because MDD treatment response had not proven to be a significant predictor.

For subsequent SUD, significant individual baseline predictors included the total number of comorbid disorders ($X^2(1, N = 192) = 5.78, OR = 2.39 [1.17-4.85], p = .016$) and the PESQ Problem Severity score ($X^2(1, N = 185) = 7.13, OR = 1.08 [1.02-1.14], p = 0.008$). Depressed adolescents who later developed SUD had a mean of 1.1 comorbid disorders, ($SD = 1.3$), compared to a mean of 0.6 comorbid disorders ($SD = 0.9$) for those who did not.

They also had higher PESQ scores at baseline ($M = 24.1$, $SD = 8.4$) than other adolescents ($M = 20.6$, $SD = 5.2$).

When these two predictors were entered into a stepwise multivariable model, both were retained as significant predictors (PESQ, $X^2(1, N = 185) = 7.25$, $OR = 1.08$ [1.02–1.14], $p = .007$; number of comorbid disorders ($X^2(1, N = 185) = 4.17$, $OR = 2.23$ [1.03–4.79], $p = .04$).

We then tested whether poor treatment response predicted subsequent SUD when the two significant baseline predictors were included in overall models, using the two definitions of treatment response. Results indicated that it did. With TADS treatment response in the final model, all three predictors were significant (TADS treatment response, $X^2(1, N = 185) = 3.84$, OR [.999–5.28], $p = .050$; PESQ, $X^2(1, N = 185) = 6.48$, $OR = 1.07$ [1.02–1.14], $p = .011$; Number of comorbid disorders, $X^2(1, N = 185) = 4.12$, $OR = 2.23$ [1.03–4.86], $p = .042$). Similarly, with symptom count response in the model, all three predictors remained significant (Symptom count response, $X^2(1, N = 185) = 4.65$, $OR = 2.61$ [1.09–6.24], $p = .031$; PESQ, $X^2(1, N = 185) = 6.95$, $OR = 1.07$ [1.02–1.14], $p = .008$; Number of comorbid disorders, $X^2(1, N = 185) = 4.28$, $OR = 2.29$ [1.04–5.02], $p = .038$). Characteristics of adolescents who developed AUD, SUD or neither are described in Table 4.

MDD Course Analysis

The course of MDD for study participants through the end of SOFTAD was as follows: 98 (51.0%) recovered from their index episode with no recurrence; 87 (45.3%) recovered but had at least one recurrence; and 7 (3.7%) experienced chronic MDD. AUD was diagnosed in 10 of the 98 recovery cases (10.2%), in 25 of the 87 recovery and recurrence cases (28.7%), and in 2 of the 7 persistent depression cases (28.6%). Comparing the 98 recovery cases to the 94 cases with either chronic or recurrent MDD, a logistic regression indicated that depression recovery was negatively associated with onset of AUD ($X^2(1, N = 192) = 9.8$, $OR = 0.28$ [0.13–0.62], $p = 0.002$).

SUD was diagnosed in 13 of the 98 recovery cases (13.3%), in 19 of the 87 recovery and recurrence cases (21.8%), and in 2 of the 7 chronic depression cases (28.6%). Logistic regression indicated a trend for the depression recovery group to have fewer cases of SUD onset ($X^2(1, N = 192) = 2.77$, $OR = 0.53$ [0.24–1.14], $p = 0.103$).

Lastly, we explored the timing of MDD recurrence in relation to AUD or SUD onset. Among the 87 participants with recurrent MDD, 62 (71.3%) did not develop AUD, one (1.1%) had MDD recurrence before AUD onset, and 24 (27.6%) had MDD recurrence after AUD onset. In this latter group the onset of first MDD recurrence was, on average, 22.7 months ($SD = 11.8$) after the AUD onset. A similar pattern was observed for MDD recurrence and SUD: 68 participants with recurrent MDD (78.2%) did not develop SUD, two (2.3%) had MDD recurrence before SUD onset, and 17 (19.5%) had MDD recurrence after SUD onset. Onset of the first recurrence was, on average, 19 months ($SD = 9.9$) after SUD onset.

Discussion

We followed the largest sample to date of adolescents who had been treated for MDD, and restricted the focus of the present study to those with no pre-existing alcohol or substance use disorder, to determine whether effective MDD treatment reduced the likelihood of developing either AUD or SUD. Five years after the end of short-term depression treatment, a quarter of the sample (25.5%) had developed either AUD or SUD. Positive response to short-term depression treatment was not related to later onset of AUD, but lowered the likelihood of future SUD, even when baseline predictors of SUD were taken into account.

Significant baseline predictors of AUD were older age and greater involvement with alcohol or drugs at entry into treatment. Significant baseline predictors of SUD were comorbid disorders and greater involvement with alcohol or drugs at entry into treatment.

The prevalence of AOSUD in this sample of adolescents and young adults can be put in perspective by comparison with community or epidemiological studies. At the end of the follow-up period the mean age of our participants was 20.1 years (range = 17 to 23). The most recent National Survey on Drug Use and Health (NSDUH; SAMHSA, 2010) indicated that the age group of 18 to 25 had the highest rate of past year diagnoses of alcohol or substance use disorders (20.8%) among three broad age groups surveyed (12–17 year-olds had a rate of 7.6%; those 26 or older had a rate of 7.0%). Two other studies of younger adolescents yielded lifetime diagnoses for AOSUD that were lower than those in our sample (12.2% by age 16 and 10.8% by age 18; Costello et al., 2003; and Lewinsohn et al., 1993, respectively). The National Comorbidity Study replication (NCS-2; Kessler et al., 2005) did not include participants under age 18, but reported an AOSUD rate of 16.7% for those ages 18 to 29. Based on comparison with these studies, the rate of AOSUD in our sample of treated, formerly depressed adolescents (25.5%) is most similar to, but exceeds that of the NSDUH for 18 to 25-year-olds. Given methodological differences, and lacking a direct comparison with matched non-depressed adolescents, our study cannot conclusively state that the rate of AOSUD in formerly depressed adolescents is elevated, but the rate is high enough to warrant concern and further study. In addition, as discussed below, the overall AOSUD rate may have been even higher if all TADS adolescents had participated in the follow-up study. Finally, we did not follow a group of untreated depressed adolescents to determine whether the overall rate of subsequent AOSUD would have been even more elevated in the absence of treatment.

Also of note is the relative frequency of AUD (19.3%) and SUD (17.7%) in our sample. Most epidemiological studies indicate that AUD occurs at a higher frequency than SUD, whereas in our study the two rates were not significantly different. A New York study (Cohen et al., 1993) found alcohol abuse far more prevalent in the 17- to 20-year-old age group than marijuana abuse (14.6% versus 2.9%). AUD was also more prevalent than SUD among 18- to 29-year-olds in the NCS-2 (Kessler et al., 2005), and about 2.5 times more prevalent in the most recent NSDUH, affecting 7.3% of the US population ages 12 through adulthood compared to 2.8% for SUD. An exception to this pattern was an Oregon study (Lewinsohn et al., 1993) that found SUD somewhat more prevalent at age 18 than AUD (8.2% versus 6.2%), suggesting that although AUD is typically more prevalent than SUD, relative rates can be affected by geographic or temporal factors.

We found that SUD was predicted by comorbid psychopathology at baseline and by failure to respond to short-term depression treatment, whereas AUD was predicted by older age, a normal developmental factor, and not by depression treatment response. Considering these findings in the context of the relatively high prevalence rate of SUD in our sample, there may be a stronger link among depressed adolescents between adolescent psychopathology and subsequent SUD than there is for AUD. Reduction in overall psychopathology through successful depression treatment may have had more impact in preventing SUD than in preventing AUD because of such a link. By contrast, AUD tends to become elevated in the age range we studied, as alcohol use becomes more normative and part of social interactions. These possibilities are, of course, speculative, but they are consistent with an earlier cross sectional study of college students in which MDD was associated with both AUD and SUD, but only SUD was also associated with comorbid diagnoses (Deykin, Levy, & Wells, 1987).

Exploratory analyses indicated that no specific TADS MDD treatment proved more effective than others in reducing risk of subsequent AUD or SUD. This finding should not be interpreted to indicate that failure to actively treat adolescent MDD would be as effective as the TADS treatments in reducing risk for subsequent AUD or SUD. Three of the four TADS conditions involved an active treatment and the acute phase PBO condition included regular clinical contact, support and symptom reviews during the first 12 weeks, generally followed by open treatment after the blind was broken (Kennard et al., 2009). Moreover, both the present study and an earlier report on this sample indicate that attaining a full response to acute depression treatment is important. In the previous study (Curry et al., 2011), a positive short-term treatment response predicted greater likelihood of full recovery from MDD within two years, whereas the present study indicated that full response to treatment lowered the risk of subsequent SUD.

Our findings indicated that positive response to depression treatment, rather than engagement in a specific treatment, reduced risk of subsequent SUD. This is consistent with studies indicating that depressive symptoms are a risk factor for later substance abuse in older adolescents (e.g., Lewinsohn, Gotlib, & Seeley, 1995). The mechanisms through which effective depression treatment reduces risk for later SUD require further research, and may vary by treatment. It is possible that problem-solving and coping skills learned in the CBT and COMB conditions, which parallel effective components of substance abuse treatment (Waldron & Turner, 2008), contributed to this positive outcome. Similarly, improved mood regulation due to medication effects, or shared elements common to all four interventions (support, psychoeducation about depression), may have been effective mechanisms. Alternatively, because adolescent depression has a negative impact on peer, family, and academic functioning (Jaycox et al., 2009), it is possible that TADS treatment responders' improved functioning, which was accounted for by reduced depression (Vitiello et al., 2006), reduced their risk for subsequent involvement with substances.

We found a trend ($p = .059$) for females to have higher rates of AUD than males. This stands in contrast to the general finding that adult males have higher rates of AUD than adult females. However, the gender difference in prevalence of AUD begins to emerge only around age 18, and is less significant among adults who have both depression and AUD (Schulte, Ramo, & Brown, 2009). In our sample of formerly depressed adolescents, female gender was not a protective factor against development of AUD.

A more negative course of MDD after acute treatment was significantly associated with AUD onset in the present sample, with a comparable trend result for SUD. Recurrent or chronic MDD was linked to higher probability of an AUD. This finding is consistent with previously noted associations between more prolonged depression and alcohol or substance abuse (King et al., 1996) in adolescent girls. When participants in the present study developed both recurrent depression and AUD, the AUD most often occurred prior to the recurrent episode of MDD. The present findings suggest that AUD raised the risk of MDD recurrence, rather than recurrence increasing the probability of AUD.

Clinical Implications

The importance of attaining a full response to MDD treatment, regardless of type, is reinforced by the present findings. The significance of attaining a full response to short-term treatment in reducing risk for SUD was evident even when considering other significant risk factors for SUD. Thus, augmenting or changing partially effective MDD treatments after a relatively brief acute intervention period is recommended for achieving the secondary benefit of reduced SUD risk. For depressed adolescent non-responders to selective serotonin reuptake inhibitors, augmenting medication treatment with CBT significantly improved outcome (Brent et al., 2008). No parallel study has been completed to investigate the

augmenting effect of medication among non-responders to CBT, but clinical guidelines advocate augmenting or changing ineffective psychotherapy after a reasonable period of time (Hughes et al., 2007).

Depressed adolescents who later develop AUD or SUD are more likely than those who do not, to already be using alcohol or drugs at the time they enter depression treatment. Indeed, a single score indicative of such involvement predicted both AUD and SUD. When combined with older age, alcohol or drug involvement at entry into depression treatment predicted AUD, and when combined with comorbid disorders, it predicted SUD. Thus, it is important to assess all levels of alcohol and drug use before starting treatment for adolescent depression, to monitor depressed adolescents who are using alcohol or drugs, and to intervene quickly if AUD or SUD develops.

After recovery from adolescent MDD, alcohol use disorders significantly increased the likelihood of depression recurrence, with a similar trend for substance use disorders. Thus our findings are more consistent with a “drinking consequences” model, than with a “self-medication” model of the relation between negative mood and drinking (Hussong, Gould, & Hersh, 2008), at least among adolescents with a history of MDD. Adolescents who have experienced successful treatment for MDD and their parents should be advised of the risk for recurrence that is associated with significant alcohol misuse. Formerly depressed adolescents who then develop AUD or SUD should be monitored for a return of depressive symptoms, and offered interventions to reduce risk of a recurrent depressive episode.

Limitations

Although this is the largest sample of treated depressed adolescents with long-term follow-up data, power to detect a significant difference when testing the main hypothesis was limited. For example, with 103 responders and 89 non-responders on the TADS acute treatment response measure, power to detect a significant difference between the rates of subsequent SUD in these two groups (11.6% versus 24.7%, respectively) was only .64. Moreover, the number of participants who developed AUD or SUD was relatively small. Therefore, conclusions based on rates of AUD or SUD must be viewed with caution, pending replication.

Another significant study limitation is that the SOFTAD sample consisted of slightly under half of the initial TADS sample. Previous follow-up studies of treated depressed adolescents have retained higher rates of participants than did SOFTAD, ranging from 97% (Birmaher et al., 2000) to approximately 60% of originally randomized and treated adolescents (Clarke et al., 1999). However, these studies were conducted in one or two sites over two years, as compared to the present multi-site, five-year project, in which both retention of later TADS completers and re-contacting of early TADS completers were required. As has been reported by others (Cotter, Burke, Loeber, & Navratil, 2002; Badawi, Eaton, Myllyluoma, Weimer, & Gallo, 1999), our retention was more challenging with older adolescents and with minority participants. On most indices, the SOFTAD sample was representative of the full TADS sample, but our sample was somewhat younger, had fewer comorbid disorders, and less involvement with alcohol or drugs at TADS baseline than non-participants who had been in the TADS sample. All three of these factors were associated in our follow-up sample with lower likelihood of developing AUD or SUD. Therefore, it is very possible that the rates of these later disorders might have been higher if the entire TADS sample had participated in the extended follow-up.

Also, because the SOFTAD sample was derived entirely from the TADS sample, it was limited to adolescents who passed TADS exclusion criteria. No adolescents with bipolar disorder, severe (violent or assaultive) conduct disorder, pervasive developmental disorder

or thought disorder were included. The first two exclusions, in particular, may also have led to lower rates of subsequent AUD or SUD than might be found in a depressed adolescent outpatient sample not similarly restricted.

Our study is also limited by the lack of a non-depressed comparison group. Without such a direct comparison, we cannot be certain that the rates of AUD or SUD among formerly depressed adolescents exceed those of similar but non-depressed adolescents. Finally, for obvious ethical reasons we did not include a group of untreated adolescents with MDD. Therefore, we do not know the rates of subsequent AUD or SUD among depressed young people who are untreated.

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Table 1**TADS Baseline Characteristics of Current Study Participants and Non-Participants**

	Participants	Non-Participants	Statistic	<i>p</i>
Gender (% Female)	56.25	53.04	$\chi^2(1, N = 439) = 0.44$	.502
Age (yrs.), <i>M</i> (<i>SD</i>)	14.3 (1.5)	14.8 (1.6)	$F(1, 437) = 9.22$	.003
Race/ethnicity (% Minority)	21.35	29.96	$\chi^2(1, N = 439) = 4.14$	.042
Family Income (% High Income) ^a	23.12	27.15	$\chi^2(1, N = 394) = 0.83$	.362
Referral source (% from Clinic)	29.17	35.63	$\chi^2(1, N = 439) = 2.05$	.153
Duration of Index MDE (wks.), <i>Mdn</i>	38	40	$z = -1.03^b$	.306
First MDE (%)	90.48	82.50	$\chi^2(1, N = 429) = 5.59$	.018
CDRS-R, <i>M</i> (<i>SD</i>)	59.4 (10.3)	60.7 (10.5)	$F(1, 437) = 1.59$	.207
RADS, <i>M</i> (<i>SD</i>)	78.4 (15.4)	79.9 (13.5)	$F(1, 426) = 1.09$	.296
SIQ-Jr, <i>Mdn</i>	15.0	18.0	$z = -1.86^b$	.063
PESQ Problem Severity, <i>M</i> (<i>SD</i>)	21.2 (6.0)	23.0 (7.7)	$F(1, 422) = 6.81$	.009
CGAS, <i>M</i> (<i>SD</i>)	50.3 (7.8)	49.2 (7.2)	$F(1, 437) = 2.28$	.132
Comorbid Disorders, <i>Mdn</i>	0.0	1.0	$z = -2.51^b$	.012
Dysthymia(%)	7.33	12.96	$\chi^2(1, N = 438) = 3.62$	.057
Anxiety Disorder (%)	22.92	30.89	$\chi^2(1, N = 438) = 3.45$	.063
Disruptive Behavior Disorder (%)	21.35	25.10	$\chi^2(1, N = 439) = 0.84$	.358
Acute Treatment Responders (%)	53.65	51.01	$\chi^2(1, N = 439) = 0.30$	.584
Randomized to COMB (%)	25.00	23.89	$\chi^2(1, N = 439) = 0.07$	.788

Note. N ranges from 185 to 192 (Participants) and from 240 to 247 (Non-Participants). TADS = Treatment for Adolescents with Depression Study; MDE = Major Depressive Episode; CDRS-R = Children's Depression Rating Scale-Revised; RADS = Reynolds Adolescent Depression Scale; SIQ-Jr. = Suicide Ideation Questionnaire-Junior High Version; PESQ = Personal Experience Screening Questionnaire; CGAS = Children's Global Assessment Scale; COMB = Combination treatment with fluoxetine and cognitive behavior therapy.

^aHigh Income = or >\$75,000 per year.

^bWilcoxon Two Sample Test.

Table 2
Onset of AUD and/or SUD in 192 Adolescents Over Five Years Following Treatment for MDD

First Diagnosis	Cumulative Diagnoses		Cumulative Summary	
	<i>n</i>		<i>n</i>	<i>n</i> %
AUD only	15	AUD only	15	AUD only 15 7.8
AA	10	AA	10	
AD	5	AA	5	
SUD only	18	SUD only	12	SUD Only 12 6.2
SA	10	SA	3	
SD	8	SD	9	
AUD & SUD	16	AUD & SUD	22	AUD & SUD 22 11.4
AA & SA	8	AA & SA	9	
AA & SD	5	AA & SD	6	
AD & SA	0	AD & SA	0	
AD & SD	3	AD & SD	7	
		Any AUD		37 19.3
		Any SUD		34 17.7
		AUD or SUD		49 25.5

Note. AUD = Alcohol Use Disorder; SUD = Substance Use Disorder; MDD = Major Depressive Disorder; AA = Alcohol Abuse; AD = Alcohol Dependence; SA = Substance Abuse; SD = Substance Dependence;

Individual Logistic Regression Analyses: TADS Baseline Predictors of Subsequent Alcohol or Substance Use Disorder

Table 3

Predictor	Alcohol Use Disorder		Substance Use Disorder	
	Wald χ^2	OR	95% CI	OR
Age	8.81***	1.49	1.14–1.93	2.54
Gender	3.56 ⁺	0.48	0.22–1.03	0.65
Race/Ethnicity (majority/minority)	0.16	1.20	0.49–2.98	1.07
CDRS-R Depression Severity	1.19	1.02	0.98–1.05	0.17
Duration of Index MDE	3.05 ⁺	1.37	0.96–1.95	0.36
CGAS Global Functioning	0.00	1.00	0.96–1.05	1.37
Number of Comorbid Disorders	0.73	1.36	0.67–2.73	5.78*
Anxiety Disorder	0.59	0.72	0.30–1.68	1.15
Disruptive Behavior Disorder	1.63	1.94	0.70–5.34	1.58
PESQ Problem Severity	11.93***	1.11	1.05–1.18	7.13***

Note. $N = 192$. TADS = Treatment for Adolescents with Depression Study; CDRS-R = Children's Depression Rating Scale-Revised; MDE = Major Depressive Episode; CGAS = Children's Global Assessment Scale; PESQ = Personal Experiences Screening Questionnaire (for PESQ, $N = 185$).

⁺ $p < .10$.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Table 4

Characteristics of Adolescents Who Developed AUD, SUD, or Neither, Following Treatment for MDD

	AUD	SUD	No AUD or SUD
	<i>n</i> = 37	<i>n</i> = 34	<i>n</i> = 143
Gender (% Female)	70.3	50.0	55.9
Age, MDD onset, <i>M</i> (<i>SD</i>)	13.1 (1.9)	13.1 (1.9)	13.1 (2.0)
Duration of Index MDE (wks.)			
<i>Mdn</i>	55.0	23.0	36.0
CDRS-R, <i>M</i> (<i>SD</i>)	61.1 (10.8)	58.7 (10.6)	59.3 (10.0)
PESQ, <i>M</i> (<i>SD</i>)	24.8 (8.2)	24.1 (8.4)	20.4 (5.0)
Comorbid Disorders <i>M</i> , (<i>SD</i>)	0.8 (1.1)	1.1 (1.3)	0.6 (0.9)
Treatment Responder (%)	48.6	35.3	56.6
Symptom Count Responder (%)	45.9	26.5	50.4
Persistent/ Recurrent MDD (%)	72.9	61.8	42.0
Age, first AUD or SUD onset, <i>M</i> (<i>SD</i>)	18.0 (1.8)	17.4 (1.7)	

Note. AUD and SUD subgroups are not mutually exclusive, since 22 adolescents developed both disorders. AUD = Alcohol Use Disorder; SUD = Substance Use Disorder; MDD = Major Depressive Disorder; AUD only = AUD without SUD; SUD only = SUD without AUD; Any AUD = AUD with or without SUD; Any SUD = SUD with or without AUD; MDE = Major Depressive Episode; CDRS-R = Children's Depression Rating Scale-Revised; PESQ = Personal Experience Screening Questionnaire.