Does Comorbid Depression Predict Subsequent Adverse Life Events in Youth with Attention-Deficit/Hyperactivity Disorders?

W. Burleson Daviss, M.D.,¹ and Rasim Diler, M.D.²

Abstract

Objectives: Studies have primarily focused on adverse life events (ALEs) as potential causes rather than as outcomes of pediatric depression. The current study prospectively examines ALEs in a sample of youth with attention-deficit/hyperactivity disorders (ADHD) to determine whether having a major depressive disorder (MDD) at baseline (T1) predicts counts of child-dependent or child-independent ALEs at a second assessment (T2) ~8 months later.

Methods: Subjects with ADHD 11–18 years old were drawn mostly from a tertiary mental health clinic and evaluated with semi-structured diagnostic interviews, and parent and teacher questionnaires of ADHD severity. Eighteen with and 61 without initial MDD at T1 were compared at T2 regarding counts of subsequent overall, child-dependent, and child-independent ALEs reported on life events questionnaires by the child or parent.

Results: The group initially with MDD had higher overall ALEs ($p=0.01$) and child-dependent ALEs ($p\leq 0.001$) but not child-independent ALEs ($p=0.12$) at T2 relative to the nondepressed group, although only 3 of 18 continued to meet full criteria for MDD. The group initially with MDD also had a higher baseline ADHD severity ($p=0.04$) and proportion of oppositional or conduct disorders ($p=0.004$). In multivariate analyses, the group initially having MDD had a higher adjusted mean at T2 of child-dependent ALEs ($p=0.02$), but not of overall ALEs ($p=0.06$), after controlling for other T1 variables, including ALEs of the same type, ADHD severity, externalizing disorders, and the interaction of externalizing disorders with MDD.

Conclusions: These findings suggest that child-dependent ALEs are potentially an important outcome after youth with ADHD have an episode of MDD. Youth with ADHD who develop comorbid MDD should be closely monitored and offered interventions to address the potential burden of child-dependent ALEs lingering after a depressive episode.

Introduction

PEDIATRIC DEPRESSION is associated with devastating long-term morbidity and an increased risk of suicide, and its prevalence rises dramatically from childhood to adolescence (Birmaher et al. 1996). Adverse life events (ALEs) have long been considered an important cause of pediatric depression, and multiple prospective studies have reported that ALEs predict subsequent pediatric depressive episodes or symptoms (Garrison et al. 1990; Reinherz et al. 1993; Pine et al. 2002; Sund and Wichstrom 2002; Patton et al. 2003; Franko et al. 2004; Luby et al. 2006; Natsuaki et al. 2007). Such ALEs may also influence the long-term course of depression, as other studies have reported that levels of ALEs prolong depressive episodes in adolescents (Goodyer et al. 1997) and reduce the likelihood of remission in adults with depression (McQuaid et al. 2000).

Investigators have also suggested that certain, so-called *child-dependent* ALEs likely stem from youth behaviors (e.g., arguments

with parents, dissolution of a friendship or romantic relationship, failing in school), while other, so-called *child-independent* ALEs are likely independent of youth's behavior or control (e.g., parent in prison, parental divorce, financial hardships in family, and death of a relative) (Williamson et al. 1995; Rice et al. 2003; Williamson et al. 2005; Harkness et al. 2006). Cross-sectional studies comparing depressed youth with normal controls have linked pediatric depression to both child-dependent ALEs (Williamson et al. 1995) and child-independent ALEs (Williamson et al. 2005). Longitudinal studies are necessary, however, to determine the causal relationships between ALEs and depression.

Two longitudinal studies in community samples have suggested that pediatric depression and ALEs have bidirectional relationships. Rohde et al. (1994) reported that adolescents who had experienced and recovered from a single depressive episode had a higher number of newly reported major ALEs 12 months later, relative to youth who had never been depressed, and concluded that such ALEs may be a residual, "psychosocial scar" of this first

¹Department of Psychiatry, Dartmouth Hitchcock Medical Center, Dartmouth Medical School, Lebanon, New Hampshire.

²Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania.

depressive episode. Patton and colleagues likewise found that depressive disorders predicted subsequent reports of ALEs 24 months later (2003). If certain ALEs are truly behaviorally dependent and an outcome of a depressive episode, then one would expect those child-dependent events to be more elevated after a depressive episode, in contrast to child-independent life events. However, neither the study just mentioned nor any longitudinal study has examined subgroups of ALEs classified by whether they were dependent on youth behaviors as potential outcomes of pediatric depression. Moreover, findings from such community samples may not extend to clinical populations where youth would likely have more psychopathology, morbidity, and life adversities.

The association of ALEs with attention-deficit/hyperactivity disorder (ADHD) has been less widely studied than with depression. Some cross-sectional studies have found a significant link between a diagnosis of ADHD and levels of ALEs or of general environmental adversities (Biederman et al. 1995; Tillman et al. 2003; Rydell 2010). Another study reported that more individual types of ALEs were associated with conduct, oppositional defiant, and depressive disorders than with ADHD (Tiet et al. 2001). This study's findings suggest the need to control for the effects of other comorbidity when assessing the relationship between a particular psychiatric diagnosis and ALEs. Only two studies have examined the associations of ADHD diagnosis or ADHD severity with ALEs, taking into consideration whether such events were likely dependent on the child's behaviors (Tillman et al. 2003; Daviss et al. 2009). The earlier study found that youth with ADHD had significantly more total, child-dependent, and child-independent ALEs than healthy controls, adjusting for age, gender, and pubertal status (Tillman et al. 2003). The second, which was exclusively in a sample of youth with ADHD, reported that there were significant univariate correlations between lifetime depression and both child-dependent and child-independent ALEs, but only child-independent ALEs remained a significant correlate of lifetime depression after controlling for the effects of ADHD severity, comorbid externalizing disorders, age, and female gender (Daviss et al. 2009). Two longitudinal studies have examined environmental adversities as predictors of the subsequent course of ADHD (Biederman et al. 1996; Kessler et al. 2005), but only the earlier study suggested that ALEs contribute to the persistence of ADHD diagnosis.

The association of depression and ALEs is clinically relevant for youth with ADHD in particular, not only because most studies just cited suggest that ALEs are increased in youth with ADHD, but also because youth with ADHD have approximately a 5.5-fold increased risk of depression, even in community samples (Angold et al. 1999). Higher ALEs in youth with ADHD may be due to the ADHD itself or to other psychiatric disorders often associated with it (Pliszka 1998). Comorbid depression, in particular, appears to confer a high level of added impairment and significantly worsens long-term course in youth with ADHD (Rohde et al. 1991; Biederman et al. 2008; Daviss 2008; Daviss et al. 2009). Perhaps ALEs in such youth with ADHD contribute to the risk of depression or prolong its course.

The current study is the first to prospectively examine child-dependent and child-independent ALEs as potential outcomes of major depressive disorder (MDD) in any pediatric sample. The sample is a group of youth with ADHD who were assessed at two time points (T1 and T2) separated by 8 months regarding depressive and other comorbid diagnoses, as well as ADHD severity, and ALEs. Cross-sectional findings regarding correlates of lifetime depression at T1 have previously been reported (Daviss et al. 2009). Other potential covariates of ALEs at T2 were included in the

current study's final multivariate analyses, such as baseline ALEs, ADHD severity, and comorbid externalizing disorders. We hypothesized that youth who initially had comorbid MDD would have higher child-dependent but not child-independent ALEs 8 months later. If true, this would suggest that ALEs, especially those dependent on child behaviors, are an important outcome of MDD that could potentially be monitored or targeted with interventions.

Methods

Participants

Participants were 11–18 years old, and completed baseline T1 and subsequent T2 assessments ~8 months later. All met the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000) criteria for a diagnosis of ADHD regarding their numbers of symptoms and levels of impairment in multiple settings. ADHD symptoms were assessed primarily by parental reports on interviews and questionnaires, supplemented by teacher reports on questionnaires, and research clinicians' observations of the child's behavior in the interview. A few participants were included who had slightly delayed onsets of ADHD that occurred between 7 and 9 years of age, based on growing empirical support for a broader age-of-onset criterion to diagnose ADHD (Barkley and Biederman 1997). Youth with mental retardation or pervasive developmental disorders were excluded. Since the main objective of the study was to examine ALEs as a potential outcome of having depression at baseline, we excluded three youth who were not depressed at T1 but developed MDD before their T2 assessments, similar to the design used by the first longitudinal study to suggest a link between MDD and subsequent ALEs (Rohde et al. 1994). Participants were recruited from an outpatient mental health clinic and research center, community referrals, and advertisements in a medical center employee newspaper. All potential subjects were offered two detailed psychiatric assessments and participant fees for their time and inconvenience. They were informed of the risks and benefits of the study and that data collected would eventually be disseminated in a manner that preserved their anonymity. Youth and parents wishing to participate then signed a consent form approved by our institutional review board to indicate their assent and consent to participate, respectively. All participants were allowed and encouraged to pursue treatment as usual while participating in the study.

Demographic measures used to characterize the sample included self-reports of *race*, which were dichotomized into white or non-white race. In addition, families' *socio-economic status* was estimated based on parent-reported information about their jobs and highest levels of education, using the Hollingshead 4-factor index (Hollingshead 1975). This measure yields a 5-point rating of socioeconomic status, ranging from 1 (highest) to 5 (lowest status).

Among 110 consecutive youth who completed initial study interviews at T1, six were excluded, because they either reported onset of ADHD symptoms beyond 9 years of age ($n=5$) or did not meet full symptom criteria for any subtype of ADHD ($n=1$). Demographic and clinic data of the 104 who remained have been previously reported (Daviss et al. 2009). Among these, no one was lost to follow up, but 22 withdrew from the study before having a T2 assessment. Another three, initially in the nondepressed group, developed an MDD episode between T1 and T2, and were also excluded from the final analysis. Relative to 22 youth who withdrew before having their T2 assessments, the final sample of 79 subjects was less likely to have an externalizing disorder (either a conduct or oppositional defiant disorder) ($p=0.05$) and had less

severe ADHD symptoms at baseline ($p=0.004$) based on a composite measure of ADHD severity described below. There were no other significant differences between youth in the final sample and youth who withdrew early regarding T1 variables related to demographics, clinical severity, depressive and other diagnoses, and counts of ALEs.

Diagnostic and other procedures

All participants and their parents underwent separate, semi-structured interviews at both T1 and T2 using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present and Lifetime Version (K-SADS-PL) (Kaufman et al. 1997). These interviews were conducted by one of four masters- or doctorate-level research clinicians, each with at least 3 years of clinical experience doing mental health assessments, under the supervision of the first author. Interviewers went through extensive training to validly administer the K-SADS-PL, including reviewing and re-rating at least three other trained interviewers' taped or live interviews, then having other trained interviewers review and re-rate their taped or live interviews. Using all available information, primary interviewers made a best estimate of adolescents' current and previous diagnoses, using guidelines recommended for ADHD, depression, and other pediatric diagnoses (Leckman et al. 1982). Consistent with others' recommendations, greater weight was typically given to child reports of internalizing symptoms, and to parent and teacher reports of ADHD and other externalizing symptoms (Happonen et al. 2002). All assessments were supervised and reviewed by the first author, a board-certified child and adolescent research psychiatrist. As previously reported, inter-rater reliabilities were acceptable for all key diagnoses examined in the current study (Daviss et al. 2009). Participants in the final sample were classified into subgroups by whether at T1 they had comorbid MDD, an externalizing disorder, or an anxiety disorder (which included a generalized anxiety, separation anxiety, obsessive compulsive, posttraumatic stress, acute stress, or social phobia disorder).

The study interviewers also rated each participant's current depressive symptoms at T1 and T2, combining data from separate child and parent interviews with the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski et al. 1985). The CDRS-R is a 17-item, clinician-rated measure and yields continuous scores of youth's depressive symptomatology. Based on conventional standards for the CDRS-R, scores <28 at T2 were used to define patients whose depressive disorders had achieved full remission, while scores >40 were considered clinically significant levels of depressive symptomatology. As previously reported, each interviewer was extensively trained regarding the proper administration of the CDRS-R, and this measure had high internal consistency ($\alpha=0.90$) and a reasonable retest reliability (ICC [interclass correlation coefficient] = 0.60) considering the 8 month time span between assessments (Daviss et al. 2007, 2009).

ALEs

Each child and a parent completed parallel versions of the 46-item Life Events Checklist (LEC) (Brand and Johnson 1882) at both T1 and T2. The LEC screens for 46 specific events within the past 12 months, and asks respondents to categorize each event experienced as being either "good" or "bad." Regarding the LEC completed at T2, respondents in the current study were asked to record events that had occurred since the T1 assessment, which was typically ~ 8 months earlier. While the LEC does not provide a

precise determination of when specific events have occurred, it is less burdensome for participants and parents and has performed well relative to an interview-based measure of ALEs in discriminating patients with and without a current depressive episode (Duggal et al. 2000). The investigators in the current study independently classified each of the 46 events on the LEC by whether it was more likely to be dependent or independent of the child's behavior, with 100% agreement regarding these classifications. A total of 27 events were classified by the investigators as child dependent (e.g., arguments with parents or teachers, suspension from school, trouble with peers, and failing a grade), and 19 other events were classified as child independent (e.g., parental separation or divorce, parental absence or incarceration, and death of a friend or relative).

Parent and child reports of ALEs are often discrepant, and while youth tend to report more events than their parents, they also may have more difficulty in recalling how long ago such events occurred (Johnston et al. 2003). For these reasons, a combination of child and parent ratings was thought to be better for the current study. As expected, levels of parent-child agreement at T1 were in the moderate range regarding total, child-dependent, and child-independent ALEs (Pearson correlation coefficients of 0.51, 0.57, and 0.40, respectively) (Daviss et al. 2009). While differences across child and parent informants were far from significant (all p -values >0.10), youth in the overall sample generally reported more ALEs at T2 than their parents, with slight differences noted for overall ALEs (3.5 vs. 3.3) and child-independent ALEs (1.5 vs. 1.3) but not child-dependent ALEs (2.0 vs. 2.0). These differences were more pronounced but still never reached significance within the subgroup with MDD (overall ALEs: 6.4 vs. 4.4; child-dependent ALEs: 3.9 vs. 2.9; child-independent ALEs: 2.5 vs. 1.5). Based on all the information just given, we used counts of ALEs at T2 that were reported to have occurred and were considered "bad" by either the child or parent as the main study outcomes, which would help reduce any potential respondent biases. The same subtypes of ALEs at T1 were used as covariates in multivariate analyses predicting ALEs at T2, in order to control for baseline differences in ALEs between groups with and without MDD. Internal consistencies for total, child-dependent, and child-independent adverse events measured in this way were acceptable (alphas of 0.73, 0.68, and 0.64, respectively), as were retest reliabilities between T1 and T2 ratings 8 months later (ICCs of 0.64, 0.61, and 0.66).

Other potential predictors of ALEs at T2

In addition to diagnostic status at T1 and other demographic factors already mentioned, we examined *current ADHD symptom severity* at T1 as a potential predictor of subsequent ALEs. ADHD symptoms were rated by the parent, and at least one teacher if possible, using the 18-item ADHD Rating Scale (ARS) (DuPaul et al. 1998). Each item of the ARS is rated on a four point Likert scale (0 = never, to 3 = very often). Both parent and teacher versions of the ARS have well-established internal consistencies and retest reliabilities (DuPaul et al. 1998), and showed good psychometrics in the original sample of 104 ADHD youth from which the current sample was drawn (Daviss et al. 2009). For each subject, an average score was calculated of all available teacher ratings at T1, whenever more than one teacher ARS was collected. Separate standardized Z scores were determined for each subject's parent and teacher total scores on the ARS, relative to total scores of the whole sample, and a single composite score was determined for each subject by taking the mean of the parent and teacher standardized scores. This

method has been recommended by other investigators for combining potentially discrepant ratings of the same construct from different informants or measures (Piacentini et al. 1992). Composite scores for a given participant of -1, 0, or 1, respectively, represented levels of ADHD severity that were 1 standard deviation below, equal to, or 1 standard deviation above the average level of ADHD severity in the entire sample. In the four youth who were missing teacher ARSs, standardized parent scores alone were used instead of composite standardized scores. Similar composite measures of ADHD severity based on parent and teacher ratings were also determined for each subject at T2.

Statistical analysis

Analyses were completed using SPSS-PC version 17.0 (SPSS, Inc., Chicago, IL). Student's *t*-tests and Fisher's Exact tests were used for univariate group comparisons of quantitative and categorical variables, respectively, comparing the groups with and without MDD at T1. Pearson correlations were used to examine associations between other potentially predictive variables at T1 and ALE outcomes at T2. Factorial Analysis of Covariance (ANCOVA) was used to adjust the means of T2 ALEs in groups with and without baseline MDD, controlling for baseline reports of the same types of ALEs, as well as other demographic or clinical variables determined to be potential confounds, because they had univariate associations with both MDD at T1 and with ALEs at T2. As an exploratory study, all *p*-values ≤ 0.05 were considered significant.

Results

The final sample consisted of 18 youth diagnosed with MDD at T1 and another 61 youth who did not have MDD at T1 and did not develop it between T1 and T2.

Table 1 summarizes univariate comparisons of groups with and without MDD at T1 regarding baseline demographic, clinical, and ALEs variables. Numbers are reported as means $\pm$ standard deviations, unless noted otherwise. As expected, depressive severity based on T1 CDRS-R scores was significantly higher in the group

initially with MDD. Regarding other T1 variables, the proportion of externalizing disorders was significantly higher in the group initially with MDD, as was the level of ADHD severity, overall ALEs, child-dependent ALEs, and child-independent ALEs. There were no other significant group differences with regard to age, sex, race, ADHD subtype, or comorbid anxiety disorders.

Among the 18 subjects with MDD at T1, only 3 continued to meet full criteria for MDD at T2, and 6 had achieved full remission from their MDD. Even so, depressive symptoms on the CDRS-R at T2 remained significantly higher in the initially depressed group relative to the nondepressed group (34.7 ± 11.9 vs. 23.4 ± 5.8 , $p = 0.002$).

Regarding common types of ALEs reported at T2 in the overall sample, child-dependent events occurring in at least 10 youth included making failing grades ($n = 39$), increasing arguments with parents ($n = 27$), trouble with a teacher ($n = 26$), trouble with a sibling ($n = 24$), trouble with classmates ($n = 22$), suspension from school ($n = 19$), break-up with boy- or girlfriend ($n = 15$), and loss of a close friend ($n = 12$). Child-independent events occurring in at least 10 youth in the final sample included injury or illness of family member ($n = 25$), increasing arguments between parents ($n = 22$), death of a family member ($n = 18$), change in parents' financial status ($n = 18$), increasing parental absence ($n = 13$), and death of a close friend ($n = 10$).

Table 2 shows Pearson correlation coefficients of ALEs at T2 with other potential predictors at T1, apart from MDD. Significant correlations ($p < 0.05$) are shown in bold. T1 variables significantly associated with ALEs at T2 included depressive severity based on the CDRS-R, ADHD severity, externalizing disorders, and T1 ALEs of the same type. As expected, clinical predictors at T1 were more strongly correlated with overall ALEs and especially with child-dependent ALEs at T2 than with child-independent ALEs at T2. The only significant T1 correlates of subsequent child-independent ALEs at T2 were child-independent ALEs and initial depressive severity on the CDRS-R. Regarding other correlations not shown in Table 2, depressive severity at T2 based on CDRS-R scores correlated significantly ($p < 0.05$) with overall ALEs ($r = 0.30$) and child-dependent ALEs ($r = 0.33$), but not with child-

TABLE 1. BASELINE COMPARISON OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER YOUTH WITH AND WITHOUT MAJOR DEPRESSIVE DISORDER AT T1

	MDD (<i>n</i> = 18)	Non-MDD (<i>n</i> = 61)	<i>p</i>
Age in years	14.4 $\pm$ 1.5	13.6 $\pm$ 1.9	0.10
Female sex: <i>n</i> (%)	9 (50.0)	22 (36.1)	0.41
Nonwhite race: <i>n</i> (%)	1 (5.6)	16 (26.2)	0.10
Socioeconomic status	1.7 $\pm$ 1.0	2.0 $\pm$ 1.2	0.23
CDRS-R score	48.5 $\pm$ 12.3	27.2 $\pm$ 7.3	<0.001
ADHD, combined subtype	10 (55.6)	32 (52.5)	1.00
ADHD severity Z score	0.2 $\pm$ 0.8	-0.2 $\pm$ 0.8	0.04
Externalizing disorder: <i>n</i> (%)	12 (66.7)	16 (26.2)	0.004
Anxiety disorder: <i>n</i> (%)	6 (33.3)	9 (14.8)	0.09
T1 overall ALEs	9.2 $\pm$ 4.4	6.0 $\pm$ 3.9	0.004
T1 dependent ALEs	5.4 $\pm$ 2.7	3.4 $\pm$ 2.6	0.005
T1 independent ALEs	3.8 $\pm$ 2.6	2.5 $\pm$ 2.3	0.05

Numbers reported are means $\pm$ standard deviations, unless noted otherwise.

ADHD = attention-deficit/hyperactivity disorder; MDD = major depressive disorder; SES = socioeconomic status; CDRS-R = Children's Depression Rating Scale-Revised; ALEs = adverse life events; T1 = baseline evaluation.

TABLE 2. PEARSON CORRELATIONS (R) BETWEEN ADVERSE LIFE EVENTS AT T2 AND OTHER POTENTIAL PREDICTORS AT T1

	Overall ALEs at T2	Dependent ALEs at T2	Independent ALEs at T2
Age	0.19	0.19	0.13
Female gender	0.25	0.22	0.21
White race	0.06	0.01	0.11
SES factor	-0.06	-0.02	-0.08
CDRS-R score	0.47	0.40	0.40
ADHD, combined subtype	0.24	0.31	0.09
ADHD severity Z score	0.22	0.27	0.10
Current externalizing disorder	0.25	0.27	0.15
Current anxiety disorder	-0.04	-0.08	0.02
Overall ALEs at T1	0.46	0.44	0.35
Dependent ALEs at T1	0.38	0.49	0.14
Independent ALEs at T1	0.38	0.22	0.45

Correlations in bold had *p*-values < 0.05 .

T1 = baseline evaluation; T2 = second evaluation 8 months later.

ADHD = attention-deficit/hyperactivity disorder; ALEs = adverse life events; CDRS-R = Children's Depression Rating Scale-Revised; SES = socioeconomic status.

TABLE 3. COMPARING ADVERSE LIFE EVENTS AT T2 IN YOUTH WITH AND WITHOUT MAJOR DEPRESSIVE DISORDER AT T1

ALEs type	Mean $\pm$ SD		p	Adjusted mean (SE)		Test	p
	MDD	Non-MDD		MDD	Non-MDD		
Overall	8.4 $\pm$ 5.9	4.4 $\pm$ 3.4	0.01	7.0 (1.0)	4.8 (0.6)	F(1,73)=3.6	0.06
Dependent	5.1 $\pm$ 3.1	2.5 $\pm$ 2.2	<0.001	4.4 (0.6)	2.8 (0.3)	F(1,73)=5.8	0.02
Independent	3.3 $\pm$ 3.4	1.9 $\pm$ 2.0	0.12	2.9 (0.5)	2.1 (0.3)	F(1,76)=2.0	0.16

Adjusted means at T2 for Overall ALEs and Dependent ALEs controlled for T1 ALEs of the same types, ADHD severity, comorbid externalizing disorders, and MDD by externalizing disorder interactions. Adjusted means for Independent ALEs at T2 controlled for T1 ALEs of the same type.

MDD=major depressive disorder; SD=standard deviation; SE=standard error; T1=baseline evaluation; T2=second evaluation 8 months after baseline.

independent ALEs ($r=0.17$) at T2. Likewise, ADHD severity at T2, based on the composite measure of ADHD severity from both parent and teacher ratings, correlated significantly with overall ALEs ($r=0.29$) and child-dependent ALEs ($r=0.32$), but not with child-independent ALEs ($r=0.17$) at T2.

Table 3 summarizes comparisons between groups with and without baseline MDD regarding ALEs at T2. Univariate comparisons are summarized in the left-most columns. The group originally with MDD at T1 had a higher mean of overall ALEs ($p=0.01$) and of child-dependent ALEs ($p<0.001$), but not of child-independent ALEs ($p=0.12$) at T2. Regarding child-dependent events, the mean number of events in the nondepressed group fell 26% from 3.4 at T1 to 2.5 events at T2, while in the depressed group, it fell only 6% from 5.4 to 5.1 events.

Comparisons of adjusted means for the same T2 ALEs from final ANCOVA models are summarized in the right-most columns of Table 3. All final ANCOVA models included not only initial MDD, but also T1 events of the same type as covariates. ANCOVAs for overall and child-dependent ALEs also included comorbid externalizing disorders, and T1 ADHD severity, along with a term for a significant interaction observed between MDD and externalizing disorders in preliminary ANCOVA models when only these interactive terms were included. The group with MDD at T1 had a significantly higher adjusted mean level of child-dependent events at T2 relative to the group without MDD ($p=0.02$). The only other significant covariate in the final model for T2 child-dependent ALEs was child-dependent ALEs at T1 ($F(1,73)=10.4$, $p=0.002$). In the final ANCOVA to predict overall ALEs at T2, MDD was no longer a significant predictor ($p=0.06$), nor was any other covariate with the exception of T1 overall events ($F(1,73)=10.1$, $p=0.002$). In the final ANCOVA to predict independent ALEs at T2, MDD was again not a significant predictor ($p=0.16$), while child-independent ALEs at T1 was ($F(1,76)=15.9$, $p<0.001$).

Discussion

The current study examines the potential effect of having MDD at T1 on reported ALEs at T2 8 months later in a sample of youth with ADHD. Strengths of the study include its prospective design and use of validated diagnostic interviews by well-trained and experienced mental health clinicians along with composite measures from multiple informants to assess ALEs and ADHD severity. While episodes meeting full diagnostic criteria for MDD persisted at T2 in only 3 of the 18 subjects diagnosed with MDD at T1, this group continued at T2 to have higher overall ALEs ($p=0.01$) and child-dependent ALEs ($p\leq 0.001$), but not child-independent ALEs ($p=0.12$) relative to the nondepressed group. After controlling for other potential confounding variables at T1, including baseline ALEs, ADHD severity, and externalizing disorders, the

group with MDD at T1 had higher child-dependent events ($p=0.02$) at T2, but not overall events ($p=0.06$), or child-independent events ($p=0.16$). The current study's findings are consistent with those of two other longitudinal studies in community samples, both of which reported that pediatric depression increases youth's vulnerability to subsequent ALEs (Rohde et al. 1994; Patton et al. 2003). Our study extends their findings to a clinical sample, and is the first to prospectively suggest that the ALEs elevated after an episode of MDD are dependent on the child's behavior.

Other observations from the current study deserve comment. First, we observed significant associations between child-dependent ALEs and both ADHD severity and externalizing disorders in univariate analyses. Although these variables were not significant independent predictors of subsequent ALEs in multivariate analyses, such diagnoses commonly occur comorbidly with depression, even in community samples (Angold et al. 1999). As such, clinicians and investigators should still be mindful of the potential effects of ADHD and externalizing disorders on later ALEs. Second, the mean count of child-dependent ALEs showed little improvement over time in the depressed subjects, dropping only 6% from T1 to T2. Child-dependent ALEs remained high in the depressed group, despite a briefer period of 8 months at T2 relative to 12 months at T1 to observe recent ALEs, and the fact that only 3 of 18 in that group continued to meet full diagnostic criteria for MDD at T2. These findings suggest that behaviorally dependent ALEs may be a true "psychosocial scar" of depression with a significant longer-term adverse impact (Rohde et al. 1994). Although the relative effect of child-independent versus child-dependent ALEs on the course of depressive episodes has not been formally studied, one could speculate from other longitudinal studies that a greater level of certain ALEs after a depressive episode might prolong a current episode (Goodyer et al. 1997; McQuaid et al. 2000) or increase youth's vulnerability to subsequent episodes (Reinherz et al. 1993; Pine et al. 2002; Patton et al. 2003; Luby et al. 2006). The potential effects of child-dependent ALEs on long-term course will need to be examined in future longitudinal studies.

Other key questions remain regarding whether the current study's findings about the association of depression with subsequent ALEs would generalize first to youth with ADHD in community settings and second to youth without ADHD. Regarding the first question, we are re-assured by a large study, which concluded that clinical samples offer more conservative estimates of the associations between ADHD comorbidities and impairment-related outcomes than community samples (Bauermeister et al. 2007). Regarding the second question, we can only speculate on the applicability of our study's findings to youth without ADHD based on other studies, because our study lacked a nonADHD comparison group. *Post hoc* analyses of clinical trials involving pharmacological and/or psychosocial treatments in depressed youth have

reported contradictory findings about the effect of comorbid ADHD on depressive response, with two studies reporting an adverse effect (Birmaher et al. 2000; Rohde et al. 2001) and two others not reporting on it (Herman et al. 2007; Kratochvil et al. 2009). As recently reviewed, observational studies have provided more consistent evidence that comorbid ADHD worsens the long-term course of depression (Daviss 2008). For example, a naturalistic study of adolescent females reported that depressive episodes occurring comorbidly with ADHD have an earlier onset, longer duration, greater impairment, and greater risk of suicidality and hospitalization (Biederman et al. 2008). While we are encouraged by the fact that our prospective study's findings in a clinical sample with ADHD are consistent with those from two other studies in community samples (Rohde et al. 1994; Patton et al. 2003), our findings will need to be replicated in other samples without ADHD, from both community and clinical settings.

Findings from the current study should be considered cautiously in light of other study limitations. First, we relied on child and parent questionnaires rather than interviews to assess ALEs, which prevented us from precisely determining when the ALEs occurred. While at T2 we asked informants to report ALEs that had occurred since the T1 assessment, and we controlled for ALEs at T1 in multivariate analyses that predicted ALEs at T2, it is possible that some ALEs reported at T2 preceded the T1 assessment or any recent depressive episode. Second, a longer period of follow-up after the initial evaluation would have helped elucidate the temporal relationship between psychopathology and ALEs and whether child-dependent ALEs in the depressed group were a more persistent outcome. Third, almost 21% of participants withdrew before their T2 assessments could be completed, and these youth were more severely affected at T1 regarding ADHD severity and rates of comorbid externalizing disorders. This may have impacted the generalizability of our study's findings to other clinical samples. Fourth, there were relatively few youth with comorbid MDD in our sample. This limited our statistical power, but made the significant association between MDD at T1 and child-dependent ALEs at T2 in the multivariate analysis even more striking. Given these limitations, our results will need to be replicated in future studies that follow the ALEs of youth over longer periods of time after depressive episodes.

Conclusions and Clinical Significance

In summary, our study suggests that youth with ADHD who have comorbid MDD have higher child-dependent ALEs 8 months later, independent of their ADHD severity, other externalizing comorbidity, and levels of the same ALEs at baseline. Child-dependent ALEs such as failing grades, and strained relationships with family members, peers, and teachers were higher despite the fact that most in the originally depressed group no longer met diagnostic criteria for MDD at their 8 month follow-ups. Our findings suggest that ADHD youth who develop MDD should be closely monitored and offered interventions to address behaviorally dependent ALEs that linger after a depressive episode. Since such ALEs are child dependent, they may represent an important, modifiable risk factor for comorbid depression that could be targeted with individual and family psychotherapy or pharmacotherapy.

Disclosures

Dr. Daviss has served as a consultant for Ava Cat, Inc., Next Wave Pharmaceuticals, and Lexicor, Inc. He has also worked as an investigator for a study sponsored by Lexicor. Dr. Diler has no potential financial conflicts of interest to disclose.

Acknowledgments

Data for this research were gathered at the University of Pittsburgh's Center for Children and Families. This study was supported by a National Alliance for Research on Schizophrenia and Depression Young Investigator's Award (PI: Dr. Daviss) and two National Institute of Mental Health grants, including K23 MH 065375 (PI: Dr. Daviss) and P30 MH066371 (PI: Dr. David Brent). Findings from this analysis were previously presented in October, 2009 at the 56th Annual Meeting of the American Academy of Child and Adolescent Psychiatry in Honolulu, HI. The authors gratefully acknowledge the key roles of Diane Holland and Renee' Weinman, who helped coordinate the study, Aaron Jennings and Kim Dever, who served as research interviewers, and David Ravee, Giovanna Porta, Rebecca Munnell, Ellie Kanal, Travis Brewer, and Deena Battista, who helped with data entry and management.

References

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000.
- Angold A, Costello EJ, Erkanli A: Comorbidity. *J Child Psychol Psychiatry* 40:57-87, 1999.
- Barkley RA, Biederman J: Toward a broader definition of the age-onset criterion for attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 36:1204-1210, 1997.
- Bauermeister JJ, Shrout PE, Ramirez R, Bravo M, Alegria M, Martinez-Taboas A, Chavez L, Rubio-Stipec M, Garcia P, Ribera JC, Canino G: ADHD correlates, comorbidity, and impairment in community and treated samples of children and adolescents. *J Abnorm Child Psychol* 35:883-898, 2007.
- Biederman J, Ball SW, Monuteaux MC, Mick E, Spencer TJ, McCreary M, Cote M, Faraone SV: New insights into the comorbidity between ADHD and major depression in adolescent and young adult females. *J Am Acad Child Adolesc Psychiatry* 47:426-434, 2008.
- Biederman J, Faraone S, Milberger S, Curtis S, Chen L, Marrs A, Ouellette C, Moore P, Spencer T: Predictors of persistence and remission of ADHD into adolescence: Results from a four-year prospective follow-up study. *J Am Acad Child Adolesc Psychiatry* 35:343-351, 1996.
- Biederman J, Milberger S, Faraone SV, Kiely K, Guite J, Mick E, Ablon S, Warburton R, Reed E: Family-environment risk factors for attention-deficit hyperactivity disorder. A test of Rutter's indicators of adversity. *Arch Gen Psychiatry* 52:464-470, 1995.
- Birmaher B, McCafferty JP, Bellew KM, Beebe KL: Comorbid ADHD and Disruptive Behavior Disorders as Predictors of Response in Adolescents Treated for Major Depression. Chicago, IL: Annual Meeting of the American Psychiatric Association, 2000 (abstract).
- Birmaher B, Ryan ND, Williamson DE, Brent DA, Kaufman J, Dahl RE, Perel JM, Nelson B: Childhood and adolescent depression: A review of the past 10 years. Part I. *J Am Acad Child Adolesc Psychiatry* 35:1427-1439, 1996.
- Brand AH, Johnson JH: Note on the reliability of the Life Events Checklist. *Psychol Rep* 50:1274, 1982.
- Daviss WB: A review of co-morbid depression in pediatric ADHD: Etiology, phenomenology, and treatment. *J Child Adolesc Psychopharmacol* 18:565-571, 2008.
- Daviss WB, Diler RS, Birmaher B: Associations of lifetime depression with trauma exposure, other environmental adversities, and impairment in adolescents with ADHD. *J Abnorm Child Psychol* 37:857-871, 2009.
- Daviss WB, Nery FG, Olvera RL, Diler RS, Mezzomo KM, Soares JC: Exploratory Factor Analysis of the CDRS-R in Youths with

- ADHD. Boston, MA: Poster, 54th Annual Meeting of the American Academy of Child and Adolescent Psychiatry, 2007 (abstract).
- Duggal S, Malkoff-Schwartz S, Birmaher B, Anderson BP, Matty MK, Houck PR, Bailey-Orr M, Williamson DE, Frank E: Assessment of life stress in adolescents: Self-report versus interview methods. *J Am Acad Child Adolesc Psychiatry* 39:445–452, 2000.
- DuPaul GJ, Power TJ, Anastopoulos AD, Reid R: *ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretation*. New York, NY: Guilford Publications, 1998.
- Franco DL, Striegel-Moore RH, Brown KM, Barton BA, McMahon RP, Schreiber GB, Crawford PB, Daniels SR: Expanding our understanding of the relationship between negative life events and depressive symptoms in black and white adolescent girls. *Psychol Med* 34:1319–1330, 2004.
- Garrison CZ, Jackson KL, Marsteller F, McKeown R, Addy C: A longitudinal study of depressive symptomatology in young adolescents. *J Am Acad Child Adolesc Psychiatry* 29:581–585, 1990.
- Goodyer IM, Herbert J, Tamplin A, Secher SM, Pearson J: Short-term outcome of major depression: II. Life events, family dysfunction, and friendship difficulties as predictors of persistent disorder. *J Am Acad Child Adolesc Psychiatry* 36:474–480, 1997.
- Happonen M, Pulkkinen L, Kaprio J, Van der Meere J, Viken RJ, Rose RJ: The heritability of depressive symptoms: Multiple informants and multiple measures. *J Child Psychol Psychiatry* 43:471–479, 2002.
- Harkness KL, Bruce AE, Lumley MN: The role of childhood abuse and neglect in the sensitization to stressful life events in adolescent depression. *J Abnorm Psychol* 115:730–741, 2006.
- Herman KC, Ostrander R, Walkup JT, Silva SG, March JS: Empirically derived subtypes of adolescent depression: Latent profile analysis of co-occurring symptoms in the Treatment for Adolescents with Depression Study (TADS). *J Consult Clin Psychol* 75:716–728, 2007.
- Hollingshead AB: *Four Factor Index of Social Status*. New Haven, CT: Yale University Press, 1975.
- Johnston CA, Steele RG, Herrera EA, Phipps S: Parent and child reporting of negative life events: Discrepancy and agreement across pediatric samples. *J Pediatr Psychol* 28:579–588, 2003.
- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N: Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 36:980–988, 1997.
- Kessler RC, Adler LA, Barkley R, Biederman J, Conners CK, Faraone SV, Greenhill LL, Jaeger S, Secnik K, Spencer T, Ustun TB, Zaslavsky AM: Patterns and predictors of attention-deficit/hyperactivity disorder persistence into adulthood: Results from the national comorbidity survey replication. *Biol Psychiatry* 57:1442–1451, 2005.
- Kratochvil CJ, May DE, Silva SG, Madaan V, Puumala SE, Curry JF, Walkup J, Kepley H, Vitiello B, March JS: Treatment response in depressed adolescents with and without co-morbid attention-deficit/hyperactivity disorder in the Treatment for Adolescents with Depression Study. *J Child Adolesc Psychopharmacol* 19:519–527, 2009.
- Leckman JF, Sholomskas D, Thompson WD, Belanger A, Weissman MM: Best estimate of lifetime psychiatric diagnosis: A methodological study. *Arch Gen Psychiatry* 39:879–883, 1982.
- Luby JL, Belden AC, Spitznagel E: Risk factors for preschool depression: The mediating role of early stressful life events. *J Child Psychol Psychiatry* 47:1292–1298, 2006.
- McQuaid JR, Monroe SM, Roberts JE, Kupfer DJ, Frank E: A comparison of two life stress assessment approaches: Prospective prediction of treatment outcome in recurrent depression. *J Abnorm Psychol* 109:787–791, 2000.
- Natsuaki MN, Ge X, Brody GH, Simons RL, Gibbons FX, Cutrona CE: African American children's depressive symptoms: The prospective effects of neighborhood disorder, stressful life events, and parenting. *Am J Community Psychol* 39:163–176, 2007.
- Patton GC, Coffey C, Posterino M, Carlin JB, Bowes G: Life events and early onset depression: Cause or consequence? *Psychol Med* 33:1203–1210, 2003.
- Piacentini JC, Cohen P, Cohen J: Combining discrepant diagnostic information from multiple sources: Are complex algorithms better than simple ones? *J Abnorm Child Psychol* 20:51–63, 1992.
- Pine DS, Cohen P, Johnson JG, Brook JS: Adolescent life events as predictors of adult depression. *J Affect Disord* 68:49–57, 2002.
- Pliszka SR: Comorbidity of attention-deficit/hyperactivity disorder with psychiatric disorder: An overview. *J Clin Psychiatry* 59:50–58, 1998.
- Poznanski EO, Freeman LN, Mokros HB: Children's depression rating scale-revised. *Psychopharmacol Bull* 21:979–989, 1985.
- Reinherz HZ, Giaconia RM, Pakiz B, Silverman AB, Frost AK, Lefkowitz ES: Psychosocial risks for major depression in late adolescence: A longitudinal community study. *J Am Acad Child Adolesc Psychiatry* 32:1155–1163, 1993.
- Rice F, Harold GT, Thapar A: Negative life events as an account of age-related differences in the genetic aetiology of depression in childhood and adolescence. *J Child Psychol Psychiatry* 44:977–987, 2003.
- Rohde P, Clarke GN, Lewinsohn PM, Seeley JR, Kaufman NK: Impact of comorbidity on a cognitive-behavioral group treatment for adolescent depression. *J Am Acad Child Adolesc Psychiatry* 40:795–802, 2001.
- Rohde P, Lewinsohn PM, Seeley JR: Are adolescents changed by an episode of major depression? *J Am Acad Child Adolesc Psychiatry* 33:1289–1298, 1994.
- Rohde P, Lewinsohn PM, Seeley JR: Comorbidity of unipolar depression: II. Comorbidity with other mental disorders in adolescents and adults. *J Abnorm Psychol* 100:214–222, 1991.
- Rydell AM: Family factors and children's disruptive behaviour: An investigation of links between demographic characteristics, negative life events and symptoms of ODD and ADHD. *Soc Psychiatry Psychiatr Epidemiol* 45:233–244, 2010.
- Sund AM, Wichstrom L: Insecure attachment as a risk factor for future depressive symptoms in early adolescence. *J Am Acad Child Adolesc Psychiatry* 41:1478–1485, 2002.
- Tiet QQ, Bird HR, Hoven CW, Moore R, Wu P, Wicks J, Jensen PS, Goodman S, Cohen P: Relationship between specific adverse life events and psychiatric disorders. *J Abnorm Child Psychol* 29:153–164, 2001.
- Tillman R, Geller B, Nickelsburg MJ, Bolhofner K, Craney JL, DelBello MP, Wigh W: Life events in a prepubertal and early adolescent bipolar disorder phenotype compared to attention-deficit hyperactive and normal controls. *J Child Adolesc Psychopharmacol* 13:243–251, 2003.
- Williamson DE, Birmaher B, Anderson BP, al-Shabbout M, Ryan ND: Stressful life events in depressed adolescents: The role of dependent events during the depressive episode. *J Am Acad Child Adolesc Psychiatry* 34:591–598, 1995.
- Williamson DE, Birmaher B, Dahl RE, Ryan ND: Stressful life events in anxious and depressed children. *J Child Adolesc Psychopharmacol* 15:571–580, 2005.

Address correspondence to:
 W. Bursleson Daviss, M.D.
 Department of Psychiatry
 Dartmouth Hitchcock Medical Center
 1 Medical Center Drive
 Lebanon, NH 03756

E-mail: william.b.daviss@hitchcock.org