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Does Pharmacotherapy for Attention-Deficit/Hyperactivity Disorder Predict Risk of Later Major Depression?

W. Burleson Daviss, M.D.,[1] Boris Birmaher, M.D.,[2] Rasim S. Diler, M.D.,[2] and James Mintz, Ph.D.[1]

Abstract

Objective: This study's goal was to determine among youths with attention-deficit/hyperactivity disorder (ADHD) how the history of ADHD pharmacotherapy influenced the risk of developing major depressive disorder (MDD), compared to other commonly reported predictors.
Method: Diagnostic and treatment history data were analyzed retrospectively in 75 youths 11–18 years old with definite or probable ADHD, enrolled in an observational study at a tertiary mental health clinic. Subjects with histories of MDD (H/o MDD) (n = 36) were compared to others who had never been depressed (Never-Depressed) (n = 39) regarding histories of ADHD pharmacotherapy, psychopathology and other potential covariates of MDD risk.
Results: H/o MDD subjects reported longer delays before initiating ADHD pharmacotherapy, were more often female, reported having experienced more traumatic event types, and had higher rates of early anxiety and externalizing disorders. With all covariates allowed to enter a backward stepwise Cox regression of survival time till first episodes of MDD, only two variables remained in the model. The time-dependent variable, ADHD pharmacotherapy, prolonged survival times ($p = .012$), while having experienced more traumatic event types shortened them ($p = .001$).
Conclusions: This study provides preliminary evidence that pharmacotherapy for ADHD may have a protective effect in ADHD youths, reducing the risk of later MDD.

Introduction

Major depressive disorders (MDD) occur in roughly 2.5% of children and 8.3% of adolescents and are chronic, recurrent, and associated with high levels of impairment and suicide risk (Birmaher et al. 1996). Some risk factors for pediatric depression in general populations are increasing age, female sex, exposure to traumatic life events, and comorbid psychiatric disorders, including anxiety disorders and externalizing disorders such as oppositional defiant disorder or conduct disorders (Angold et al. 1999; Birmaher et al. 1996; Caspi et al. 2003; Chapman et al. 2004; Flament et al. 2001; Kendler et al. 2004; Widom et al. 2007). Youths with attention-deficit/hyperactivity disorder (ADHD) are at particular risk of developing MDD, with rates ranging from 10–40% (Pliszka 1998; Spencer et al. 1999), approximately 5 times higher than in the general population (Angold et al. 1999). Such depressive disorders tend to occur several years after the onset of ADHD, suggesting the possibility that earlier recognition and treatment of ADHD may affect the long-term risk of developing comorbid MDD (Waxmonsky 2003).

Stimulants are generally considered first-line treatment for ADHD, and are the most widely used psychotropic medication in the pediatric age range (Pliszka and AACAP-Work-Group-on-Quality-Issues 2007; Wilens and Spencer 2000). However, the effect of stimulant pharmacotherapy on the risk of eventually developing MDD in youths with ADHD is unclear. Animal studies have suggested that early stimulant exposure may increase the long-term risk of de-

[1]University of Texas Health Science Center at San Antonio, San Antonio, TX.
[2]Western Psychiatric Institute and Clinic, Pittsburgh, PA.
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pressive behaviors and stress intolerance in adulthood (Bolanos et al. 2003; Carlezon et al. 2003). One retrospective study found that stimulant treatment in children was associated with a younger age of onset of bipolar disorders, independent of ADHD severity (DelBello et al. 2001). In contrast, others have argued that earlier pharmacotherapy of ADHD may lessen the long-term risk of depressive disorders in ADHD youths, perhaps by reducing the psychosocial impairment associated with the primary ADHD (Waxmonsky 2003). A single prospective study found that MDD occurring in youths with ADHD remitted independently of ADHD severity (Biederman et al. 1998). This study, however, did not report whether there were differences in ADHD pharmacotherapy between those who remitted or did not remit from MDD. Clearly, the effect of earlier ADHD pharmacotherapy on long-term risk of depression in youths with ADHD remains an open question.

We report findings from a case-control study of youths with ADHD, ages 11–18, all participating in a longitudinal observational study of risk factors for depressive disorders. Two groups of adolescents with ADHD were categorized based on whether they had ever experienced episodes of MDD: youths with histories of major depressive episodes (H/o MDD), or youths with no history of MDD or even minor depressive episodes (Never-Depressed). These groups were compared regarding retrospective reports of previous pharmacological treatment of ADHD, and other potential predictors of depressive disorders.

Methods

Subjects

Subjects were recruited from an outpatient mental health clinic and research center, and from advertisements in a medical center newspaper. Subjects and their parents were offered a detailed explanation of the risks and benefits of study participation and signed IRB-approved forms indicating their assent/consent to participate. Potential subjects were offered two detailed psychiatric assessments over an 8-month period, as well as participant fees. All subjects were allowed to pursue treatment through their regular psychotherapist, psychiatrist, or primary care physician while in the study.

Subjects were 11–18 years old and had to at some point have met full DSM-IV (APA, 1994) symptom and impairment criteria for ADHD, and had to have sufficient language skills along with their parents to complete study interviews and questionnaires. Five subjects met full DSM-IV symptom criteria for ADHD except that their reported onset of ADHD symptoms was between 7 and 9 years of age. These were also included in the study and labeled as having "probable ADHD," based on previous arguments for broadened age of onset criteria in ADHD (Barkley and Biederman 1997). Subjects with mental retardation or pervasive developmental disorders were excluded. Also excluded were subjects who had experienced minor depressive disorders (dysthymic disorder, depressive disorder not otherwise specified) but not MDD. Finally, we excluded subjects who had experienced an episode of MDD before they had developed symptoms of ADHD, and those for whom dates of first ADHD pharmacotherapy were uncertain.

Current and lifetime diagnoses and clinical history

All subjects and their parents underwent semi-structured interviews using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL) (Kaufman et al. 1997). After separately interviewing both the child and the parent, interviewers made a "best estimate" of subjects' current and previous psychiatric diagnoses, based on all available information. Interview data were also used to determine ages of onset, durations, and numbers of episodes of previous diagnoses, lifetime histories of prior suicidal ideations and behaviors, and prior inpatient treatments and types of pharmacotherapy. All interviewers were masters- or doctorate-level research clinicians who had undergone extensive training to validly administer this interview. Assessments were supervised and personally reviewed by the lead author, a board-certified child and adolescent research psychiatrist.

Treatment history

Data about subjects' cumulative lifetime history of pharmacotherapy, and inpatient care were obtained from the initial treatment section of the KSADS-PL interview, with results verified by reviewing the outpatient and inpatient records of patients whenever such records were available. Parents were specifically asked about the age that their child first received pharmacotherapy for ADHD. For this analysis, stimulants, alpha agonists, atomoxetine, bupropion and tricyclic antidepressants were considered treatments for ADHD. Treatments with bupropion, tricyclic antidepressants or any other types of antidepressants were also classified as antidepressant treatments. Different formulations of the same medication (e.g. short- and long-acting methylphenidate or bupropion) were not counted as separate medication when tallying subjects' exposure to different medications.

Demographic, symptomatology, trauma exposure and impairment data

Socieconomic status. Parents were asked about their occupational status and educational level to estimate the socioeconomic status of the family, using the Hollingshead 4-factor index (Hollingshead 1975).

Current depressive symptomatology. To measure current depressive symptomatology, each child and parent completed respective versions of the Mood and Feelings Questionnaire (MFQ-C, MFQ-P) (Costello et al. 1991), recently revalidated as a screening measure in both clinical and nonclinical samples (Daviss et al. 2006). The MFQ-C and MFQ-P contain 33 or 34 depressive symptom items, respectively, rated on a Likert scale (0 = Not true, 1 = Sometimes, 2 = True) according to their presence over the last 2 weeks. The highest rating on item 19 of the MFQ-C and MFQ-P, regarding whether children had had recent thoughts of killing themselves, was used to screen for current suicidal ideations, and considered positive if endorsed at least "sometimes" by either rater. The interviewer also assessed each subject's current depressive symptoms, combining data from separate child and parent interviews with the Children's Depression Rating Scale (CDRS-R) (Poznanski et al. 1985), a 17-item clin-

ician-rated measure. Scores on the CDRS-R ≥40 are often used as an inclusion criterion for clinical trials of youths with MDD, while scores <28 in youths previously depressed suggest full remission from depression (Emslie et al. 2002).

Past and current ADHD symptomatology. Past ADHD symptomatology was measured as a count of the number of ADHD symptoms reported at onset of ADHD on the KSADS-PL. Current ADHD symptomatology was measured using the 18-item, ADHD Rating Scales (DuPaul et al. 1998), rated by both the parent and if possible at least one teacher, although teacher ratings were unavailable for 24 subjects evaluated outside of the school year. If more than one teacher's rating was available, total teacher scores were averaged. The ADHD Rating Scale contains the 18 DSM-IV symptoms of ADHD, each rated on a 4-point Likert scale (0 = not true, 4 = very true).

Trauma exposure. Each child completed the Trauma Events Screening Inventory–Brief Child Version (TESI-BC), a 14-item questionnaire adapted from a child-interview (Ford et al. 1999), which screens for trauma exposure throughout the child's life to various types of traumatic events (e.g. serious accidents, disaster, illness of self or others, physical abuse or threats of it, sexual abuse, being the victim of violent crime, or witnessing community or family violence). Others have reported that experiencing a larger number of traumatic event types in childhood is an important predictor of subsequent depression (Chapman et al. 2004). Following these investigators' example, we determined each child's number of event types reported on the TESI-BC (range: 0 to 14). A more comprehensive comparison of subjects' exposure to specific types of traumatic events will be reported in a subsequent paper.

Current global impairment. Youths rated their social, academic and other impairment using the 23-item Social Adjustment Scale-Self Report (SAS-SR) (Weissman et al. 1981). Parents rated their children's impairment using the 13-item Parent Version of the Columbia Impairment Scale (CIS-P) (Bird et al. 1993). For both measures, higher scores suggest worse impairment.

Statistical analysis

Only data from subjects' initial research assessments are presented here. All analyses were completed using SPSS-PC version 14.0 (SPSS Inc., Chicago, IL). Student t-tests and Chi Squared tests were used to compare H/o MDD and the Never-Depressed groups regarding continuous and categorical variables, respectively. Analysis of covariance (ANCOVA) was used to compare impairment ratings between these two groups, controlling for the effects of presence of an externalizing disorder and female sex, after a preliminary model tested the assumption of nonsignificant interactions of the covariates with H/o MDD in a fully crossed design. Survival analysis was used to estimate survival times till first episodes of MDD. The rationale for using such analyses of observational data to examine the potential effects of treatment is well described (Bull and Spiegelhalter 1997). A Cox regression survival analysis with ADHD pharmacotherapy as a time-dependent variable (ADHD-PT) was used to model time-to-event data, with MDD considered the event, and time measured as the span between first onset of ADHD symptoms and the first episode, if any, of MDD. In this model, ADHD-PT changed from "untreated" to "treated" at the time subjects received their first episode of ADHD pharmacotherapy. The effect of having had any ADHD pharmacotherapy on survival times till MDD was first examined with only ADHD-PT in the model. Other survival regression analyses with stepwise selection were used to evaluate the significance of ADHD-PT relative to other variables also predictive of MDD and to estimate the most parsimonious predictive model. Our emphasis was on descriptive and exploratory rather than confirmatory analyses. P values $< .05$ were considered significant, and p values $< .10$ were considered trends toward significance.

Results

Final sample

From among 110 consecutive youths having initial study interviews, six were excluded because they either never had met full symptom criteria for a subtype of ADHD or reported ADHD onset after 10 years of age. Another 23 were excluded who had a history of minor depressive disorders but no MDD, and three were excluded because their first episode of MDD preceded their onset of ADHD symptoms. Finally, 3 others were excluded because their parents were uncertain when they had received their first ADHD pharmacotherapy, and their medical records were unavailable. The final sample included 75 subjects, including 70 who met full DSM-IV criteria for ADHD and another 5 who met study criteria for "probable ADHD." Results did not differ substantively when the 5 subjects with probable ADHD were excluded from the analyses. All findings reported below include both groups.

Among the 75 subjects in the final sample, 36 were classified as H/o MDD and 39 as Never-Depressed. Group comparisons are shown as means ± standard deviations, or as numbers (percentages). Among those in the H/o MDD group, 13 (36.1%) met full DSM-IV criteria for a current MDD episode, and 12 (33.3%) met criteria for a current minor depressive episode, including 9 with a partially remitted MDD episode (4 also with dysthymia), 2 with a current depressive disorder not-otherwise-specified, and 1 with a current dysthymia alone. The mean age of onset of the first MDD episode was 10.4 ± 3.2 years. The H/o MDD group had experienced 1.4 ± 0.5 total MDD episodes, lasting a total duration of 17.9 ± 16.2 months. The total duration of any previous depressive episodes in the H/o MDD group, including both major and minor episodes, was 35.1 ± 31.2 months.

Table 1 compares the H/o MDD and the Never-Depressed groups regarding demographic data, clinical histories of ADHD and other disorders, as well as current psychiatric diagnoses and symptoms. The H/o MDD group was older (p = .006) and more often female (p = .008) than the Never-Depressed group. The two groups had similar socioeconomic statuses, ages of ADHD onset, subtypes of ADHD, and symptoms of ADHD both at past onset and currently. As expected, the H/o MDD group had higher current depressive symptoms and recent suicidal ideations, and lower rates of depressive remission based on CDRS-R scores ($p < .0005$ for all comparisons). The H/o MDD group had higher rates of current comorbid anxiety disorders (p = .015) or externaliz-

Table 1. Demographics, Clinical History, Current Diagnoses and Symptoms

	Never-Depressed (n = *39*)	*H/o MDD* (n = *36*)	p *value*
Demographics			
Age in years	13.2 ± 1.8	14.5 ± 2.1	.006
Female: *n* (%)	10 (25.6)	20 (55.6)	.008
Nonwhite race: *n* (%)	9 (23.1)	5 (13.9)	.308
Hollingshead socioeconomic status	3.8 ± 1.3	4.1 ± 1.0	.248
Clinical History			
Age of first ADHD symptoms: years	5.6 ± 1.7	5.5 ± 1.4	.825
Number of ADHD symptoms at onset	12.6 ± 3.9	11.7 ± 4.3	.389
Early history of an anxiety disorder	8 (20.5)	15 (41.7)	.047
Early history of externalizing disorder	14 (35.9)	21 (58.3)	.052
Number of traumatic event types experienced	3.1 ± 1.9	4.9 ± 2.6	.001
Prior suicidal ideations: *n* (%)	1 (2.6)	19 (52.8)	<.0005
Prior suicidal gestures or attempts: *n* (%)	1 (2.6)	12 (33.3)	<.0005
Current Diagnoses: n (%)			
ADHD, inattentive subtype	19 (48.7)	16 (44.4)	.711
Externalizing disorder	10 (25.6)	20 (55.6)	.008
Anxiety disorder	4 (10.3)	12 (33.3)	.015
Current Depressive Symptoms			
CDRS-R total score	23.8 ± 4.2	42.7 ± 14.9	<.0005
CDRS-R score < 28 (remission): *n* (%)	2 (81.6)	4 (11.4)	<.0005
Mood and Feelings Questionnaire – Child	7.9 ± 7.2	23.0 ± 14.0	<.0005
Mood and Feelings Questionnaire – Parent	9.5 ± 7.5	24.1 ±13.5	<.0005
Recent suicidal thoughts: *n* (%)	1 (2.6)	14 (38.9)	<.0005
Current ADHD Symptoms			
ADHD Rating Scale – Parent	26.6 ± 11.7	28.3 ± 11.4	.537
ADHD Rating Scale – Teacher	25.2 ± 14.0	22.3 ± 12.6	.373
Current Global Maladjustment/Impairment			
Social Adjustment Scale – Revised, Child	20.8 ± 8.2	31.5 ± 11.4	<.0005
Columbia Impairment Scale – Parent	15.9 ± 10.4	25.1 ± 11.1	<.0005

Shown are group means ± SD, unless otherwise noted.

H/o MDD = current or previous major depressive episode; H/o Minor Depression = current or previous dysthymia or depressive disorder not-otherwise-specified, without MDD; Current minor depression = dysthymia, depressive disorder not otherwise specified, or major depressive disorder in partial remission; ADHD = attention-deficit/hyperactivity disorder, inattentive or combined subtype; CDRS-R = Children's Depression Rating Scale- Revised. Recent suicidal thoughts based on item 19 on Child- or Parent-Version of Mood and Feelings Questionnaire Item ("had thoughts about killing him/herself"); Externalizing disorder = oppositional defiant disorder or conduct disorder.

ing disorders ($p = .008$). However, to rule out the possibility that such current comorbidity could be an effect rather than a cause of MDD history, we also compared groups regarding early histories of externalizing disorders or anxiety disorders, with "early history" considered positive when the disorder began before or simultaneous to the first episode of MDD in the H/o MDD group, or at any time prior to the study evaluation in the Never-Depressed group. In this analysis, the H/o MDD group had higher rates of early comorbid anxiety disorders ($p = .047$) and early comorbid externalizing disorders ($p = .052$). The H/o MDD group also reported having experienced a significantly larger number of different traumatic event types than the Never-Depressed group ($p = .001$), but the timing of such traumatic events could not be determined relative to first episodes of MDD. Girls reported a trend toward a larger number of different traumatic event types than boys (Girls: 4.5 ± 2.8, Boys: 3.6 ± 2.1, $p = .10$).

Although most in the H/o MDD group did not have a current episode of MDD, they had significantly higher levels of current impairment, as reported by both subjects and their parents ($p < .0005$ for both). Differences in child-reported impairment on the SAS-SR persisted, even after using ANCOVA to adjust for higher rates of early externalizing disorders and female sex in the H/o MDD group ($F(1,71) = 14.42$, $p = .0003$), as did differences in parent-reported impairment on the CIS-P ($F(1,70) = 12.78$, $p = .001$).

Comparison of treatment histories

The two groups were next compared regarding lifetime histories of various mental health treatments, as shown in Table 2. A significantly higher rate of subjects in the H/o MDD group had received inpatient hospitalizations ($p = .041$), and antidepressant pharmacotherapy ($p < .0005$). All but one patient in the Never-Depressed group had received

TABKE 2. COMPARISON OF LIFETIME HISTORIES OF MENTAL HEALTH TREATMENT

	Never-Depressed (n = *39*)	*H/o MDD* (n = *36*)	p *value*
H/o ADHD pharmacotherapy: *n* (%)	38 (97.4)	27 (75.0)	.006
Number of ADHD medications tried	1.9 ± 1.1	1.6 ± 1.2	.160
Age of first ADHD pharmacotherapy: years	9.2 ± 2.7	11.6 ± 3.5	.002
Time after ADHD onset of first ADHD pharmacotherapy: years	3.7 ± 2.6	6.1 ± 3.6	.001
Number of stimulants tried	1.6 ± 0.6	1.2 ± 0.9	.039
H/o stimulant pharmacotherapy: *n* (%)	38 (97.4)	26 (72.2)	.002
H/o methylphenidate pharmacotherapy: *n* (%)	36 (92.3)	25 (69.4)	.011
H/o mixed amphetamine salts pharmacotherapy: *n* (%)	23 (59.0)	18 (50.0)	.435
H/o dextroamphetamine pharmacotherapy: *n* (%)	2 (5.1)	0 (0)	.494
H/o atomoxetine pharmacotherapy: *n* (%)	6 (15.4)	6 (16.7)	.880
H/o alpha agonist pharmacotherapy: *n* (%)	5 (12.8)	3 (8.3)	.713*
H/o bupropion pharmacotherapy: *n* (%)	3 (7.7)	4 (11.1)	.611
H/o tricyclic pharmacotherapy: *n* (%)	0 (0)	1 (2.8)	.480
Number of antidepressants tried	0.2 ± 0.5	1.3 ± 1.3	<.0005
H/o antidepressant pharmacotherapy: *n* (%)	15.4	22 (61.1)	<.0005
H/o any pharmacotherapy: *n* (%)	97.4	31 (86.1)	.099
Cumulative number of medications tried	2.1 ± 1.1	3.0 ± 2.3	.053
H/o any inpatient hospitalization(s): *n* (%)	3 (7.7)	9 (25.0)	.041

Shown are group means ± standard deviation, unless otherwise noted. H/o = history of; MDD = current or previous major depressive episode; ADHD = attention-deficit/hyperactivity disorder.

ADHD pharmacotherapy, while a quarter in the H/o MDD had not. Rates of having received any ADHD pharmacotherapy ($p = .006$), any stimulant pharmacotherapy ($p = .002$), or any methylphenidate pharmacotherapy ($p = .011$) were significantly higher in the Never-Depressed group. No other rates of having received other specific ADHD medications were significantly different between groups. The means of total numbers of different ADHD medications tried were similar between groups (p = .16), but subjects in the H/o MDD group had received fewer different stimulant medications than the Never-Depressed group ($p = .039$). Using subjects' age at the time of their study assessment as their age of first ADHD pharmacotherapy in the few subjects who had never received ADHD pharmacotherapy, age of first ADHD pharmacotherapy ($p = .002$) and the time delay between the onset of ADHD symptoms and ADHD pharmacotherapy ($p = .001$) were significantly greater in the H/o MDD group than in the Never-Depressed group.

Survival analyses

An initial survival analysis with Cox regression was performed to model time-to-event data in the presence of censored cases (subjects who had not had an episode of MDD by the time of their study evaluation). In this model, the events were subjects' first episodes of MDD, and time was considered the delay in years after onset of ADHD symptoms until subjects either had had their first MDD episode (in the H/o MDD group) or a study evaluation (in the Never-Depressed group). With the time-dependent variable, ADHD-PT, as the only covariate entered, the model was significantly predictive of first episodes of MDD (Wald $\chi^2 = 4.35$, DF = 1, $p = .037$), indicating that delayed ADHD-PT was associated with a higher subsequent risk of MDD onset. Fig. 1 shows survival curves for the treated and untreated groups. The survival curves were created using Kaplan-Meier methods, modified by moving subjects from the untreated to the treated group at the time they first received ADHD pharmacotherapy, and by showing group proportions only from 1 to 10 years after ADHD onset, during which there were at least 10 subjects in both the untreated and treated groups.

To further explore the association between risk of MDD and time delay of ADHD-PT, we examined other potential correlates of this time delay, using a separate univariate Cox regression survival analysis for each variable and onset of ADHD-PT as the outcome event. Girls had a significantly longer delay in ADHD-PT than boys (Wald $\chi^2 = 4.82$, df = 1, $p = .028$), as did children with relative to those without early externalizing disorders (Wald $\chi^2 = 4.40$, df = 1, $p = .036$). Other variables, including race, socioeconomic status, number of different traumatic event types experienced, early anxiety disorder, ADHD subtype, and age and number of ADHD symptoms at ADHD onset were not significantly associated with delays in ADHD-PT. Among potential predictors of shorter MDD survival apart from ADHD-PT, only the number of different traumatic event types showed a significant effect (Wald $\chi^2 = 9.92$, df = 1, $p = .002$), while female sex showed a trend toward significance (Wald $\chi^2 = 3.28$, df = 1, $p = .070$).

Because girls had a significantly greater delay in ADHD-PT, and a trend toward shorter MDD survival, we examined a model including the sex by treatment interaction. The results were in the same direction for both sexes, and the interaction was not significant ($\chi^2 = 1.85$, df = 1, $p = .17$), but the treatment effect was somewhat stronger for boys (n = 45, $\chi^2 = 2.73$, $p = .10$) than for girls (n = 30, $\chi^2 = 0.19$, $p = .67$). With both ADHD-PT and sex entered into a Cox regression model together, neither ADHD-PT (Wald $\chi^2 = 2.35$, df = 1, $p = .125$) nor sex (Wald $\chi^2 = 1.26$, df = 1, $p = .26$) was a significant unique predictor of MDD survival.

With ADHD-PT and all other predictors allowed to enter

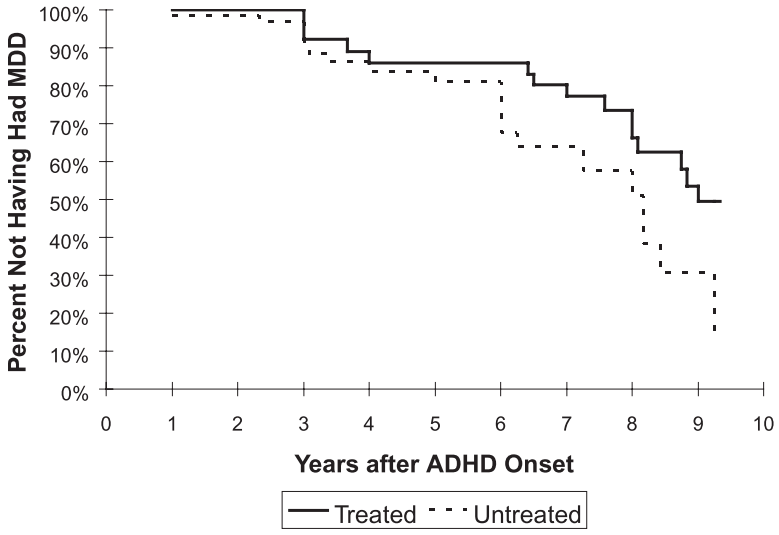

FIG. 1. Survival till first MDD episode predicated by first ADHD pharmacotherapy. This figure shows results from a Cox regression, and models the risk of developing first episode of MDD on the vertical axis and years after onset of ADHD till first episode of MDD on the horizontal axis and. ADHD pharmacotherapy is a time-dependent variable. Two groups are compared, patients who have been treated and patients who have not been treated with ADHD pharmacotherapy. The untreated group shows a significantly higher risk of developing MDD ($p = .037$) with no other predictors in the model. MDD, major depressive disorder; ADHD, attention-deficit/hyperactivity disorder.

and exit a backward stepwise Cox regression model, only ADHD-PT (Wald $\chi^2 = 6.26$, $p = .012$) and the number of different traumatic event types experienced (Wald $\chi^2 = 12.01$, df = 1, $p = .001$) remained in the final model predicting MDD survival, ADHD-PT in a protective fashion and traumatic events in a harmful fashion. Thus ADHD-PT and trauma exposure as measured here each had an independent effect. However, of these two variables, only ADHD-PT was an unequivocal predictor, clearly preceding the onset of any first MDD episodes. The same final result was obtained using a Cox regression with forward stepwise methods.

Discussion

In this sample of ADHD adolescents, delayed ADHD pharmacotherapy proved to be a strong predictor of MDD onset, relative to previously reported risk factors of depression, and had a significant effect independent of the number of different traumatic event types experienced. The H/o MDD group reported longer delays before initiating ADHD pharmacotherapy, less extensive numbers of stimulant medications tried, and a lower percentage of treatment with any ADHD pharmacotherapy. This is the first study we are aware of to demonstrate that ADHD pharmacotherapy in childhood may have a protective effect regarding risk of subsequent MDD.

Additional findings of continuing levels of depressive symptomatology and impairment in the H/o MDD group replicate previous studies of MDD in general pediatric-aged samples (Birmaher et al. 1996; Flament et al. 2001; Kovacs et al. 1997). The H/o MDD group had experienced on average between one and two MDD episodes, lasting a total of 1.5 years, with an additional 1.5 years spent having minor depressive episodes. Although 70% in the H/o MDD group did not have a current MDD episode by DSM-IV criteria, many continued to report high levels of current depressive symptoms and suicidal ideations. Particularly striking was their higher current impairment relative to the Never-Depressed group, findings which persisted independent of the effects of comorbid externalizing disorders and female sex. Echoing findings from a longitudinal study of ADHD youths with comorbid MDD (Biederman et al. 1998), youths in the H/o MDD group appeared to have had "true" major depression.

Others have suggested that depressive disorders may occur in ADHD youths due to the cumulative effects of ongoing problems related to ADHD and its morbidity (Waxmonsky 2003). First depressive episodes in the H/o MDD group occurred on average about 4 years *after* the onset of ADHD symptoms. It is unclear whether this delayed onset of MDD was due to the cumulative adverse effects of having ADHD or simply reflected the usual increase in risk seen from pre-adolescence to adolescence. Consistent with the first explanation, H/o MDD was associated with greater latency of first pharmacotherapy for ADHD, and lower overall exposure to various types of ADHD pharmacotherapy. However, both groups had similar ages of ADHD onset, and similar levels of ADHD symptomatology at onset of ADHD and currently.

We also noted girls were more delayed in starting ADHD pharmacotherapy and were more likely to have had MDD than boys. Others have reported that girls are more likely to have MDD than boys (Birmaher et al. 2006). Girls at any age who have ADHD are less likely than boys to be diagnosed with ADHD and to receive pharmacological treatment for it (Barbaresi et al. 2006; Bussing et al. 2003). While delayed ADHD pharmacotherapy was a strong predictor for subsequent MDD, we cannot entirely rule out a confounding influence of female sex. In a survival regression model that included both ADHD-PT and sex, ADHD-PT was no longer a significant predictor. The multivariate regression results

were somewhat more suggestive of a direct causal role of ADHD pharmacotherapy, as the delay in starting ADHD pharmacotherapy was consistently a stronger predictor than female sex. ADHD-PT was the only variable to remain in the final stepwise predictive model of MDD, along with trauma exposure when measured as the number of different traumatic event types experienced.

While other studies have clearly implicated trauma exposure as a risk factor for depression (Caspi et al. 2003; Chapman et al. 2004; Kendler et al. 2004; Widom et al. 2007), the link observed here between the number of traumatic event types experienced and shortened survival till MDD episodes should be interpreted with caution. Unlike ADHD-PT and other variables studied as predictors in our survival analysis, we cannot say whether all of the traumatic event types reported actually preceded first MDD episodes, due to the limitations of the trauma measure. Without establishing such a temporal relationship, one could also theorize that MDD episodes were a cause rather than an effect of increasing trauma exposure in youths with ADHD.

Limitations

Findings in the current study should be considered cautiously in light of other study limitations, apart from those related to our trauma exposure measure. First, other factors that might influence risk of depression or initiation of ADHD pharmacotherapy were not measured in the current study. For instance, family psychopathology and family dysfunction might influence decisions to seek treatment, and are clear risk factors for pediatric depression (Birmaher et al. 1996). Second, respondents may have been biased in their ratings by knowledge of prior depressive episodes in these youths. Third, because the current sample was primarily white and clinically referred, findings here may not generalize to other samples of ADHD youths. Fourth, because youths with depressive histories were actively recruited, they were more prevalent in the current sample than would be expected in the general population of ADHD youth. Ultimately, a prospective, randomized, placebo-controlled trial of ADHD pharmacotherapy with assigned treatments maintained over many years would be the optimal design to determine the long-term effects of ADHD pharmacotherapy and other environmental factors on subsequent risk for MDD. However, such a design would be infeasible and unethical given the strong empirical support for the effectiveness of pharmacotherapy in pediatric ADHD.

Conclusions

Clinical trials have provided increasingly strong evidence for the short-term clinical benefits of ADHD pharmacotherapy in children with ADHD. Our findings provide preliminary evidence that early ADHD pharmacotherapy in youths with ADHD does not increase but may significantly reduce the longer-term risk of developing comorbid MDD. While these findings are somewhat clouded by the confounding effects of delayed ADHD pharmacotherapy and female sex, delayed ADHD pharmacotherapy was the single strongest predictor that unequivocally preceded the onset of any first MDD episode. Such comorbid MDD adds significantly to the long-term impairment and psychosocial burdens experienced by youths already challenged by having ADHD alone. Our findings suggest that the risks of later comorbid MDD in children with ADHD are a potential argument *for* rather than *against* early pharmacotherapy for the ADHD.

Disclosures

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Address reprint requests to:
W. Burleson Daviss, M.D.
Department of Psychiatry
University of Texas Health Science Center of San Antonio
7703 Floyd Curl Drive
San Antonio, TX, 78229-3900

E-mail: davissw@uthscsa.edu