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Do stimulants have a protective effect on the development of psychiatric disorders in youth with ADHD? A ten-year follow-up study

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Abstract

Objective—Little is known about the effect of stimulant treatment in youth with ADHD on the subsequent development of comorbid psychiatric disorders. We tested the association between stimulant treatment and the subsequent development of psychiatric comorbidity in a longitudinal sample of ADHD patients.

Patients and Methods—We conducted a case-control, ten-year prospective follow-up study into young adult years of youth with ADHD grown up. At baseline, we assessed consecutively referred male, Caucasian children with (n=140) and without (n=120) ADHD, aged 6–18. At the ten-year follow-up, 112 (80%) and 105 (88%) of the ADHD and control children, respectively, were re-assessed (mean age 22 years). We examined the association between stimulant treatment in childhood and adolescence and subsequent comorbid disorders and grade retention using proportional hazards survival models.

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Results—Of the 112 ADHD subjects, 82 (73%) were previously treated with stimulants. ADHD subjects who were treated with stimulants were significantly less likely to subsequently develop depressive, disruptive behavior and anxiety disorders and less likely to repeat a grade compared with ADHD subjects who were not treated.

Conclusions—We found evidence that stimulant treatment decreases the risk for subsequent comorbid psychiatric disorders and academic failure in youth with ADHD grown up.

Keywords

ADHD; psychopharmacology; stimulants; comorbidity

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a childhood-onset, neuropsychiatric disorder (1), affecting up to 10% of children (2). ADHD is associated with high rates of comorbid psychiatric disorders (3–6) and academic impairment (7–9). While treatment with stimulants have been shown to improve the core symptoms of ADHD and remain the mainstay of treatment (10,11), less information is available as to their effects on the development of comorbid psychiatric disorders.

A recent study examined the association between stimulant treatment for ADHD and the risk for subsequent major depression (MD) (12), based on the high comorbidity between ADHD and MD (13,14) and animal studies showing an association between exposure to stimulants and depressive behaviors (15,16), by comparing the rates of pharmacotherapy in a sample of ADHD teenagers with (n=36) and without (n=39) a lifetime history of MD. These investigators found that stimulant therapy protected ADHD youth against subsequent MD.

However, little is known about the effect of stimulant treatment on the subsequent development of other disorders associated with ADHD, such as conduct disorder (CD), oppositional-defiant disorder (ODD), anxiety disorders, and bipolar disorder (BD). Clinical trials of ADHD youth suggested a beneficial effect of short-term stimulant therapy on symptoms of CD and ODD (17–19), but the long-term effect remains undefined. Chart reviews of patients with BD provide conflicting evidence for the clinical utility of stimulants for treating BD symptoms (20–22). However, in a randomized, placebo-controlled clinical trial of mixed amphetamine salts in youth with BD and ADHD stabilized on divalproex sodium, Scheffer et al (23) found that stimulant therapy improved ADHD symptoms while not exacerbating manic symptoms, consistent with earlier chart reviews (24,25). Finally, while there is disagreement about the clinical utility of stimulant therapy to treat ADHD symptoms in patients with anxiety (26,27), there are no long-term studies examining the effect of naturalistic treatment on subsequent anxiety disorders.

Naturalistic follow-up studies of children with ADHD suggest that stimulant treatment improves academic test scores (28,29), but this effect did not extend to the risk for grade retention (28). In a recent review, Raggi and Chronis (30) concluded that, although stimulant therapy improves short-term academic performance, there are no data that extend this beneficial effect to long-term academic outcomes.

Determining the effect of stimulant treatment on psychiatric and academic outcomes can provide important prognostic information to clinicians treating ADHD youth. Thus, the goal of the present study was to evaluate the association between stimulant treatment and the subsequent development of mood, anxiety, and disruptive disorders, as well as educational outcomes. To this end we use data form a study of referred boys with ADHD followed

prospectively for ten years from childhood into young adult years. We hypothesized that naturalistic stimulant therapy would be associated with decreased risks for these outcomes.

Patients and Methods

Patients

Subjects were derived from a longitudinal case-control family study of ADHD (7,31). At baseline, we ascertained male Caucasian subjects aged 6–17 years with (N=140) and without (N=120) DSM-III-R ADHD from pediatric and psychiatric clinics. Potential subjects were excluded if they had been adopted, or if their nuclear family was not available for study. We also excluded potential subjects if they had major sensorimotor handicaps (paralysis, deafness, blindness), psychosis, autism, inadequate command of the English language, or a Full Scale IQ less than 80. All of the ADHD subjects met full DSM-III-R diagnostic criteria for ADHD at the time of the clinical referral; at the time of recruitment they all had active symptoms of the disorder. This sample (both ADHD and control groups) was followed-up at one, four, and ten years after baseline. The present study reports on the 10-year follow-up of only the ADHD probands, of which 112 were successfully re-ascertained (age range 15–30 years at the 10-year follow-up).

Parents and adult offspring provided written informed consent to participate, and parents also provided consent for offspring under the age of 18. Children and adolescents provided written assent to participate. The human research committee at Massachusetts General Hospital approved this study.

Two independent sources provided the index children. The “psychiatric referral source” was a major academic medical center, where we selected ADHD subjects from consecutive referrals to its pediatric psychopharmacology clinic. We selected normal controls from outpatients referred for routine physical examinations to its pediatric medical clinics. The “pediatric referral source” was a major Health Maintenance Organization (HMO), where we selected ADHD subjects from consecutively ascertained pediatric clinic outpatients, identified from their records as having ADHD. We have previously demonstrated no clinically or statistically significant differences between ADHD subjects ascertained from these two referral sources on measures of psychopathology, cognitive performance or psychosocial functioning (32).

We used a three-stage ascertainment procedure to select subjects to improve the accuracy of psychiatric diagnoses (33,34). The first stage was their referral, resulting in a diagnosis of ADHD by a child psychiatrist or pediatrician. The second stage confirmed the diagnosis by administering a telephone questionnaire to their mother. Eligible children meeting study entry criteria were recruited for the study and received the third stage, a diagnostic assessment with a structured interview. Only patients who received a positive diagnosis at all three stages were included.

Follow-up Assessment Procedures

Psychiatric assessments at the 10 year follow-up relied on the K-SADS-E (Epidemiologic Version) (35) for subjects younger than 18 years of age and the Structured Clinical Interview for DSM-IV (SCID) (36) (supplemented with modules from the K-SADS-E to assess childhood diagnoses) for subjects ≥18 years of age. We conducted direct interviews with subjects and indirect interviews with their mothers (i.e., mothers complete the structured interview about their offspring). We combined data from direct and indirect interviews by considering a diagnostic criterion positive if it was endorsed in either interview. During these interviews, we also collected data on lifetime history of grade retention.

We considered a disorder positive if DSM-IV diagnostic criteria were unequivocally met. Although standardized algorithms were used to determine each diagnosis, interviewers needed a mechanism to determine the clinical relevance of symptoms when subjects provided unclear or imprecise information. Thus, a committee of board-certified child and adult psychiatrists who were blind to the subject's ADHD status, referral source and all other data resolved diagnostic uncertainties. Diagnoses presented for review were considered positive only when the committee determined that diagnostic criteria were met to a clinically meaningful degree.

The interviewers were blind to the subject's ascertainment and all prior assessments. The interviewers had undergraduate degrees in psychology and were extensively trained. First, they spent several weeks learning interview mechanics, diagnostic criteria and coding algorithms. Then, they observed interviews by experienced raters and clinicians. They subsequently conducted at least six practice interviews and at least three study interviews, observed by senior interviewers. Trainees did not conduct interviews independently until they executed at least three interviews that achieved perfect diagnostic agreement with a senior interviewer. The principal investigator (JB) supervised the interviewers. We computed kappa coefficients by having experienced, board certified child and adult psychiatrists and licensed clinical psychologists diagnose subjects from audio taped interviews. Based on 500 assessments from interviews of children and adults, the median kappa coefficient was .98. Kappa coefficients for individual diagnoses included: ADHD (0.88), CD (1.0), MD (1.0), BD (0.95), agoraphobia (1.0), panic disorder (.95), GAD (0.95), specific phobia (0.95). and social phobia (1.0).

Socioeconomic status (SES) was measured using the 5-point Hollingshead scale (37). To measure psychopharmacological treatment, we collected the following information for each subject, for each medication used: name of the medication, age at onset of treatment, and age of treatment termination.

Statistical Analysis

To assess the impact of attrition, we compared baseline characteristics of subjects who were and were not assessed at the 10-year follow-up. Then, we stratified the ADHD subjects according to a lifetime history of receiving any stimulant therapy (amphetamine products (mixed amphetamine salts, d-amphetamine), methylphenidate products (IR methylphenidate, OROS methylphenidate, transdermal methylphenidate, d-methylphenidate, ext release methylphenidate), and pemoline). Among subjects who were followed-up at the 10-year assessment, we compared ADHD subjects with and without a lifetime history of stimulant treatment on follow-up demographic factors.

To estimate the lifetime risk for comorbid psychiatric disorders associated with stimulant therapy, we used Cox proportional hazard survival models. We evaluated the following outcomes: MD with severe impairment, multiple (≥2) anxiety disorder, BD, CD, ODD and grade retention. For each outcome, rates are defined as a positive response at any assessment versus a negative response at all assessments. These models utilize all available data for each subject, including those not assessed at the 10-year follow-up; thus, all 140 subjects are included, using as many waves of follow-up data as are available. We used the age of outcome onset as the survival time for cases and the age at most recent interview as the time of censoring for non-cases. Subjects entered the analysis on the reported age of ADHD onset; thus, any subjects with failures (i.e., the onset of the comorbid disorder) that occurred prior to their ADHD onset would be excluded from the model for that outcome. Each outcome was modeled as a function of lifetime stimulant treatment, parental lifetime history of the outcome, and ADHD impairment measured at baseline (i.e., a binary indicator coded as severe versus moderate or minimal).

To create a measure of lifetime stimulant treatment, we created a binary indicator variable for each outcome, defined as positive if: 1) subjects reported a lifetime history of stimulant treatment; and 2) they did not meet criteria for the outcome before the onset of treatment. Thus, the stimulant treatment variable for a given outcome was coded positive only for subjects who had not yet reported the onset of the outcome at the age when their stimulant therapy began. Untreated subjects and subjects who began stimulant treatment after the reported onset of the given outcome were defined as negative on this variable. Subjects whose treatment and outcome began at the same age were impossible to categorize and were dropped from the analysis of that outcome. Since we assessed multiple outcomes, each with its own age of onset, the number of subjects dropped ranged from two for MD and multiple anxiety to five for repeated grade.

The statistical significance of each covariate was determined by Wald's test, and our alpha level was set at 0.05. All tests were two-tailed, and we reported hazard ratios (HR) and 95% confidence intervals (95% CI) for each model.

Results

Of the 140 ADHD subjects recruited at baseline, 112 (80%) were successfully reassessed at the 10-year follow-up. As stated in a previous report, there were no significant differences between those successfully followed up and those lost on age, familial intactness, ascertainment source, or psychiatric outcomes (all p values $\geq$0.05) (6). However, a significant difference was found in SES, with ADHD subjects lost to follow-up having a lower mean SES compared to subjects successfully re-assessed (2.4±1.2 versus 1.8±0.9, respectively; $t_{(138)} = 3.1$, $p<0.01$).

Details about stimulant treatment histories can be found in prior reports (6,38). Briefly, of the 140 ADHD probands, 92 (66%) reported a lifetime history of stimulant treatment. Of the 112 ADHD subjects assessed at the 10-year follow-up, 82 (73%) were treated with stimulant medications at some time in their lives. The mean age of stimulant treatment onset was 8.8 years (standard deviation of 3.5; range: 3 to 21 years). Fifty percent of subjects began their treatment between ages six and ten. The mean duration of treatment was six years (standard deviation of 4.7), with fifty percent of subjects undergoing stimulant treatment for two to ten years. Nine subjects did not provide information on stimulant therapy, and were dropped from subsequent analyses.

Among subjects in the No Stimulant Therapy group, 13 (33%) reported a lifetime history of treatment with a non-stimulant medication. Specifically, 13 (33%) were treated with a tricyclic antidepressant, 1 (3%) was treated with clonidine, and one (3%) with guanfacine.

As depicted in Table 1, no significant differences were detected in rates of intactness of the family of origin, baseline ADHD severity, baseline psychopathology, social class or parental history of psychopathology between ADHD subjects with and without stimulant therapy, with the exception of parental BD. The parents of the No Stimulant Therapy group reported a significantly higher rate of BD compared to the parents of subjects of the Stimulant Therapy group. Also, significant differences were detected in both baseline and follow-up ages, with the No Stimulant Therapy group having a younger mean age compared to the Stimulant Therapy group.

ADHD subjects who were treated with stimulants were significantly less likely to subsequently develop MD, CD, ODD, and multiple anxiety disorder compared with ADHD subjects who were not treated (see table 2). Also, the Stimulant Therapy group had significantly lower lifetime rates of grade retention compared to the No Stimulant Therapy group. The association between stimulant treatment and the risk for BD was not statistically significant. Additional statistical adjustment for baseline age did not alter the results. Likewise, the statistical

significance of the stimulant therapy term was not changed after adding parental BD to each model. Finally, the pattern of findings was the same when restricting the analysis to the 112 subjects who were re-assessed at the 10-year follow-up.

Discussion

In a sample of males diagnosed with ADHD in childhood followed up for ten years, prior treatment with stimulants was associated with a subsequently decreased risk for depressive, disruptive, and anxiety disorders, and for grade retention. These findings suggest that treatment of ADHD with stimulants has protective effects against the development of some psychiatric and functional outcomes.

Our study confirms the results of Daviss et al (12), who also found a protective effect of pharmacotherapy against subsequent MD in ADHD youth. However, our results extend this finding by documenting the protective effect while statistically adjusting for parental lifetime history of MD, as well as baseline severity of ADHD.

Our results failed to detect an association between stimulant treatment and the risk for BD. Similarly, published chart reviews of stimulant treatment in patients with BD have also been inconclusive (20–22). Given the large and bi-directional comorbidity between ADHD and BD, and the standing of stimulants as the first-line therapeutic approach for ADHD, additional research into the effect of stimulant therapy on the subsequent risk of BD is warranted.

Our results also suggest that stimulant therapy, in addition to exerting a therapeutic effect in the short-term (17–19), may also reduce the risk for CD and ODD across much longer time intervals. However, our study was not consistent with a report by Molina et al (39), which found a positive association between past year treatment and delinquency in a large sample of children with ADHD. Two factors may explain this discrepancy. First, our study examined the onset of CD, while Molina et al examined delinquency; in the same study (39), the proportion of subjects with delinquency who also had CD was only 33%. Second, the Molina et al study examined the use of any prescription medication for ADHD, while our study focused on stimulants specifically.

Our study disagrees with prior work suggesting that stimulant treatment does not protect against grade retention (28). Several factors may have contributed to this discrepancy. For example, the sample size of Powers et al was smaller (n=90) than that tested in this study (n=122 for the repeated grade model), providing relatively less statistical power in the former study. Secondly, the mean age of the subjects from the Powers et al study was younger at follow-up (mean age in years of 18.2). Thus, the subjects from the Powers et al study may not have completely aged through the period of risk for grade retention.

What explains this inverse association between stimulant treatment and adverse psychiatric and educational outcomes? Efficacious stimulant therapy may interrupt the pathogenic trajectory leading toward other disorders. For example, a child under efficacious ADHD treatment may experience improved self-esteem and behavioral compliance in school, attendant improvement in his standing with teachers as well as association with a normative peer group. Over time, these detours may provide an alternate developmental trajectory for this child, ultimately resulting in decreased risk for major depression and disruptive behavior disorders. However, this explanation assumes continued efficacy of stimulant therapy across time, which may not be tenable (40). Alternatively, our findings may be due to unmeasured confounding factors that predict which children with ADHD are provided treatment, and also are predictive of psychopathology, such that children who are unlikely to receive treatment for ADHD are also more likely to develop comorbid disorders, regardless of treatment.

These results must be considered in the light of methodological limitations. Our sample was originally ascertained according to DSM-III-R criteria, and our results may not generalize to samples ascertained by DSM-IV. However, considering the high overlap between the two definitions (93% of DSM-III-R cases received a DSM-IV diagnosis (41)), any effect should be minimal. Because our sample consisted of referred Caucasian boys, we do not know if our results will generalize to ADHD children in the general population, or to other racial groups, or to females. Although our study was prospective, we relied on retrospectively (i.e. within the intervals between assessments) reported ages of onset for treatment and comorbid disorders to establish the temporal sequence. Thus, our results may suffer from misclassification (and thus a reduction in precision) to the degree that these ages were incorrectly recalled. However, while the exact ages may not have been recalled accurately, the relative ordering is likely to be correct, so that any misclassification of our exposure and outcome variables should be minimal. Also, we cannot address in these data the reasons why subjects were treated with stimulant versus non-stimulant medications. Finally, our naturalistic study design cannot provide the more informative evidence that would be produced by a randomized, controlled study.

Conclusion

Our study provides novel evidence that stimulant treatment is associated with a lower risk for the subsequent development of psychopathology and grade retention. If confirmed by clinical trials, these findings could assist clinicians in treatment planning for forecasting prognosis for ADHD youth, and could contribute to our understanding of the trajectories leading to these disorders.

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Table 1

Demographic and clinical characteristics of ADHD males, stratified by stimulant treatment

	No Stimulant Therapy (n=39)	Lifetime Stimulant Therapy (n=92)	Test Statistic, p value
Proband Characteristics			
Familial Intactness [1]	13 (33)	24 (26)	$\chi^2_{(1)}$ =0.7, p=0.40
Social Class, baseline [2]	1.94±1.0	1.83±1.0	t (129)=0.7, p=0.52
Social Class, follow-up [2]	2.23±1.0	2.12±1.1	t (110)=0.6, p=0.53
Age, Baseline	12.1±3.0	9.9±2.7	t (129)=4.1, p=<0.01
Age, Follow-up [3]	23.2±3.7	21.0±3.0	t (110)=3.1, p=<0.01
ADHD Severity [4]	19 (49)	55 (60)	$\chi^2_{(1)}$ =1.5, p=0.22
Major Depression [5]	15 (38)	23 (25)	$\chi^2_{(1)}$ =2.4, p=0.12
Conduct Disorder [5]	11 (28)	18 (20)	$\chi^2_{(1)}$ =1.2, p=0.28
Multiple Anxiety Disorder [5]	9 (23)	27 (29)	$\chi^2_{(1)}$ =0.5, p=0.46
Oppositional-Defiant Disorder[5]	30 (77)	55 (60)	$\chi^2_{(1)}$ =3.5, p=0.06
Repeated Grade[5]	11 (28)	30 (33)	$\chi^2_{(1)}$ =0.2, p=0.62
Bipolar Disorder[5]	7 (18)	7 (8)	$\chi^2_{(1)}$ =3.1, p=0.08
Parental Psychopathology [6]			
ADHD	10 (26)	28 (30)	$\chi^2_{(1)}$ =0.3, p=0.58
Major Depression	10 (26)	26 (28)	$\chi^2_{(1)}$ =0.1, p=0.76
Conduct Disorder	6 (15)	20 (22)	$\chi^2_{(1)}$ =0.7, p=0.40
Multiple Anxiety Disorder	16 (41)	40 (43)	$\chi^2_{(1)}$ =0.1, p=0.80
Oppositional-Defiant Disorder	4 (10)	18 (20)	$\chi^2_{(1)}$ =1.7, p=0.19
Repeated Grade	15 (38)	28 (30)	$\chi^2_{(1)}$ =0.8, p=0.37
Bipolar Disorder	7 (18)	6 (7)	$\chi^2_{(1)}$ =4.0, p=0.045

Values in table represent *frequency (percent)* or *mean±standard deviation*

[1] Parents divorced or separated at baseline;

[2] Hollingshead Socioeconomic status scale;

[3] Samples restricted to subjects who were assessed at the 10-year follow-up: No Stimulant Therapy n=30, Lifetime Stimulant Therapy n=82;

[4] Proportion with severe impairment (versus moderate or minimal);

[5] Lifetime history at baseline;

[6] Lifetime parental history of each condition

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Table 2

Cumulative morbidity risks and hazard ratios for association between stimulant treatment and subsequent psychiatric comorbidity in ADHD males

Outcome	Age of Onset	Events prior to ADHD onset[1]	Subjects used in model	MR (95%CI)		Hazard Ratio	Test statistic, p value
	mean±sd, range			No Stimulant Therapy	Stimulant Therapy		
Major Depression	8.0±3.9, 2–16	20	107	0.69 (0.55, 0.82)	0.24 (0.15, 0.37)	0.22	$\chi^2_{(1)}$ =19.7, p<0.001
Conduct Disorder	10.8±4.0, 3–18	13	112	0.67 (0.53, 0.81)	0.22 (0.14, 0.34)	0.21	$\chi^2_{(1)}$ =21.4, p<0.001
MA Disorder	8.5±6.0, 2–23	18	108	0.60 (0.47, 0.75)	0.07 (0.03, 0.19)	0.15	$\chi^2_{(1)}$ =17.8, p<0.001
ODD	7.4±3.5, 2–18	46	79	0.88 (0.78, 0.95)	0.40 (0.25, 0.58)	0.21	$\chi^2_{(1)}$ =19.9, p<0.001
Bipolar Disorder	11.4±5.2, 3–18	9	116	0.42 (0.27, 0.61)	0.20 (0.12, 0.32)	0.47	$\chi^2_{(1)}$ =3.5, p=0.063
Repeated Grade	8.4±4.0, 4–18	2	122	0.63 (0.51, 0.75)	0.26 (0.16, 0.40)	0.25	$\chi^2_{(1)}$ =18.4, p<0.001

[1] subjects excluded from given model

MR = Cumulative morbidity risk of disorder by age 21 as estimated by Kaplan-Meier failure function

MA = Multiple (≥2) Anxiety

ODD = Oppositional defiant disorder