Response to Methylphenidate in Children with Attention Deficit Hyperactivity Disorder and Manic Symptoms in the Multimodal Treatment Study of Children with Attention Deficit Hyperactivity Disorder Titration Trial

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Abstract

Objective:

Recent reports raise concern that children with attention deficit hyperactivity disorder (ADHD) and some manic symptoms may worsen with stimulant treatment. This study examines the response to methylphenidate in such children.

Methods:

Data from children participating in the 1-month methylphenidate titration trial of the Multimodal Treatment Study of Children with ADHD were reanalyzed by dividing the sample into children with and without some manic symptoms. Two "mania proxies" were constructed using items from the Diagnostic Interview Schedule for Children (DISC) or the Child Behavior Checklist (CBCL). Treatment response and side effects are compared between participants with and without proxies.

Results:

Thirty-two (11%) and 29 (10%) participants fulfilled criteria for the CBCL mania proxy and DISC mania proxy, respectively. Presence or absence of either proxy did not predict a greater or lesser response or side effects.

Conclusion:

Findings suggest that children with ADHD and manic symptoms respond robustly to

methylphenidate during the first month of treatment and that these children are not more likely to have an adverse response to methylphenidate. Further research is needed to explore how such children will respond during long-term treatment. Clinicians should not a priori avoid stimulants in children with ADHD and some manic symptoms.

Introduction

Recent reports document children who have attention deficit hyperactivity disorder (ADHD), severe irritability, and mood symptoms but who do not meet all the criteria for bipolar disorder (Carlson 1984, 1990, Carlson and Kelly 1998, Wozniak et al. 1995). Investigators deliberate about how to characterize, diagnose, and treat these children. Some clinicians claim that a child's poor response to stimulants suggests bipolar disorder. Similarly, clinicians and authors cite examples of children who are initially diagnosed with ADHD, have adverse reactions to stimulants, and are later diagnosed with bipolar disorder (Papolos and Papolos 1999). There is little systematic evidence to support these suppositions.

Stimulants are proven to be effective in treating ADHD (Connor et al. 2002; Gillberg et al. 1997; Spencer et al. 1996; Swanson 1993). However, it is unclear if they pose a risk for premature development of mania in the subset of children who have manic symptoms in addition to their ADHD. Compared to the numerous case reports on mania development with antidepressants, there is only one of mania development with stimulant treatment in a child (Koehler-Troy et al. 1986). Of the few describing psychotic symptoms in children (Lucas and Weiss 1971; Ney 1967; Winsberg et al. 1972), only one of these children had symptoms that may have been symptoms of mania, "I felt strong like I could tear everything apart" (Lucas and Weiss 1971). Whether this was mania induction or stimulant toxicity is not clear. Additionally, in a chart review of children with ADHD receiving stimulants, Cherland and colleagues reported that 9 of 98 children developed psychotic symptoms (Cherland and Fitzpatrick 1999). Two of these children were later diagnosed with mania.

DelBello and colleagues conducted a retrospective study of a group of adolescents admitted to a psychiatric inpatient unit for mania disorder. They found an association between a past history of treatment with stimulants and an earlier onset of bipolar disorder (DelBello et al. 2001) and suggested that stimulant exposure led to the earlier onset of bipolar disorder. However, this was not a prospective study, and it did not control for severity of psychopathology. That is, the authors did not address whether these children were more symptomatic at a younger age, leading to earlier treatment with stimulants. Carlson and colleagues used a "follow-back" approach to examine 6- to 12-year-old boys who had been diagnosed with and treated for "minimal brain dysfunction" (Carlson et al. 2000). They found that participants who were diagnosed with mania spectrum disorders as young adults responded well to stimulants as children. Moreover, children with ADHD and high rates of comorbidity did not develop higher rates of bipolar I disorder than children with uncomplicated ADHD as might have been expected if that group had included children with mania. Authors have suggested that the high reports of bipolar diagnoses in children with ADHD may actually be due to stimulant rebound and not to true bipolar disorder (Sarampote et al. 2002). Studies that have examined the effect of stimulants on the mood symptoms in general and irritability specifically have generally found improvement rather than exacerbation (Barkley et al. 1990; Firestone et al. 1998; Greenhill et al. 2001; Klein et al. 1997; Swanson et al. 1998). Similarly, aggression-related behaviors improved in a meta-analysis of children with ADHD treated with stimulants (Connor et al. 2002).

Given the physician's mandate to "first do no harm," the question of how to treat children with ADHD and manic-like symptoms is important. Should stimulants be avoided completely?

Should stimulants be prescribed only after prior treatment with mood stabilizers (Biederman et al. 1999)? If one encounters a child who becomes irritable or decompensates with stimulant treatment, are there diagnostic implications?

We used a large dataset of children with well-characterized ADHD, the Multimodal Treatment Study of Children with ADHD (MTA), to answer the following questions: Do children with ADHD and some manic symptoms respond differently to stimulants than children with ADHD without manic symptoms? Are these children more likely to get taken off stimulants because they become more irritable?

Methods

This study reports on the participants from the MTA. The recruitment, screening, diagnostic instruments, outcome measures, randomization, methods, informed consent, institutional board review at the performance sites, and the basic characteristics of the full MTA sample have been described previously (Arnold et al. 1997a, 1997b, MTA Cooperative Group 1999a). Parents participated in the Diagnostic Interview Schedule for Children, Version 2.3 (DISC; Shaffer et al. 1996), with a 3.0 supplement for disruptive behavior disorders. Participants ($n = 579$) in the original study had ADHD, combined subtype on the DISC, Version 3.0, as supplemented with up to two symptoms identified by children's teachers for cases falling just below DISC diagnostic threshold. They were randomized to one of four groups: (a) medication management (MedMgt), (b) behavioral treatment (Beh), (c) the combination of MedMgt and Beh (Comb), or (d) community comparison. During the first month of treatment, 270 of the 289 children assigned MedMgt or Comb groups participated in a placebo-controlled, double-blind titration. This article addresses the medication and side effects of those participants who were in the titration trial.

Titration procedure

The titration rationale and procedure has been described previously (Greenhill et al. 1996, 2001). Briefly, it began with a 4-day, single-blind, safety lead-in period, during which subjects were exposed to three progressively higher daily methylphenidate (MPH) doses given three times daily. Thereafter, for 28 days, subjects received one of three doses of MPH or placebo in a randomized crossover daily-switching, double-blind protocol (five school day repeats of each of the four conditions, balanced for day of week and order).

Measurements

The measurements of significance to our study are described below. A full description of the assessment measurements used in the MTA appears in a previous article (Hinshaw et al. 1997). In addition to the DISC, both the participants' parents (or primary caretakers) and teachers completed a Child Behavior Checklist (CBCL; Achenbach 1991a, 1991b). ADHD symptoms were measured at baseline with the SNAP (an acronym denoting the names of the instrument's developers), completed by the primary caretaker and the teacher (Swanson 1992). The measure generates subscales for inattention, hyperactivity/impulsivity, and oppositional defiant disorder (ODD) symptoms. During the titration phase, ADHD symptoms were assessed daily by parents and teachers using a 16-item Conners, Loney, and Milich (CLAM) scale, which generates Inattentive/Overactive (I/O), Aggressive/Defiant (A/D), and Mixed (I/O+A/D) subscales (Loney and Milich 1982; Swanson 1992). Parents and teachers also rated daily the presence and severity of 10 adverse events commonly associated with MPH on the Pittsburgh Side Effect Rating Scale (Pelham 1993). Only the weekday ratings are included in this study.

Manic symptoms

To compare the children with some manic symptoms to the children without manic symptoms, we constructed two proxies. These proxies were created to capture the participants who had some manic symptoms and do not represent participants who fulfill full criteria for bipolar disorder. One proxy was based on the mania section of the DISC. A variable was created using a "yes" response to severe irritability and at least one additional mania item (happy/excited, more energy than usual, more confident than usual). Specifically, the informant needed to answer yes to the irritability lead-in question: "Was there a time when [he/ she] was very irritable, jumpy or edgy so that any little thing would upset [him/her] or make [him/her] mad?" and then answer yes to the severe irritability question: "Was [he/she] so much more irritable than usual that you or others thought that something was wrong with [him/her]?" In addition to answering yes to the severe irritability question, the informant had to answer yes to at least one of the following: "In the past 6 months was there a time when __ seemed much too happy or excited?" "Was there a time when [he/she] had a lot more energy than usual, quite different from [his/her] usual self?" or "In the past 6 months, was there a time when [he/she] seemed very sure of [him/herself] for no good reason, like [he/she] could do anything and it would work out?" Hereafter, this construct will be referred to as "DISC mania proxy." The second proxy, hereafter referred to as "CBCL mania proxy," was based on a response pattern on CBCL T scores that several authors have found characterize children with bipolar disorder (Biederman et al. 1995; Carlson and Kelly 1998; Dienes et al. 2002; Geller et al. 1998; Hazell et al. 1999). Biederman et al. found that severity of T scores discriminated children with mania from those with ADHD (Bieder-man et al. 1995). Additionally, there appeared to be a characteristic pattern of T scores greater than 70 in the aggressive behavior, anxious/ depressed, and attention categories. In that all children in our study by definition had inattention problems, the inattention factor was not expected to distinguish those with manic symptoms from those without, and its use might confound severity of ADHD with the mania proxy. Therefore, our CBCL mania proxy included the children who had T scores greater than 70 on both the anxious/depressed and aggressive subscales.

Exclusion criteria and bipolar disorder

The original intent of the MTA was to study children with ADHD regardless of comorbid disorders, with the exception of children who had comorbid bipolar disorder, schizophrenia, or autism. In actuality, the exclusion of subjects with bipolar disorder was not implemented. We reviewed the exclusion process to determine if children with bipolar disorder had been systematically excluded from the MTA sample. The screening process and exclusionary data are described in full in a previous article from the MTA (MTA Cooperative Group 1999a). Pertinent to our analysis is that neither parent report of bipolar disorder nor DISC diagnosis of mania was sufficient for exclusion. The steering committee was not confident in the DISC's ability to generate valid diagnoses of mania, and a research interview such as the Kiddie Schedule for Affective Disorders and Schizophrenia in School Age Children was beyond the capacity of the MTA. Additionally, we hypothesized that children with bipolar disorder might have taken antipsychotic medication in the 6 months prior to screening, an exclusion criteria for the study. We reviewed the data from the first two screening assessments, both a convenience sample of 1,614 phone screens and all of the 1,518 written screens. Of the phone screens reviewed, 4 of 1,614 participants (0.2%) were taking antipsychotic medication and were excluded from the study, but none of the subjects whose parents participated in the written screen had taken antipsychotic medication in the past 6 months. In summary, no one was excluded for a bipolar diagnosis;

however, a few potential participants were excluded for taking antipsychotic medication.

Statistical analysis

We compared baseline data of the proxy-positive and proxy-negative groups using a two-sample Student's *t* test for continuous variables and chi-square tests for nominal data. When chi-square was not valid due to cells with low counts, we used Fisher's exact test. We used random effects regression techniques to do the outcome analyses. Response variables were parent and teacher versions of the three CLAM subscales (I/O, A/D, I/O+A/D) and parent and teacher side-effect ratings. Fixed effects were: site, medication dose (placebo, low, medium, or high), mania proxy (either DISC mania proxy or CBCL mania proxy), and Medication Dose x Mania Proxy. Random effects were the parameters (intercept and slope) of the regression of the response on dose. Finding a Dose x Mania Proxy interaction would provide evidence that children with the proxy had a different response than nonproxy children with change in dose. When Medication Dose x Mania Proxy was significant, time was added to the model to control for the situation that participants might improve over the course of the titration trial, independent of their medication dose. This effect was added as a fixed effect. Graphic representations of CLAM responses were reviewed. The outcome score at each dose level was estimated based on the regression model where CLAM score, proxy, site, and dose are included in the model. For all analyses, because previous studies (March et al. 2000, MTA Cooperative Group 1999b) demonstrated that neither gender nor ethnicity impacted significantly on results, these two variables were not included as covariates. Statistical significance was set at $p < 0.05$, two-tailed.

Results

Baseline data

Five hundred seventy-nine 7- to 9.9-year-olds were randomized to one of the four treatment groups. Of the 289 subjects who were randomized to either MedMgt or Comb, 270 participated in the titration trial, and they make up our sample. There were 29 (10%) subjects who had the DISC mania proxy and 32 (11.1%) subjects who had the CBCL mania proxy. Seven participants satisfied criteria for both proxies. The degree of agreement between the proxy measures was low (kappa = 0.14)

Baseline characteristics were compared between proxy-positive and proxy-negative groups and are shown in Table 1. For the DISC mania proxy and CBCL mania proxy positive and negative groups, there are no significant differences for age, gender, and IQ. The children

	DISC mania proxy			CBCL mania proxy		
	Positive	Negative		Positive	Negative	
Variable	(n=29)	(n=260)	Significance[a]	(n=32)	(n=257)	Significance[a]
Age in years	7.7	7.8	0.09	7.9	7.8	0.40
Male *n* (%)	24 (83)	208 (80)	0.72	28 (88)	194 (79)	0.28
Female n (%)	5 (17)	51 (20)	—	4 (13)	51 (21)	—
Ethnicity n (%)						
Caucasian	16 (55)	162 (63)	0.45	20 (63)	155 (64)	0.93
African American/Black	11 (38)	42 (16)	0.004	5 (16)	42 (17)	0.83
Non-Black Hispanic	1 (3)	20 (8)	0.71	1 (3)	18 (7)	0.37
Black Hispanic	1 (3)	4 (2)	0.41	0	4 (2)	1.0
Asian American/ Pacific Islander	0	1 (0)	1.0	0	1 (0)	1.0

Mixed	0	27 (10)	0.09	5 (16)	22 (10)	0.22
Other	0	3 (1)	1.0	1 (3)	2 (1)	0.31
Household income	$20–40000	$30–50000	0.05	$30–50000	$30–50000	0.29
WISC-III IQ mean						
Verbal	100.8	99.8	0.74	99.5	100.0	0.88
Performance	101.6	100.7	0.76	98.3	100.9	0.37
Full Scale	101.1	100.1	0.72	98.7	100.3	0.56
SNAP parent mean score						
Inattention	2.14	2.06	0.52	2.43	2.02	0.000
Hyperactive/Impulsive	2.09	1.89	0.11	2.36	1.85	0.000
ODD	1.92	1.37	0.000	2.27	1.32	0.000
SNAP teacher mean score						
Inattention	2.13	2.21	0.51	2.32	2.19	0.02
Hyperactive/Impulsive	2.09	1.96	0.38	2.32	1.92	0.001
ODD	1.61	1.32	0.11	1.72	1.30	0.26
Family history n (%)						
ADHD	14 (50)	98 (39)	0.25	15 (47)	93 (39)	0.41
Alcohol abuse	15 (52)	125 (49)	0.75	17 (53)	122 (50)	0.77
Drug use	13 (45)	94 (37)	0.39	13 (41)	91 (38)	0.75
Depression	18 (62)	91(36)	0.006	13 (40)	96 (40)	0.98
Manic depression	2 (7)	15 (6)	0.69	1 (3)	16 (7)	0.70

ADHD = attention deficit hyperactivity disorder; CBCL = Child Behavior Checklist; DISC = Diagnostic Interview Schedule for Children; ODD = oppositional defiant disorder symptom subscale; SNAP = ADHD symptom rating scale named for developers of the scale; WISC-III = Wechsler Intelligence Scale for Children–Third Edition.

[a]Continuous characteristics compared with independent t test; nominal data measured using chi-square and Fisher 's exact test.

Table 1. Baseline Characteristics of the Sample (N = 289)

in the DISC mania proxy group were more likely to be African American and have a lower household income. Children with the proxies were more symptomatic at baseline on a number of the ADHD symptoms as measured by the SNAP. Specifically, participants who were positive for the DISC proxy scored higher on parent-rated ODD, and participants with the CBCL proxy were more symptomatic on parent-rated scores of inattention, hyperactivity/impulsivity, and ODD and teacher scores of inattention and hyperactivity/impulsivity. There were no significant differences in family history of psychiatric illness by parent report, with the exception of depression, which was more frequent in the DISC mania proxy positive group than the DISC mania proxy negative group.

On the DISC, four (1.4%) subjects were diagnosed with mania, three (1.0%) subjects with hypomania, and none with cyclothymia or bipolar II. The comorbidities in each proxy group, as diagnosed by the DISC, are described in Table 2.

Interestingly, children with either mania proxy were more likely to have DISC diagnoses of generalized anxiety disorder, obsessive-compulsive disorder, major depressive disorder, dysthymia, and conduct disorder. In addition, participants with the CBCL mania proxy were also more likely to have agoraphobia and any tic disorder (diagnosis of at least one of the following: chronic motor tic, chronic vocal tic, transient tic disorder), and those with the DISC mania proxy were more likely to have social phobia, bipolar disorder, and conduct disorder.

Parent and teacher ratings of behavior using the DISC mania proxy

Table 3 shows the mean ratings on the CLAM outcomes at each dose and also represents

the results from the random regression analyses. For both the parent- and teacher-rated ADHD symptoms, the analysis yields significant medication dose effects for all measures, indicating that participants were less symptomatic with higher doses of medication. There were no significant DISC mania proxy effects or DISC Mania Proxy Medication Dose interactions for all subscales, meaning there were no significant differences on CLAM measures between children with and without the proxy and that participants with the DISC mania proxy did not have a different degree of improvement with increasing dose.

Parent and teacher behavior ratings using the CBCL mania proxy

Table 3 also shows the mean ratings for the three symptom subscale scores from the CLAM for the participants with and without the CBCL mania proxy and the results from the random regression analyses. For the parent- and teacher-rated outcomes of home behavior, the analysis yielded significant dose effects on all three measures (I/O, A/D, and I/O+A/D); CBCL mania proxy effects on parent-rated A/D, I/O, and I/O+A/D, and teacher-rated A/D. In other words, increased dose led to improvement on all subscales, and the CBCL proxy positive participants were more impaired on four of six subscales. Additionally, for teacher-rated A/D, there was a CBCL Mania Proxy Dose interaction, meaning proxy participants improved more than the nonproxy participants as a function of medication dose. However, when time was added to the model, this difference was no longer significant. Both parent-rated A/D+I/O and teacher-rated A/D are shown graphically in Fig. 1, where the CLAM outcome at each dose level is estimated based on the regression model. Note that both are significant for dose, parent-rated A/D+I/O is significant for proxy (as demonstrated by the higher scores in the proxy group), and teacher-rated A/D is significant for Dose Proxy effects, as illustrated by the different slopes.

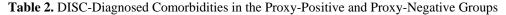Adverse events related to methylphenidate

Overall side effects.

Four subjects were removed during the lead-in period due to prohibitive side effects as described by Greenhill and colleagues (Greenhill et al. 2001). One child had buccal movements, one had skin picking, another
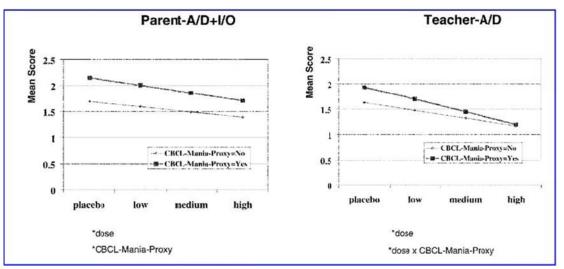
Diagnosis	DISC mania proxy, n (%)			CBCL, n (%)		
	Positive	Negative	Significance	Positive	Negative	Significance
Any anxiety disorder	20 (69)	94 (36)	0.0006	16 (50)	95 (39)	0.22
Simple phobia	3 (10)	31 (12)	1.0	7 (22)	26 (11)	.08
Social phobia	10 (34)	41 (16)	0.01	5 (16)	45 (18)	0.81
Panic disorder	0	0	NS	0	0	NS
Agoraphobia	1 (3)	4 (2)	0.41	3 (9)	2 (1)	0.01
GAD	7 (24)	13 (5)	0.002	5 (16)	12 (5)	0.03
OCD	4 (14)	4 (2)	0.004	3 (9)	4 (2)	0.04
SAD	4 (14)	32 (12)	0.77	6 (19)	29 (12)	0.36
Any tic disorder	6 (21)	23 (9)	0.05	8 (25)	21 (9)	0.01
Tourette's disorder	1 (4)	1 (0)	0.19	0	2 (1)	1.0
MDD	7 (24)	3 (1)	>0.0001	5 (13)	4 (2)	0.001
Dysthymia	7 (24)	1 (0)	>0.0001	3 (9)	4 (2)	0.04
Mania (bipolar disorder)	2 (7)	2 (1)	0.05	1 (3)	3 (1)	0.39
Hypomania	1 (3)	2 (1)	0.27	3 (1)	0	1.0
Bipolar II	0	0	NS	0	0	NS
Cyclothymia	0	0	NS	0	0	NS

Any DBD	25 (86)	126 (48)	0.0001	25 (78)	121 (49)	0.002
Conduct disorder	9 (31)	34 (13)	0.02	11 (34)	31 (13)	0.003
ODD	16 (55)	92 (35)	0.04	14 (44)	90 (37)	0.44

Any anxiety disorder = diagnosis of at least one of the following: simple phobia, social phobia, agoraphobia, generalized anxiety disorder; Any DBD = diagnosis of conduct disorder or oppositional defiant disorder; Any tic disorder = diagnosis of at least one of the following: chronic motor tic, chronic vocal tic, transient tic disorder; DBD = disruptive behavior disorder; GAD = generalized anxiety disorder; MDD = major depressive disorder; NS = not significant; OCD = obsessive-compulsive disorder; ODD = oppositional defiant disorder; SAD = separation anxiety disorder.

[a]Significance determined using chi-square test and Fisher's exact test.

Table 2. DISC-Diagnosed Comorbidities in the Proxy-Positive and Proxy-Negative Groups

Fig. 1. CLAM Outcomes 3 Dose for CBCL mania proxy positive and CBCL Mania proxy negative participants. "Low" indicates dose of 5/5/5 mg, "medium" indicates dose of 10/10/5 mg, "high" indicates dose of 15/15/5 mg for children less than 25 kg and 20/20/10 mg for children 25 kg and greater. A/D = Aggressive/Defiant subscale; A/D + I/O = mixed Aggressive/Defiant and Inattentive/Overactive subscale; CBCL = Child Behavior Checklist; CLAM = Conners, Loney, and Milich attention deficit hyperactivity disorder symptom scale.

Informant/subscale	Presence of proxy	Placebo	Low MPH dose (5/5/5 mg)	Middle MPH dose (10/10/5 mg)	High MPH dose[a] (15/15/5 mg or 20/20/10 mg)	Dose × proxy interaction		
						F	df	p
Parent								
CLAM I/O[b]	DISC+	1.86	1.58	1.51	1.43	0.25	1, 3662	0.62
	DISC−	1.77	1.56	1.48	1.41			
CLAM A/D[b]	DISC+	1.94	1.67	1.61	1.62	0.00	1, 3661	0.98
	DISC−	1.68	1.51	1.44	1.39			
CLAM mixed[b]	DISC+	1.88	1.67	1.59	1.53	0.00	1, 3663	0.98
	DISC−	1.79	1.56	1.50	1.44			
Teacher								
CLAM I/O[b]	DISC+	2.42	1.81	1.60	1.50	0.18	1, 2749	0.67
	DISC−	2.34	1.89	1.65	1.52			
CLAM A/D[b]	DISC+	1.93	1.59	1.25	1.31	0.85	1, 2748	0.36
	DISC−	1.70	1.42	1.27	1.21			
CLAM mixed[b]	DISC+	2.33	1.88	1.59	1.55	0.17	1, 2750	0.68
	DISC−	2.16	1.88	1.58	1.46			
Parent								
CLAM I/O[b,c]	CBCL+	2.16	1.82	1.69	1.64	2.09	1, 3619	0.15
	CBCL−	1.73	1.53	1.45	1.39			
CLAM A/D[b,c]	CBCL+	2.22	1.98	1.79	1.81	0.19	1, 3618	0.34
	CBCL−	1.64	1.46	1.42	1.36			
CLAM mixed[b,c]	CBCL+	2.22	1.92	1.81	1.71	2.28	1, 3620	0.13
	CBCL−	1.74	1.53	1.47	1.42			
Teacher								
CLAM I/O[b]	CBCL+	2.35	1.96	1.65	1.50	0.20	1, 2734	0.66
	CBCL−	2.34	1.87	1.65	1.52			
CLAM A/D[b,c]	CBCL+	2.10	1.67	1.40	1.28	4.0	1, 2732	0.05
	CBCL−	1.68	1.41	1.26	1.21			
CLAM mixed[b]	CBCL+	2.42	1.92	1.70	1.69	1.94	1, 2734	0.16
	CBCL−	2.15	1.80	1.57	1.51			

A/D = Aggressive/Defiant; CBCL = Child Behavior Checklist; CLAM = 16-item Conners, Loney, and Milich scale for attention deficit hyperactivity disorder symptoms; DISC = Diagnostic Interview Schedule for Children; I/O = Inattentive/Overactive; MPH = methylphenidate.

[a]The 198 children weighing 25 kg or more received an upper titration of MPH dose of 20/20/10 mg, while the 58 weighing less than 25 kg received an upper MPH titration dose of 15/15/5 mg.

[b]Significant medication dose effects.

[c]Significant proxy effects.

Table 3. Summary Subscale Scores while Receiving Placebo, Low, Middle, and High Doses of Methylphenidate for Participants with and Without the DISC Mania Proxy and CBCLMania Proxy

had depressed mood, crying, sleep delay, and appetite loss; and the last had anorexia, listlessness, and emotional constriction. There was no association of either proxy group with removal during the lead-in period due to side effects. No children were removed due to prohibitive irritability or psychotic symptoms. During the double-blind titration period, no children were removed from the MPH treatment group due to prohibitive side effects.

For this study, we report on those adverse events that reflect irritability, mood symptoms, and possibly mania. These include parent and teacher reports of crabbiness, tearfulness, and worrying and parent reports of trouble sleeping. Using the DISC mania proxy, there were significant dose effects for teacher-rated crabbiness and worry (which both decreased with increasing dose) and parent-rated trouble sleeping (which increased with increasing dose). There were no significant proxy effects. There was a Dose DISC Mania Proxy interaction for parent-rated worrying where parent ratings for the DISC proxy group improved with increasing doses, $F(1, 3629) = 3.93$, $p < 0.05$. This difference remained when time was added to the model,

$F(3, 738) = 4.29$, $p = 0.005$. For the CBCL mania proxy, there were medication dose effects for teacher-rated crabbiness (decreasing with increasing dose) and trouble sleeping (increasing with increasing dose) and proxy effects of parent-rated worry (participants with proxy were more symptomatic). There were no Dose Proxy interactions, meaning that proxy-positive subjects respond similarly to proxy-negative subjects with higher doses of medication.

Discussion

Summary

      Our main findings are as follows:

1. In a large sample of children with well-characterized ADHD, parent-DISC-diagnosed bipolar disorder is rare (1.4%). However, children with manic symptoms were more common. Ten percent of children had the DISC mania proxy, and 11.1% of children had the CBCL mania proxy. Children with either mania proxies were more likely to have comorbid illness as diagnosed by the DISC.

2. Children with ADHD with symptoms of mania, not fulfilling full criteria for bipolar disorder, responded well to MPH during a 1-month titration trial. Children with the mania proxy responded the same on ADHD symptom scales, improving on measures of attention, impulsivity, and aggression.

3. During the titration trial, proxy subjects responded similarly to nonproxy subjects with respect to side effects. They did not have more irritability or more adverse effects in response to stimulants and were not more likely to discontinue medication due to side effects. However, children with DISC mania proxy had a decrease in parent-reported worry compared to those without the proxy.

Limitations

      There are limitations to this study. First, the MTA was not originally designed to examine children with ADHD and manic symptoms. It is possible that some potential participants with ADHD and manic symptoms were excluded through the screening process because subjects were excluded if they had been treated with antipsychotic medication in the last 6 months, were currently hospitalized, had missed one fourth of school days in the past 2 months, or were suicidal.

      Second, due to the low number of participants with manic symptoms, the study had limited power. This may have altered our capacity to show further differences in treatment and side-effect outcomes between the DISC mania proxy positive and negative groups.
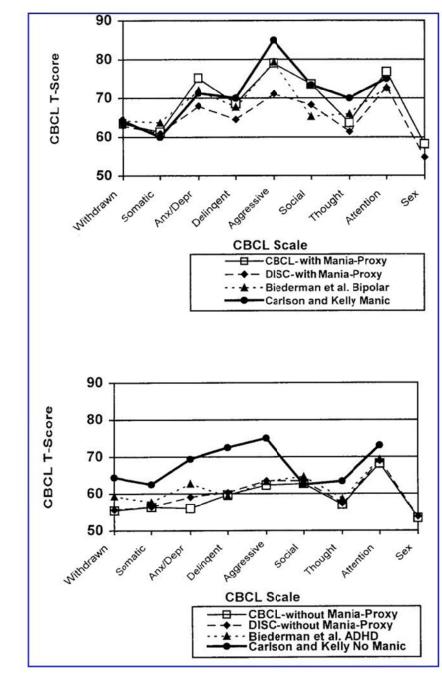
      Third, the results from our study may not generalize to other ADHD treatment settings. One could argue that the participants, all volunteers, may have been healthier than those seen in other tertiary care settings. This, in addition to our exclusion criteria, could explain why our sample had less bipolar comorbidity than described by other authors. For example, Biederman and colleagues described a sample of children with ADHD drawn from a variety of outpatient settings and found that 11% had bipolar disorder (Biederman et al. 1996), compared to the 1.4% of our subjects. Alternatively, differences in rates of bipolar disorder might be due to variation in assessment, qualifications for caseness, and inclusion of bi-polar variants. It should be noted that our patients were referred from a variety of sources including private practitioners, pediatricians, advertisements, advocacy groups, and tertiary care referrals, so our findings might be expected to approximate what might be found in an outpatient university setting.

      To compare the children from the MTA trial to participants examined by other authors, we

compared the CBCL *T* score profiles of our participants to those studied by Biederman et al. (1995) and to those studied by Carlson and Kelly (1998). Our intent was to see how the MTA subjects may have differed from those seen at the outpatient clinic of a tertiary medical care center where there has been a high report of prepubertal bipolar disorder and to those seen in inpatient settings (see Fig. 2).

The participants from the MTA who were positive for the CBCL mania proxy had similar profiles to the bipolar children described by Biederman and colleagues and Carlson and Kelly, as did the DISC mania proxy positive subjects, but to a lesser degree. However, the

Fig. 2. Mean *T* scores on CBCL clinical scales, from MTA, Biederman et al. (1995), and Carlson and Kelly (1998). (A) Participants with manic symptoms or mania proxy. (B) Participants without manic symptoms or

similarity between the CBCL mania proxy group and other authors' bipolar participants is not surprising, as this proxy was defined to capture participants with similar CBCL profiles. The CBCL mania negative and DISC mania negative participants were similar to the Biederman and colleagues ADHD subjects. Additionally, mean T scores were significantly different between the proxy-negative and proxy-positive groups in all the scales, with the exception of sex problems in the DISC group (data not shown). Interestingly, the MTA participants with manic symptoms had similar profiles to those described by Biederman and colleagues and, as our study shows, responded as well to stimulants as those without manic symptoms in this 1-month titration trial. This lack of adverse effects has also been shown in sicker children who have been admitted to the hospital. Carlson and Kelly (1998) compared the response to stimulants in inpatient children with ADHD with and without manic symptoms and found that there was a statistically significant yet clinically mild improvement in both groups.

A fourth limitation to our study stems from the lack of valid instruments to assess children with ADHD and manic symptoms. More accurate measurement tools and definitions are needed for children with comorbid ADHD and bipolar disorder and ADHD with manic symptoms. We are unaware of measures that look specifically at children with ADHD and manic symptoms. We adapted two instruments to identify children with some manic symptoms. However, the instruments had not been validated for these purposes. The degree of agreement between the two proxies was remarkably low, suggesting limitations with one or both of these measures. Additionally, we analyzed the data using a third proxy that combined the above-mentioned proxies using an "or" rule. Our results were similar (data available on request). Researchers are trying to create measures that will differentiate children with bipolar disorder from children with ADHD (Geller et al. 2002). Similarly, Geller and colleagues have reported acceptable reliability with the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (Geller et al. 2001). However, diagnosing mania with structured interviews has been problematic even in adults (Kessler 1997). There is a great need for improved and consistent measurement tools for children with ADHD and manic symptoms, ADHD and comorbid bipolar disorder, and bipolar variants such as bipolar disorder not otherwise specified.

A fifth limitation is that this study only examines data from the 1-month titration trial. Therefore, we are only able to draw conclusions about brief treatment with stimulants, albeit one which differs from real-world practice. We did not examine the effects of longer treatments or long-term effects. The analysis does not address the concern that children with subsyndromal symptoms of bipolar disorder or children with ADHD and manic symptoms might respond well to stimulants initially but develop an adverse reaction over time. Similarly, we are not able to predict long-term outcome from this 1-month analysis. Our group will later be examining participants' responses at 14 and 24 months. A theoretical sixth limitation is the nature of the titration trial, with random daily dose switching and intermittent placebo, different from the usual no-placebo escalating clinical titration. This might conceivably make a difference in elicitation or aggravation of manic symptoms, though we doubt it.

Recommendations

Children with perceived ADHD and manic symptoms need a thorough evaluation to establish the presence or absence of ADHD and comorbid diagnoses. Children with ADHD and manic symptoms may benefit from a carefully monitored MPH trial. Our study did not look

specifically at children with ADHD and bipolar disorder. Such studies are still needed. Studies that examine the response to stimulants of children with ADHD and manic symptoms over longer courses of treatment are needed. Our group intends to examine this in subsequent studies. Prospective studies of children with ADHD as adults do not show an increased rate of mood disorders (Mannuzza et al. 1998) or *Diagnostic and Statistical Manual of Mental Disorders,* third edition (American Psychiatric Association 1980) diagnoses except antisocial personality disorder (Weiss et al. 1985). However, future studies that examine children with ADHD in spite of comorbidities, in particular, classic mood disorders using *Diagnostic Statistical Manual of Mental Disorders,* fourth edition (American Psychiatric Association 1994), criteria and bipolar variants, are needed. There is a similar need for prospective research examining what long-term risks if any may be associated with treatment of stimulants in these populations.

Acknowledgments

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