ORIGINAL ARTICLE

Long-term Methylphenidate Therapy in Children With Comorbid Attention-Deficit Hyperactivity Disorder and Chronic Multiple Tic Disorder

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Background: This study examined changes in attention-deficit hyperactivity (ADHD) behaviors and motor and vocal tics during long-term treatment with methylphenidate.

Methods: Thirty-four prepubertal children with ADHD and chronic multiple tic disorder (who had participated in an 8-week, double-blind, placebo-controlled methylphenidate evaluation) were evaluated at 6-month intervals for 2 years as part of a prospective, nonblind, follow-up study. Treatment effects were assessed using direct observations of child behavior in a simulated (clinic-based) classroom and behavior rating scales completed by parents and physician. Videotapes of the simulated classroom were scored by coders who were blind to treatment status.

Results: There was no evidence (group data) that motor tics or vocal tics changed in frequency or severity during maintenance therapy compared with diagnostic or initial double-blind placebo evaluations. Behavioral improvements demonstrated during the acute drug trial were maintained during follow-up. There was no evidence (group data) of clinically significant adverse drug effects on cardiovascular function or growth at the end of 2 years of treatment.

Conclusions: Long-term treatment with methylphenidate seems to be safe and effective for the management of ADHD behaviors in many (but not necessarily all) children with mild to moderate tic disorder. Nevertheless, careful clinical monitoring is mandatory to rule out the possibility of drug-induced tic exacerbation in individual patients.

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ONE OF THE most significant clinical implications of motor and vocal tics in children is their association with attention-deficit hyperactivity disorder (ADHD), because the most popular treatment for ADHD, stimulant medication,[1] is purported to exacerbate tics.[2-4] Because the evidence supporting this observation consists mostly of uncontrolled case reports, some researchers questioned the alleged pervasiveness of stimulant-induced tic exacerbation and the notion that these medications were contraindicated for this clinical population.[5] However, it was not until the results of controlled studies conducted by several different research teams were published that perceptions of safety and efficacy began to change.[6-14] It is now generally accepted that methylphenidate and dextroamphetamine are safe and effective treatments for ADHD in many (but not necessarily all) children with comorbid tic disorder.[15] Nevertheless, an early report that stimulant medication can exacerbate tics during maintenance treatment,[2] a recent uncontrolled study suggesting that tics improve when drug therapy is withdrawn,[16] the stated preference for nonstimulant medications as the initial treatment for ADHD symptoms,[16] and the opinion of some experts[4] that there are "strong indications that stimulants pose a serious risk of tic symptom exacerbation" keep this controversy alive.

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The primary objective of the present study is to determine if long-term exposure to methylphenidate results in increased tic frequency or severity. Subjects are prepubertal children who were referred to a child psychiatry outpatient service and who participated in an 8-week controlled trial of methylphenidate and placebo. After the establishment of an initial maintenance dose based on operationally defined decision rules, their clinical progress was prospectively monitored with a rigorous assessment battery that required clinical evaluations at 6-month intervals for 2 years.

RESULTS

HOW DID TREATMENT REGIMENS CHANGE OVER TIME?

The treatment regimens changed very little during the course of the study. Twenty-

SUBJECTS AND METHODS

SUBJECTS

Subjects were 34 children (31 boys, 3 girls) who were between the ages of 6.1 and 11.9 years (mean = 8.8 years, SD = 1.9 years) at time of diagnostic assessment and who met *DSM-III-R*[17] diagnostic criteria for ADHD and either chronic motor tic disorder or Tourette disorder (established on the basis of a clinical interview with the parent) and, in general, were above cutoff on 2 of 3 parent-completed and 2 of 3 teacher-completed hyperactivity and ADHD behavior rating scales. The parent-completed ADHD measures that were part of the diagnostic and subsequent follow-up evaluations included the Revised Conners' Parent Rating Scale,[18] the Child Symptom Inventory–3R (CSI-3R),[19,20] and the Mother's Method for Subgrouping (MOMS) checklist.[21] A comprehensive description of the study sample, including scores on the diagnostic measures, appears in an earlier publication.[9]

The tic measures completed by the physician at the diagnostic and subsequent follow-up evaluations included 4 subscales (Total Motor Tic score, Total Phonic Tic score, Overall Impairment Rating, Global Severity Score) from the Yale Global Tic Severity Scale (YGTSS),[22] which focused on tics and not comorbidities, the Tourette Syndrome Clinical Global Impression Scale (TS-CGI),[23] the Shapiro Tourette Syndrome Severity Scale,[24] 3 subscales from the Tourette Syndrome Unified Rating scale,[25] total number of tics, number of tics observed in 2 minutes of quiet conversation with the physician, the LeWitt Disability Scale, which assesses tics and the symptoms of comorbidities, and the Global Tic Rating Scale (GTRS).[26] Obsessive-compulsive symptoms were assessed with the Clinical Global Impression Scale–Obsessive-Compulsive Disorder (CGI-OC).[27] All children met research diagnostic criteria[28,29] for Tourette syndrome, either definite (n = 22) or by history (n = 12).

Subjects received placebo and 3 doses of methylphenidate (0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg) for 2 weeks each during a short-term dose trial. Each medication-treated child experienced a marked diminution in ADHD symptom severity when receiving methylphenidate compared with placebo.[8,9] A minimal effective dose (MED) was determined by calculating the percentage of improvement compared with placebo and changes in tic status during the course of the medication evaluation.[9,30]

PROCEDURE

After the MED was established, each child and at least 1 parent was required to return to the clinic every 6 months for a thorough follow-up evaluation of clinical status. Follow-up evaluations included the aforementioned parent- and physician-completed rating scales and a clinical status questionnaire. Parents were asked to rate their child's behavior during the previous 2 weeks using the MOMS, Peer Conflict Scale,[31,32] GTRS, and the Stimulant Side Effects Checklist (SSEC),[32,33] and during the previous 2 months using the Revised Conners' Parent Rating Scale and the CSI-3R. Clinician tic measures focused on symptoms during the previous 2 weeks.

During the follow-up visit, the child was involved in a videotaping session in a simulated classroom[34] and a continuous performance test[35-37] evaluation. Child testing began approximately 1.5 hours after administration of medication. In the simulated classroom, the child sits alone at a desk in a small classroom and is instructed to complete worksheets and not to play with toys on an adjacent table. Clinic sessions are videotaped to facilitate ease of scoring. The 15-minute observation sessions are divided into 180 five-second intervals, and behaviors are coded as either present or not present in each interval. The 3 ADHD behaviors were On Task, Fidgeting, and Worksheets. To code the frequency of motor tics, 2 experienced raters reviewed a list of the child's known tics and coded the diagnostic session. The 2 coders plus a third judge then met and reached a consensus on the identity of each tic (tic inventory). If interrater reliability for the diagnostic session was below criterion ($\kappa < .60$), the diagnostic tape was recoded until the minimum reliability criterion was met. All remaining study conditions were then evaluated by the primary coder, and approximately one fourth were scored by the secondary coder to assess reliability. Although the coders used the tic inventory as a guide, any new tics that emerged during the drug evaluation were also coded. The overall κ was .71 for all conditions.

During the course of the follow-up study, attrition was limited. At 2-year follow-up, 2 subjects were no longer available for data collection as a result of moving to another state, and 2 were no longer interested in participating in the study (medication discontinued). (One additional child failed to show up for his appointment.) The number of subjects at each follow-up visit/number receiving stimulants was as follows: first visit (28/27), second visit (33/30), third visit (29/26), and fourth visit (29/26). Because the first 6 subjects were not scheduled for a 6-month follow-up, this condition was not included in the analyses. A total of 27 subjects attended each of the remaining 3 follow-up visits.

STATISTICAL ANALYSES

For all measures, the initial diagnostic, placebo, MED, and 3 follow-up treatment conditions were analyzed with 1-way repeated-measures analyses of variance (ANOVAs). Given our concern about the possibility of making a type II error (ie, erroneously concluding that methylphenidate did not have an adverse effect on tics), individual repeated-measures ANOVAs were conducted for each tic measure. Subject attrition (although limited), combined with the fact that a few children had discontinued taking medication, resulted in uneven numbers of subjects at the different time points. Several ANOVAs were therefore conducted using restricted maximum likelihood estimation to compute the between- and within-subject variance estimates because these provide superior estimates (as compared with ordinary least squares) for unbalanced data. Post hoc Tukey honestly significant difference tests were performed to localize differences between conditions ($P < .05$). For the diagnostic visit, we report comparisons only with the placebo condition. A modified Bonferroni correction was applied to comparisons of the tic measures.

Age was significantly correlated with ADHD performance scores for the simulated classroom and was therefore controlled in subsequent analyses of these measures. Age was not, however, significantly correlated with parent ratings.

For the heart rate, blood pressure, weight, and height measurements, data were not available for the first 11 subjects at diagnostic evaluation. However, because there were no significant differences between diagnostic visit and placebo for these measures, diagnostic visit was not a condition in these analyses.

Table 1. Means (SDs) and Analyses of Variance for Observations and Ratings of Motor and Vocal Tics

Measure	Diagnostic	Placebo	MED	Follow-up 2 (12 mo)	Follow-up 3 (18 mo)	Follow-up 4 (24 mo)	F	*P*
Physician ratings								
YGTSS								
Total Motor Tics	13.9 (3.3)	11.4 (3.9)	12.1 (4.1)	12.2 (3.7)	13.0 (3.0)	12.6 (3.5)	4.74	<.001
Total Phonic Tics	11.2 (3.8)	7.9 (4.9)	7.6 (7.5)	8.1 (4.7)	8.3 (5.4)	8.0 (4.7)	3.31	.007
Overall Impairment Rating	19.5 (14.0)	7.6 (8.4)	9.7 (10.4)	9.4 (10.1)	10.2 (9.6)	8.5 (10.8)	9.91	<.001
Global Severity Score	42.9 (16.7)	26.5 (15.1)	27.1 (16.5)	30.0 (16.7)	31.3 (15.4)	29.9 (17.0)	8.55	<.001
STSSS	2.9 (1.3)	1.6 (0.8)	1.8 (0.9)	2.0 (1.1)	1.9 (1.1)	1.9 (1.2)	9.91	<.001
TS-CGI	2.6 (0.7)	3.1 (0.4)	3.1 (0.4)	2.3 (0.6)	2.4 (0.6)	2.3 (0.7)	30.62	<.001
TS Unified Rating Scale								
Shapiro Symptom Checklist								
No. of Motor Tics	13.2 (7.6)	11.7 (6.3)	12.0 (5.0)	12.8 (6.3)	14.0 (4.6)	13.4 (4.1)	1.59	.17
No. of Vocal Tics	5.0 (4.0)	3.1 (2.8)	2.5 (2.8)	2.9 (2.1)	2.8 (2.2)	2.5 (2.0)	5.86	<.001
2-Minute Tic Count								
Motor Tic Count	10.0 (8.0)	9.5 (7.1)	13.8 (14.0)	14.4 (9.1)	18.1 (15.1)	17.2 (13.7)	4.90	<.001
Vocal Tic Count	1.1 (2.6)	0.6 (0.8)	0.4 (0.5)	1.1 (0.3)	1.3 (1.0)	1.5 (1.4)	2.65	.03
GTRS								
Motor Tic Index	4.8 (1.4)	4.9 (1.0)	5.0 (1.1)	5.0 (1.3)	4.8 (1.2)	4.8 (1.1)	0.20	.96
Vocal Tic Index	1.9 (1.2)	1.0 (0.7)	1.1 (0.5)	1.1 (0.9)	1.4 (1.0)	1.4 (1.0)	5.00	<.001
Tic Severity Index	3.2 (2.1)	1.4 (1.0)	1.8 (1.3)	2.2 (2.0)	2.5 (2.7)	2.6 (2.3)	3.09	.01
LeWitt Disability Scale	61.9 (13.6)	68.6 (11.8)	72.9 (9.8)	72.4 (11.5)	70.7 (10.3)	73.1 (8.5)	6.79	<.001
CGI-OC	2.7 (2.0)	1.6 (1.6)	1.8 (1.2)	1.7 (1.2)	1.9 (1.3)	1.8 (1.5)	4.24	.001
Parent ratings								
GTRS								
Motor Tic Index	3.7 (2.7)	2.2 (1.8)	2.4 (2.5)	3.2 (1.7)	2.5 (1.6)	2.4 (1.7)	2.57	.03
Vocal Tic Index	1.8 (1.6)	0.9 (1.0)	0.9 (1.1)	1.2 (1.3)	0.8 (1.1)	0.6 (0.8)	3.37	.007
Tic Severity Index	3.3 (3.1)	1.6 (1.8)	1.8 (2.1)	2.4 (2.8)	1.9 (1.9)	2.1 (2.3)	3.26	.008
Classroom observations								
Motor tic frequency	18.6 (12.8)	18.6 (13.2)	23.8 (20.7)	21.0 (17.3)	19.5 (21.4)	18.9 (18.4)	0.81	.54

**MED indicates minimal effective dose; YGTSS, Yale Global Tic Severity Scale[22]; STSSS, Shapiro Tourette Syndrome Severity Scale[24]; TS-CGI, Tourette Syndrome Clinical Global Impression Scale[23]; TS, Tourette syndrome; GTRS, Global Tic Rating Scale[26]; and CGI-OC, Clinical Global Impression Scale–Obsessive-Compulsive Disorder.[27]*

six of the children received stimulant medication throughout the follow-up interval, and of these children, 1 was switched to dextroamphetamine. In 3 cases, treatment was terminated before the second follow-up visit owing to therapeutic improvement (n = 2) and concerns about tic exacerbation (n = 1), which a controlled trial with a reversal condition failed to confirm.[38] Four children were treated with an anti-tic medication in combination with methylphenidate at some time during the course of the follow-up (neuroleptic [n = 3] and clonidine [n = 1]). Two of these children were receiving anti-tic medication prior to the short-term dose trial, which was later reinstated throughout the entire follow-up interval, and 2 children began receiving anti-tic medication between the third and fourth follow-up.

The mean morning dose of methylphenidate (laboratory assessments) for each condition was as follows: MED (0.3 mg/kg, mean = 8.3 mg, range = 2.5-20 mg); second visit (0.4 mg/kg, mean = 13.2 mg, range = 8-25 mg); third visit (0.4 mg/kg, mean = 13.3 mg, range = 5-30 mg); and fourth visit (0.4 mg/kg, mean = 16.2 mg, range = 8-40 mg). The total daily dose of methylphenidate was as follows: MED (mean = 16.5 mg, range = 5-40 mg); second visit (mean = 28.5 mg, range = 15-60 mg); third visit (mean = 29.2 mg, range = 10-90 mg); and fourth visit (mean = 34.5 mg, range = 15-92 mg).

DOES METHYLPHENIDATE EXACERBATE TICS?

There were significant effects of condition for all but 2 physician-completed tic measures (**Table 1**). For almost every measure, tics were rated as being worse at the initial diagnostic visit than the placebo condition. (With the exception of the LeWitt Disability Scale, increasing mean values indicate a worsening in tic status.) Differences between these 2 conditions were significant for all measures except the 2-minute tic count and the LeWitt Disability Scale. Of the 56 post hoc comparisons between placebo and the 4 medication conditions, only 2 comparisons indicated that tics were worse on medication. Only 1 was significant with the modified Bonferroni correction, the 2-minute tic count (placebo vs fourth follow-up visit). Three comparisons (TS-CGI) indicated that tics were more severe during the placebo condition. Obsessive-compulsive symptoms were rated as being worse at the initial diagnostic visit than during the placebo condition, but none of the comparisons between placebo and the medication conditions were significant.

Analyses for the parent-completed GTRS were highly consistent with the physician scales (Table 1). In general, tics were rated as being worse at diagnosis than with placebo, but there were no significant differences be-

Table 2. Untransformed Means (SDs) and Analyses of Variance for Parent Behavior Rating Scales

	Diagnosis	Placebo	MED	Follow-up 2 (12 mo)	Follow-up 3 (18 mo)	Follow-up 4 (24 mo)	F	*P*
Parents (past 2 wk)								
MOMS								
Hyperactivity	4.1 (1.1)	2.9 (1.6)	2.3 (1.4)	3.0 (1.3)	2.4 (1.3)	2.6 (1.6)	7.54	<.001
Aggression	2.8 (1.8)	2.1 (2.0)	1.6 (1.6)	2.4 (1.9)	2.0 (1.9)	2.1 (2.0)	2.37	.04
Peer Conflict Scale	8.7 (6.3)	5.2 (4.8)	3.9 (3.6)	5.6 (4.1)	4.7 (4.7)	5.0 (5.8)	5.38	<.001
Parents (past 2 mo)								
Conners' Parent Rating Scale	18.7 (4.7)	11.3 (7.3)	9.5 (4.9)	12.3 (5.3)	11.7 (5.7)	11.0 (7.1)	11.62	<.001
CSI-3R								
ADHD	28.6 (6.4)	. . .	. . .	17.3 (7.2)	18.9 (7.5)	17.5 (10.6)	32.49	<.001
Oppositional	13.3 (7.6)	. . .	. . .	9.9 (5.9)	10.3 (4.7)	10.2 (7.2)	3.65	.02
Conduct	2.2 (3.1)	. . .	. . .	1.9 (2.7)	1.4 (2.3)	1.9 (3.4)	0.80	.50
Overanxious	6.4 (5.5)	. . .	. . .	4.0 (3.6)	5.4 (4.3)	2.5 (3.0)	9.00	<.001
MDD	4.4 (4.2)	. . .	. . .	2.5 (3.0)	2.6 (2.7)	2.9 (3.3)	5.91	.002
Avoidant	1.0 (1.2)	. . .	. . .	0.5 (0.9)	0.7 (1.1)	0.8 (1.2)	2.03	.12
Separation anxiety	3.6 (5.0)	. . .	. . .	2.1 (4.2)	1.1 (1.3)	1.5 (2.2)	5.81	.002
Classroom observations								
On Task	76.9 (20.0)	71.4 (29.1)	92.5 (7.9)	91.3 (12.1)	92.8 (11.9)	94.4 (8.40)	11.17	<.001
Fidgets	23.3 (16.6)	29.0 (19.3)	18.3 (18.4)	12.6 (15.3)	15.0 (15.3)	9.9 (9.82)	6.05	<.001
Worksheets	211 (103)	210 (118)	277 (116)	321 (122)	347 (127)	377 (125)	16.44	<.001
CPT								
Inattention	7.5 (7.0)	7.7 (6.0)	5.4 (6.6)	1.2 (1.6)	1.3 (2.3)	1.0 (2.0)	7.04	<.001
Dyscontrol	4.2 (6.2)	7.5 (9.8)	3.3 (5.3)	1.3 (1.9)	1.0 (2.4)	0.7 (1.0)	3.25	.008
Impulsivity	2.6 (4.7)	2.2 (3.2)	2.1 (4.9)	1.3 (3.3)	1.5 (4.2)	2.1 (8.2)	0.26	.93

**MED indicates minimal effective dose; MOMS, Mothers' Method for Subgrouping Checklist[21]; CSI-3R, Child Symptom Inventory–3R[19,20]; ADHD, attention-deficit/hyperactivity disorder; MDD, major depressive disorder; CPT, continuous performance task; and ellipses, not applicable.*

tween placebo and the follow-up conditions or among follow-up conditions.

Motor tic frequency in the simulated classroom did not vary as a function of treatment condition (Table 1). In fact, the mean frequency of tic occurrence at diagnosis and at placebo were nearly identical to the mean frequency of occurrence at the 2-year follow-up assessment. Not surprisingly, a paired *t* test comparing diagnostic visit and 2-year follow-up was not significant ($t_{28} = 0.36$, $P = .97$).

ARE TREATMENT GAINS FOR ADHD SYMPTOMS MAINTAINED OVER TIME?

There were significant effects of condition for most of the behavioral measures (**Table 2**). Diagnostic visit ratings of ADHD (Hyperkinesis Index, MOMS) and aggressive (Peer Conflict Scale) behaviors were significantly higher than placebo, but placebo ratings did not differ from the other conditions. The diagnostic ratings for the ADHD category of the CSI-3R were significantly higher than for all 3 follow-up conditions. The CSI-3R Symptom Severity scores indicated significant differences for 3 of the 4 mood and anxiety disorder symptom categories (Table 2). Scores for the diagnostic evaluation were significantly higher than those at the second follow-up visit; however, for only 1 symptom measure (Overanxious disorder category) were these differences still significant (Bonferroni correction) at the fourth follow-up visit.

Condition effects for the 3 simulated classroom ADHD measures (On Task, Fidgeting, Worksheets) were all highly significant (Table 2). Differences between diagnostic and placebo conditions were not significant. Children spent significantly more time on task during the medication conditions than placebo. With respect to fidgeting, placebo differed from all medication conditions. The number of worksheet items completed increased in a linear fashion with time; however, the only significant differences between conditions were the MED and the last 2 follow-up visits.

IS LONG-TERM EXPOSURE TO METHYLPHENIDATE ASSOCIATED WITH ADVERSE DRUG REACTIONS?

Condition effects were evident for systolic blood pressure ($F_{4,76} = 2.98$, $P = .02$) and heart rate ($F_{4,83} = 3.31$, $P = .01$), but not diastolic blood pressure ($F_{4,76} = 1.01$, $P = .41$). Examination of group means indicated increasing values over time for systolic blood pressure and heart rate. The only significant difference between conditions was for heart rate (higher at the fourth follow-up vs placebo).

To examine the possibility of less than expected growth, individual weight and height measurements were converted to percentiles based on growth tables.[39] The mean difference between expected (mean = 41.95 kg, SD = 15.58 kg) and actual (mean = 41.23 kg, SD = 16.20 kg) weight at the end of 2 years of treatment was only 0.72 kg, and this difference was not statistically significant ($t = 0.55$, $P = .59$). Similarly, the mean difference between expected (mean = 147.48 cm, SD = 11.74 cm) and actual (mean = 146.81 cm, SD = 13.22 cm) height at the end of

2 years of treatment was only 0.67 cm, and this difference was not statistically significant ($t = 0.58$, $P = .57$).

Parent-completed SSEC ratings were significant ($P<.05$) for all but the Somatic Complaints index, and there were significant differences between scores for the diagnostic evaluation and the placebo condition for all measures. Of the remaining 28 possible comparisons, the tic rating for the second follow-up was significantly higher than the placebo condtition ($P = .06$) and MED ($P = .003$).

COMMENT

The findings from this study do not support the notion that maintenance methylphenidate therapy results in exacerbation of either motor or vocal tics. In fact, direct observations of the frequency of motor tics in a simulated classroom prior to the onset of drug therapy and during the double-blind placebo condition are almost identical to observations conducted 2 years later. It is important to emphasize that the intended design of the study was to address the issue of potential tic exacerbation from the standpoint of group data (ie, is treatment ill-advised in this clinic population?), and not to verify possible tic exacerbations in individual children. This is best done with reversal designs, where the treatment condition that seemingly produces a worsening in tic symptoms is reintroduced at a later time to see if symptom exacerbation is replicable.[38]

Nevertheless, data plots for individual children show considerable fluctuations in the frequency and severity of tics in children who are receiving maintenance methylphenidate therapy, which strongly suggests that spontaneous exacerbations of tic disorder symptoms are a natural occurrence. Furthermore, these fluctuations in tic symptoms likely explain some (but not necessarily all) reports of stimulant-induced tic exacerbations in children with preexisting tic disorder.[38] The implications of this phenomenon for clinical management and the importance of research methodology in the conduct of drug trials are self-evident.

Treatment gains that were experimentally demonstrated in an 8-week controlled drug trial were still present at 2-year follow-up, and were most dramatically documented in the simulated classroom setting. The parent rating scales used in this study were less sensitive to initial treatment effects during the controlled trial,[9] and failed to show significant improvement between placebo and follow-up evaluations. Gillberg et al[40] also found continuing treatment gains in long-term (15 month), double-blind, randomized, parallel-group design (placebo vs amphetamine) study of children with ADHD but, as expected, attrition in the placebo group was considerable. An alternative strategy for documenting the maintenance of clinical gains during long-term therapy is a double-blind crossover to placebo.[41] To do this, we enrolled 19 children (a subsample of whom were participants in the present study) who had ADHD and chronic multiple tic disorder and who had received stimulant medication for a minimum of 1 year into a double-blind, placebo-controlled, medication withdrawal study.[42] When methylphenidate was substituted with placebo, there was significant deterioration in ADHD symptoms (but no change in tics). It should not be inferred, however, that continuing clinical improvement in children receiving long-term stimulant drug therapy implies complete normalization of behavioral symptoms, because the findings from our 8-week classmate comparison study indicate that at commonly prescribed doses of methylphenidate (0.5 mg/kg), many children still exhibit deviant levels of at least 1 problematic behavior.[12]

In contrast with continuing overall improvement in ADHD behaviors during the 2-year follow-up interval, global assessments of other psychiatric symptoms were less encouraging, although the mean severity of these symptoms remained lower at follow-up than during the initial diagnostic visit. For example, the behavioral symptoms of oppositional defiant disorder did not show continued improvement at the third follow-up, and the symptoms of conduct disorder showed no difference from initial assessment, possibly due to floor effects (ie, initial scores were very low). Improvement in mood and anxiety symptoms, which are fairly common in this clinical population,[43,44] were less dramatic at the fourth follow-up visit, with the exception of overanxious disorder symptoms. However, this category contains several symptoms that overlap with ADHD.

The dramatic decrease in symptom severity (both ADHD and tics) between diagnostic and placebo evaluations has been commented on in the literature for many years, at least with regard to ADHD behaviors. In our study, this "effect" was most evident in rating scales (ADHD, oppositional, and aggressive behaviors; motor and vocal tics; and adverse effects) but virtually nonexistent in our laboratory-based measures (eg, simulated classroom observations of ADHD and tic symptoms, continuous performance tasks, blood pressure, and heart rate). There are many different hypotheses that purport to explain this phenomenon,[45,46] one of which pertains to the time frame that serves as the basis for the rating.[47] Typically, the time frame for the diagnostic evaluation captures the rater's global impression of the child and is almost always retrospective, whereas treatment evaluations are typically anchored to a specific, relatively short time interval and are almost always prospective. Evidence for this interpretation is the difference between the physician's 2-minute tic count and the physician-completed rating scales for baseline and placebo conditions. The former are nearly identical for both conditions and are anchored to the same time frame, whereas the physician's ratings are not. The clinical significance of this phenomenon is considerable, and suggests that when placebo comparisons are not possible, clinicians should conduct baseline evaluations using the same procedure and time frame as are used for subsequent treatment conditions.[47]

There was little evidence of adverse drug reactions during long-term therapy. Parent SSEC ratings, which initially indicated a significant increase in somatic complaints for the 0.5-mg/kg dose in our short-term dose trial,[9] failed to show significant differences between placebo and follow-up evaluations. At the end of 2 years of treatment, there were only small changes in systolic (+6 mm Hg) and diastolic (−3 mm Hg) blood pressure compared with placebo. These assessments were made approximately 2 hours after medication was administered,

and are consistent with the 2-year follow-up evaluations of Satterfield et al[48] (tests conducted while subjects were not receiving medication), in that observed changes were of relatively small magnitude. The significant increase in heart rate (approximately 10 beats per minute) during follow-up is consistent with the findings from the short-term drug trial,[9] but is generally not considered to be clinically significant. Similarly, the slightly lower than expected weight (0.72 kg) and height (0.67 cm) gain at 2-year follow-up have been reported in many other studies,[49] and are of marginal concern for most children, at least at the doses used in this study.

Our findings are subject to several limitations. First, the 2-year follow-up component was not blind. Although the obstacles in creating and maintaining a long-term double-blind study with a placebo group are daunting,[40] the failure to do so does introduce the possibility of bias. Second, the absence of a no-treatment group does not allow inferences about natural changes in tic status over time. For example, it is possible that if left untreated, our sample may have actually experienced an improvement in tic symptoms. In this regard, it is noteworthy that Leckman et al[50] reported on developmental changes in tic severity in a retrospective follow-up study of 36 children and adolescents with Tourette syndrome. Based on parental recall of the age at which their child's tics were the most severe, these investigators describe a pattern of increasing tic severity from early childhood that peaked between age 10 and 11 years and then began to decline. Our sample, however, showed no change in tic severity (Global Severity Score of the YGTSS) between the ages of 7 to 12 years when the data were plotted by age. Collectively, the results of these 2 studies suggest that stimulant drug therapy may actually have a salutary effect on the natural history of chronic multiple tic disorder, a hypothesis for which there is some, albeit limited, support.[51-55] Third, the generalizability of our findings are limited by the size of the study sample and to children whose tics are primarily of mild to moderate severity.

We would be remiss in our responsibilities as clinical researchers if we did not state the all too infrequently heeded caveat that although these findings do contribute to our knowledge of pharmacotherapy for children with Tourette syndrome, they cannot and must not be misconstrued as certainty, and our results do not rule out the possibility of tic exacerbation in individual cases. Nevertheless, when compared with the scores of other medications that are prescribed for children with ADHD and chronic, multiple tic disorder, about which we know relatively little in terms of their effect on academic performance, peer interactions, and long-term exposure, one can at least take satisfaction in measured judgment when prescribing stimulant medication for these children.

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REFERENCES

1. Gadow KD. An overview of three decades of research in pediatric psychopharmacoepidemiology. *J Child Adolesc Psychopharmacol*. 1997;7:219-236.
2. Lowe TL, Cohen DJ, Detlor J, Kremenitzer MW, Shaywitz BA. Stimulant medications precipitate Tourette's syndrome. *JAMA*. 1982;247:1729-1731.
3. Golden GS. Tics and Tourette syndrome. *Hosp Pract*. 1979;14:91-100.
4. Peterson BS, Cohen DJ. The treatment of Tourette's syndrome: multimodal, developmental intervention. *J Clin Psychiatry*. 1998;59:62-72.
5. Shapiro AK, Shapiro E. Do stimulants provoke, cause or exacerbate tics and Tourette syndrome? *Comp Psychiatry*. 1981;22:265-273.
6. Castellanos FX, Giedd JN, Ella J, Marsh WL, Ritchie GF, Hamburger SD, Rapoport JL. Controlled stimulant treatment of ADHD and comorbid Tourette's syndrome: effects of stimulant and dose. *J Am Acad Child Adolesc Psychiatry*. 1997; 36:589-596.
7. Gadow KD, Nolan EE, Sverd J. Methylphenidate in hyperactive boys with comorbid tic disorder, II: short-term behavioral effects in school settings. *J Am Acad Child Adolesc Psychiatry*. 1992;31:462-471.
8. Gadow KD, Nolan EE, Sprafkin J, Sverd J. School observations of children with attention-deficit/hyperactivity disorder and comorbid tic disorder: effects of methylphenidate treatment. *J Dev Behav Pediatr*. 1995;16:167-176.
9. Gadow KD, Sverd J, Sprafkin J, Nolan EE, Ezor SN. Efficacy of methylphenidate for attention-deficit hyperactivity disorder in children with tic disorder. *Arch Gen Psychiatry*. 1995;52:444-455.
10. Konkol R J, Fischer M, Newby RF. Double-blind, placebo-controlled stimulant trial in children with Tourette's syndrome and attention-deficit hyperactivity disorder [abstract]. *Ann Neurol*. 1990;28:424.
11. Law S, Schachar R. Does methylphenidate cause tics [abstract]? In: *Scientific Proceedings of the Annual Meeting of the American Academy of Child and Adolescent Psychiatry*. Washington, DC: American Academy of Child and Adolescent Psychiatry; 1997;13:106.
12. Nolan EE, Gadow KD. Children with ADHD and tic disorder and their classmates: behavioral normalization with methylphenidate. *J Am Acad Child Adolesc Psychiatry*. 1997;36:597-604.
13. Sverd J, Gadow KD, Paolicelli LM. Methylphenidate treatment of attention-deficit hyperactivity disorder in boys with Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry*. 1989;28:574-579.
14. Sverd J, Gadow KD, Nolan EE, Sprafkin J, Ezor SN. Methylphenidate in hyperactive boys with comorbid tic disorder, I: clinic evaluations. In: Chase TN, Friedhoff A J, Cohen DJ, eds. *Tourette Syndrome: Genetics, Neurobiology and Treatment*. New York, NY: Raven Press; 1992:271-281.
15. Freeman RD. *The Use of Stimulant Drugs in Attention Deficit/Hyperactivity Disorder Combined With Tics or Tourette Syndrome*. Bayside, NY: Tourette Syndrome Association Inc; 1994.
16. Riddle MA, Lynch KA, Scahill L, deVries A, Cohen DJ, Leckman J. Methylphenidate discontinuation and reinitiation during long-term treatment of children with Tourette's disorder and attention-deficit hyperactivity disorder: a pilot study. *J Child Adolesc Psychopharmacol*. 1995;5:205-214.
17. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*. Washington, DC: American Psychiatric Association; 1987.
18. Goyette CH, Conners CK, Ulrich RF. Normative data on revised Conners' Parent and Teacher Rating Scales. *J Abnorm Child Psychol*. 1978;6:221-236.
19. Gadow KD, Sprafkin J. *Child Symptom Inventories Manual*. Stony Brook, NY: Checkmate Plus; 1994.
20. Grayson P, Carlson GA. The utility of a *DSM-III-R*–based checklist in screening child psychiatric patients. *J Am Acad Child Adolesc Psychiatry*. 1991;30:669-673.
21. Loney J. A short parent scale for subgrouping childhood hyperactivity and aggression. Presented at: the annual meeting of the American Psychological Association; August 1994; Toronto, Ontario.
22. Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, Cohen DJ. The Yale Global Tic Severity Scale: initial testing of a clinic-rated scale of tic severity. *J Am Acad Child Adolesc Psychiatry*. 1989;28:566-573.
23. Leckman JF, Towbin KE, Ort SI, Cohen DJ. Clinical assessment of tic disorder severity. In: Cohen DJ, Bruun RD, Leckman JF, eds. *Tourette Syndrome and Tic Disorders*. New York, NY: John Wiley & Sons; 1988:55-78.
24. Shapiro A, Shapiro E, Young J, Feinberg T. *Gilles de la Tourette Syndrome*. 2nd ed. New York, NY: Raven Press; 1988.

25. Kurlan R, Riddle M, Como P. *Tourette Syndrome Unified Rating Scale*. Bayside, NY: Tourette Syndrome Association Inc; 1988.
26. Gadow KD, Paolicelli L. *Global Tic Rating Scale*. Stony Brook, NY: State University of New York at Stony Brook; 1986.
27. Cohen DJ, Bruun RD, Leckman JF, eds. *Tourette's Syndrome and Tic Disorders*. New York, NY: John Wiley & Sons Inc; 1988.
28. Kurlan R. Tourette's syndrome: current concepts. *Neurology*. 1989;39:1625-1630.
29. Tourette Syndrome Workshop Committee on Classification and Rating Scales. *Report of the Tourette Syndrome Workshop on Definitions of Tic Disorders*. Bayside, NY: Tourette Syndrome Association Inc; 1988.
30. Gadow KD, Nolan EE, Paolicelli LM, Sprafkin J. A procedure for assessing the effects of methylphenidate on hyperactive children in public school settings. *J Clin Child Psychol*. 1991;20:268-276.
31. Gadow KD. Peer *Conflict Scale*. Stony Brook, NY: State University of New York at Stony Brook; 1986.
32. Gadow KD, Sprafkin J. *ADHD Symptom Checklist–4 Manual*. Stony Brook, NY: Checkmate Plus; 1997.
33. Gadow KD. *Stimulant Side Effects Checklist*. Stony Brook, NY: State University of New York at Stony Brook; 1986.
34. Roberts MA, Ray RS, Roberts RJ. A playroom observational procedure for assessing hyperactive boys. *J Pediatr Psychol*. 1984;9:177-191.
35. Halperin JM, Wolf LE, Pascualvaca DM, Newcorn JH, Healey JM, O'Brien JD, Morganstein A, Young G. Differential assessment of attention and impulsivity in children. *J Am Acad Child Adolesc Psychiatry*. 1988;27:326-329.
36. Halperin JM, Matier K, Bedi G, Sharma V, Newcorn JH. Specificity of in attention, impulsivity, and hyperactivity to the diagnosis of attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 1992;31:190-196.
37. Matier K, Halperin JM, Sharma V, Newcorn JH, Sathaye N. Methylphenidate response in aggressive and non-aggressive ADHD children: distinctions on laboratory measures of symptoms. *J Am Acad Child Adolesc Psychiatry*. 1992;31: 219-225.
38. Sprafkin J, Gadow KD. Four purported cases of methylphenidate-induced tic exacerbation: methodological and clinical doubts. *J Child Adolesc Psychopharmacol*. 1993;3:231-244.
39. Hamill Pr, Drizd TA, Johnson CL, Reed RB, Roche AF, Moore WM. Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr*. 1979;32:607-629.
40. Gillberg C, Melander H, von Knorring AL, Janols LO, Thernlund G, Hagglof B, Eidevall-Wallin L, Gustafsson P, Kopp S. Long-term stimulant treatment of children with attention-deficit hyperactivity disorder symptoms. *Arch Gen Psychiatry*. 1997;54:857-864.
41. Sleator EK, von Neumann AW, Sprague RL. Hyperactive children: a continuous long-term placebo controlled follow-up. *JAMA*. 1974;229:316-317.
42. Nolan EE, Gadow KD, Sprafkin J. Stimulant medication withdrawal during long-term therapy in children with comorbid attention-deficit hyperactivity disorder and chronic multiple tic disorder. *Pediatrics*. In press.
43. Nolan EE, Sverd J, Gadow KD, Sprafkin J, Ezor SN. Associated psychopathology in children with both ADHD and chronic tic disorder. *J Am Acad Child Adolesc Psychiatry*. 1996;35:1622-1630.
44. Pierre CB, Nolan EE, Gadow KD, Sverd J, Sprafkin J. Comparison of internalizing and externalizing symptoms in children with attention-deficit hyperactivity disorder with and without comorbid tic disorder. *J Dev Behav Pediatr*. In press.
45. Gadow KD, White L, Ferguson DG. Placebo controls and double-blind conditions: placebo theory in experimental design. In: Gadow KD, Poling AD, eds. *Methodological Issues in Human Psychopharmacology*. Greenwich, Conn: JAI Press; 1986;41-83.
46. Gadow KD, White L, Ferguson DG. Placebo controls and double-blind conditions: experimenter bias, conditioned placebo response, and drug-psychotherapy comparisons. In: Gadow KD, Poling AD, eds. *Methodological Issues in Human Psychopharmacology*. Greenwich, Conn: JAI Press; 1986;85-114.
47. Gadow KD. A school-based medication evaluation program. In: JL Matson, ed. *Handbook of Hyperactivity in Children*. Needham Heights, Mass: Allyn & Bacon; 1993:186-219.
48. Satterfield JH, Schell AM, Barb SD. Potential risk of prolonged administration of stimulant medication in hyperactive children. *J Dev Behav Pediatr*. 1980;1: 102-107.
49. Satterfield JH, Cantwell DP, Schell A, Blaschke T. Growth of hyperactive children treated with methylphenidate. *Arch Gen Psychiatry*. 1979;36:212-217.
50. Leckman JF, Zhang H, Vitale A, Lahnin F, Lynch K, Bondi C, Kim YS, Peterson BS. Course of tic severity in Tourette syndrome: the first two decades. *Pediatr Electron Pages*. 1998;1:14-19.
51. Comings DE. A controlled study of Tourette syndrome, I: attention-deficit disorder, learning disorder, and school problems. *Am J Hum Genet*. 1987;41: 701-741.
52. Comings DE, Comings BG. Tourette's syndrome and attention deficit disorder with hyperactivity: are they genetically related? *J Am Acad Child Psychiatry*. 1984; 23:138-146.
53. Friedhoff AJ. Receptor maturation in pathogenesis and treatment of Tourette syndrome. In: Friedhoff JA, Chase TN, eds. *Gilles de la Tourette Syndrome*. New York, NY: Raven Press; 1982:133-140. *Advances in Neurology*; vol 35.
54. Price RA, Leckman JF, Pauls DL, Cohen DJ, Kidd KK. Gilles de la Tourette's syndrome: tics and central nervous system stimulants in twins and nontwins. *Neurology*. 1986;36:232-237.
55. Waserman J, Lal S, Gauthier S. Gilles de la Tourette's syndrome in monozygotic twins. *J Neurol Neurosurg Psychiatry*. 1983;46:75-77.