Immediate-Release Methylphenidate for ADHD in Children With Comorbid Chronic Multiple Tic Disorder

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ABSTRACT

Objective: To examine the safety and efficacy of immediate-release methylphenidate (MPH-IR) for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children (ages 6–12 years) with Tourette's syndrome (96%) or chronic motor tic disorder (4%). **Method:** Two cohorts of prepubertal children ($N = 71$) received placebo and three doses of MPH (0.1, 0.3, and 0.5 mg/kg) twice daily for 2 weeks each, under double-blind conditions as part of their involvement in a long-term observation study (1989–2004). Treatment effects were assessed with an extensive battery of parent-, teacher-, child-, and physician-completed rating scales and laboratory tasks. **Results:** MPH-IR effectively suppressed ADHD, oppositional defiant disorder, and peer aggression behaviors. There was no evidence that MPH-IR altered the overall severity of tic disorder or obsessive-compulsive disorder behaviors. Teacher ratings indicated that MPH-IR therapy decreased tic frequency and severity. **Conclusions:** MPH-IR appears to be a safe and effective short-term treatment for ADHD in the majority of children with chronic tic disorder; nevertheless, the possibility of tic exacerbation in susceptible individuals warrants careful monitoring of all patients. *J. Am. Acad. Child Adolesc. Psychiatry,* 2007;46(7):840–848.
Key Words: attention-deficit/hyperactivity disorder, methylphenidate, aggression, chronic multiple tic disorder, Tourette's syndrome.

Historically, one of the more contentious issues in the clinical management of attention-deficit/hyperactivity (ADHD) is whether the preferred agents for treatment (i.e., stimulants) exacerbate tics in children with comorbid chronic tic disorder (CTD; Tourette's syndrome, chronic motor tic disorder). It was once asserted that stimulants were ill-advised or contraindicated in this clinical population and for ADHD children with a first- or second-degree relative with a tic disorder, a belief based primarily on case reports (Golden, 1982; Lowe et al., 1982). The seriousness of this issue is underscored by the fact that both disorders are relatively common and genetically related, their co-occurrence is associated with more severe impairment, and CTD is often undiagnosed (e.g., Comings et al., 1996; Gadow et al., 2002; Pierre et al., 1999; Sverd, 2000). Based initially on our own clinical experience and controlled case studies of four children with ADHD+CTD (Sverd et al., 1989), we initiated a program of research to examine the safety and efficacy of immediate-release methylphenidate (MPH-IR) in these patients. Our first group study examined clinical response in 34 children who participated in a placebo-controlled, double-blind, 8-week, crossover trial (Gadow et al., 1995a,b). Evidence from multiple measures, settings, and informants indicated that MPH-IR was highly effective in suppressing ADHD

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and oppositional and aggressive behaviors, particularly in school settings and even at relatively low (0.1 mg/kg) doses. Even more gratifying was the finding that rate of tic worsening was comparable for placebo and medication conditions according to numerous clinician- and parent-completed measures, and no child had to be withdrawn from treatment owing to tic exacerbation. Moreover, teacher ratings actually indicated improvement in tic frequency and severity with medication.

Although controlled trials of stimulant medication in children with ADHD+CTD have generally concluded that stimulants are safe and effective in many cases, careful examination of reported outcomes indicates that agreement for specific treatment effects ranges from mixed to highly inconsistent, even for identical measures (Castellanos et al., 1997; Law and Schachar, 1999; Tourette Syndrome Study Group, 2002). For example, the Tourette's Syndrome Study Group (2002) compared children randomly assigned to individually titrated doses of MPH-IR (n = 37) or placebo (n = 32), administered for 16 weeks. Although patients and doses were similar and some measures identical to our initial study, their placebo versus MPH-IR effect sizes for teacher ADHD ratings and classroom observations of on task behavior were markedly smaller than our previously reported treatment effects. Moreover, clinician and parent reports indicated MPH-IR actually suppressed tics, but teacher ratings did not. These and other inconsistencies highlight the need for continued research with larger samples. Moreover, practitioners continue to receive mixed messages with regard to the appropriateness of this treatment. For example, (a) the package inserts and advertising for most U.S. Food and Drug Administration–approved and commercially available stimulants for the treatment of ADHD include warnings against the use of these drugs for children with a preexisting tic disorder; (b) there continues to be uncontrolled reports of ADHD medications inducing tics in children with ADHD (e.g., Feldman et al., 2005; Lee et al., 2004); and (c) stimulant drugs are still considered alternative medications for the management of ADHD in children with CTD (e.g., Robertson, 2000, 2006) or share first-line status with medications generally not shown to be particularly effective for the management of core ADHD symptoms (e.g., Zinner, 2004).

To better establish the safety and efficacy of MPH-IR for children with ADHD+CTD, we expanded our initial sample to include a second cohort of children using the same methodology and personnel as our first trial. This allowed us to aggregate data for more detailed drug-response analyses with greater statistical power, particularly with regard to potentially lower frequency side effects such as drug-induced tic exacerbation.

METHOD

Subjects

The subjects were 71 children (57 boys, 14 girls) between 6 and 12 years old (mean 8.9; SD 1.9) who were recruited from a variety of sources including referrals from clinicians, schools, media advertisements, and parent support groups. Subject characteristics are described in Table 1. The study sample includes two cohorts of children; the initial group was recruited primarily to assess short-term MPH-IR effects (n = 39, cohort 1 [Gadow et al., 1995a,b]), which was followed by a naturalistic observation study through age

TABLE 1
Patient Characteristics: Mean/Frequency (M/F) and SD/%

Demographics	M/F	SD/%
Age	8.95	1.4
IQ (n = 49)	103.8	11.0
Age at tic onset	5.6	1.6
Ethnicity		
European	62	87
Hispanic	4	6
African	4	6
Asian	1	1
Parent ADHD		
Conners Hyperactivity Index	17.7	4.6
MOMS hyperactivity index	3.6	1.1
Teacher ADHD		
Conners HK Index	17.9	5.9
IOWA I-O	11.0	2.8
Tic measures		
YGTSS		
Total motor	13.4	3.3
Total phonic	9.7	3.4
Overall impairment	13.8	10.1
Global Severity Score	36.9	14.6
Videotape tic counts		
Frequency of motor tics	18.4	9.1
Special education		
Full time	19	27
Part time	22	31
None	30	42

Note: ADHD = attention-deficit/hyperactivity disorder; HK = Hyperkinesis; MOMS = Mothers' Objective Method for Subgrouping; I-O = Inattention-Overactivity subscale; YGTSS = Yale Global Tic Severity Scale.