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Unexpected Effects of Methylphenidate in Attention-Deficit/Hyperactivity Disorder Reflect Decreases in Core/Secondary Symptoms and Physical Complaints Common to All Children

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Abstract

Hypotheses concerning unexpected, psychostimulant-related effects reported in previous studies were examined by separating behavioral/physical complaints highly specific to methylphenidate (MPH) from those that (a) may mimic core/secondary symptoms of the disorder, or (b) are commonly reported by unmedicated children in the general population. Sixty-five children with attention-deficit/hyperactivity disorder (ADHD) participated in a double-blind, placebo-controlled, within-subject (crossover) experimental design and received a placebo and four MPH doses in counterbalanced order following baseline assessment. Behavioral and physical complaints were significantly higher under baseline relative to placebo and the four immediate-release MPH conditions (5 mg, 10 mg, 15 mg, and 20 mg) across three symptom categories: ADHD core/secondary symptoms; symptoms commonly reported in the general population, including unmedicated children with ADHD; and symptoms highly specific to MPH. No significant differences were found among active drug conditions. Past unexpected findings of psychostimulant effects in ADHD may be due to the inclusion of scale items that reflect core/secondary features of ADHD and normally occurring behavioral/physical complaints in children.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is a complex and chronic disorder of brain, behavior, and development whose behavioral and cognitive consequences pervade multiple areas of functioning. Core features of the disorder involve difficulties with attention, impulsiveness, and hyperactivity (APA 2000) and are hypothesized to affect behavioral and cognitive functioning to the extent that the latter are dependent upon the former for successful execution (Rapport et al. 2001). Treatment of ADHD traditionally involves using behavior or pharmacological therapy alone or in combination (for reviews, see Chronis et al. 2004; Conners et al. 2001; Jensen 1999).

Pharmacological interventions (and particularly the psychostimulants), however, are generally considered more cost effective and have the added benefit of affecting both behavioral and cognitive domains throughout the day without the specific programming and oversight required by behavior therapy (DuPaul and Eckert 1997; Gittelman-Klein and Klein 1976; MTA Cooperative Group 1999). Methylphenidate (MPH) is by far the most commonly prescribed pharmacological treatment for ADHD (Faraone et al. 2002; Grcevich et al. 2001; Jensen 1999; Swanson and Volkow 2002), and its reputation is well deserved based on traditional benchmarks, including breadth of effectiveness and overall response rate among affected individuals (Barkley, 2006; Denney and Rapport 2001; Rapport et al. 1994). As with all therapies, however, treatment emergent symptoms can and do occur.

Side effects associated with psychostimulant treatment are well documented in the literature and fall primarily into one of three categories: cardiovascular effects (i.e., heart rate, blood pressure), physical effects (i.e., weight and growth), and physical and behavioral complaints. Recent reviews indicate that cardiovascular and physical effects associated with psychostimulant therapy are usually transient, dose dependent, readily resolved by discontinuing therapy, and fail to remain significant in long-term follow-up studies (Rapport and Moffitt 2002). Psychostimulant-related physical and behavioral complaints, on the other hand, have received renewed interest secondary to the unexpected effects reported in recent, well-controlled studies. For example, parents

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report that their children experience fewer behavioral (Gorman et al. 2006) and physical complaints such as daydreaming, irritability, anxiety, staring, and nail biting under MPH relative to placebo or baseline (Ahman et al. 1993; Findling et al. 2001; Greenhill et al. 2001b; Short et al. 2004). Teachers also report more severe physical and behavioral complaints for children under placebo relative to low MPH doses (Barkley et al. 1990; DuPaul et al. 1996; Fischer and Newby 1991).

Two hypotheses have been proposed to account for the unexpected findings: (1) Adult raters (parents, teachers) confuse some symptoms of ADHD (e.g., daydreaming and staring) with drug-related side effects (Fine and Johnson 1993; Firestone et al., 1998); and (2) ratings under no medication conditions (i.e., baseline, placebo) reflect normal levels of physical and behavioral complaints for boys in general, including unmedicated children with ADHD, that may occur less frequently as a function of treatment (Rapport et al. 2002). Both hypotheses are possible because of the nonspecific nature of side effect rating scales. Most scales are designed to assess a wide range of possible symptoms rather than emergent symptoms associated with a specific pharmacological regimen.

The rater confusion hypothesis can be addressed by examining the type of physical and behavioral complaints reported under no-drug conditions, and changes from this state that occur under placebo and active drug conditions (Barkley et al. 1990; Greenhill et al. 2001). Results indicating treatment-related decreases in only complaints that mimic core/secondary features of ADHD (e.g., inattentiveness, difficulty concentrating, staring, daydreaming), coupled with no change or a worsening of complaints not typically associated with the disorder (e.g., cardiovascular, gastrointestinal, and pseudoneurological symptoms), would lend empirical support to the rater confusion hypothesis. The pre-existing/normal level complaints hypothesis, on the other hand, can be examined by juxtaposing the psychostimulant emergent symptom literature with extant literature concerning the prevalence of physical and behavioral complaints in samples of non-referred and clinically diagnosed children.

The occurrence of physical and behavioral complaints in community samples of non-referred children and adolescents is well documented. For example, nearly half of the 540 children and adolescents in a community sample attending third through twelfth grade reported at least one physical symptom during the preceding two weeks (Garber et al. 1991), with the highest frequency of complaints involving headaches (25%), low energy (23%), sore muscles (21%), and abdominal discomfort (17%). Literature reviews confirm that headaches represent the most commonly reported painful physical or behavioral symptom, and occur at least weekly in 10% to 30% of children in community samples (Campo and Fritsch 1994). Epidemiological studies corroborate these findings, wherein 50% to 80% of children report some type of headache within the past year (Barea et al. 1996), and upwards to 15% experience headaches of a migrainous nature (Abu-Arefeh and Russell 1996). Recurrent abdominal pain is also common (10% to 25% of school-age children and adolescents), and nearly 15% of children complain of daily fatigue (Apley 1975; Garber et al. 1991; Linna et al. 1991). Other physical and behavioral complaints commonly reported by children include musculoskeletal pain, back pain, and dizziness (Campo and Fritsch 1994).

Physical and behavioral complaints in children are not limited to Western culture (cf. Belmaker et al. 1985), and extant evidence suggests that the frequency and type of physical and behavioral complaints vary with age and gender (Last 1991). For example, recurrent abdominal pain appears to be more common in early childhood, whereas headaches, limb pain, and polysymptomatic complaints in general increase with age (Achenbach 1989). Psychiatric disability confers additional risk for physical and behavioral complaints. Twenty percent to 69% of children and adolescents with at least one psychiatric diagnosis experience physical and behavioral complaints (Egger et al. 1999; Masi et al. 2000; Taylor et al. 1996), particularly children with anxiety and mood disorders (Carlson and Kashani 1998; Pine 2002). Children with externalizing disorders are also at greater risk than non-psychiatric controls for physical and behavioral complaints. Boys with conduct disorder report twice as many headaches as boys without the disorder, and unmedicated children with ADHD complain more frequently of stomachaches (Egger et al. 1999), polydipsia, and polyuria (Mitchell et al. 1987) relative to non-psychiatrically-disabled children.

Collectively, the physical and behavioral complaint literature indicates that moderate to elevated complaints of headaches, low energy, sore muscles, abdominal discomfort, daily fatigue, musculoskeletal pain, back pain, and dizziness are common among children, and that a diagnosis of ADHD confers additive risk for stomachaches, polydipsia, and polyuria. These findings suggest that a substantial number of physical and behavioral complaints attributed to medication in past studies may have been confounded with high base rate occurrences of these behaviors in children with ADHD. This hypothesis can be examined by comparing base rate occurrences of the above physical and behavioral complaints reported in the literature with those reported under placebo and active medication conditions, as previously suggested by Barkley and colleagues (1990) and more recently by Greenhill and colleagues (2001a). A stable or decreasing frequency of complaints under placebo and active medication conditions relative to baseline levels would support the pre-existing/normal level complaints hypothesis.

Other types of emergent symptoms specific to MPH therapy (e.g., cardiovascular symptoms, upset stomach, reduced appetite)—other than those commonly reported by children or potentially confused with core and secondary symptoms of ADHD—may worsen as a function of increasing MPH dose. These can be extracted from side effect rating scales and examined separately to determine whether changes in frequency occur as a function of expectancy (placebo) or active drug over and above base rate levels (i.e., true emergent symptoms).

The present study examined rival hypotheses that may account for past reports of unexpected reductions in physical and behavioral complaints in children with ADHD receiving psychostimulant therapy. Adverse events endorsed by parents and children under baseline, placebo, and four MPH conditions (5 mg, 10 mg, 15 mg, 20 mg) were allocated to one of three categories using the empirically-driven rational approach described below—behavioral/physical complaints

that (1) may mimic core/secondary features of ADHD; (2) are commonly reported by children in the general population, including unmedicated children with ADHD; or (3) are commonly associated with psychostimulant treatment (i.e., true emergent symptoms)—then subjected to analysis.

Method

Participants

Sixty-five children (58 boys, 7 girls) referred by community psychiatrists, pediatricians, and school personnel met the following inclusion criteria and participated in the study: (a) diagnosis of ADHD based on parent clinical interview using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS; Kaufman et al. 1997); (b) problems in at least 50% of the situations on Barkley's (2006) Home Situations Questionnaire; (c) a maternal rating at least two standard deviations above the mean on the Werry-Weiss-Peters Activity Scale (Routh et al. 1974); (d) a teacher rating of at least two standard deviations above the mean on the Abbreviated Conners' Teacher Rating Scale (ACTRS; Conners et al. 1998); (e) absence of conduct disorder; and (f) absence of gross neurological, sensory, or motor impairment as determined by pediatric examination. The University Internal Review Board approved the study, parents provided informed consent, and children provided assent to participate in the study. Children were from 6 to 11 years of age ($M = 8.56$, $SD = 1.25$) and fell within the average range of intelligence ($M = 102.8$, $SD = 10.0$) based on the Peabody Picture Vocabulary Test (Dunn and Dunn 1997). They were all Caucasian and from families of low to middle socioeconomic status (Hollingshead 1975). Eight had experienced brief trials of stimulant therapy within the previous 4 years. None were prescribed psychostimulants immediately prior to beginning the current study.

Several children showed symptoms of—but did not meet formal criteria for—mood, anxiety, oppositional defiant disorder, and conduct disorders. Increasing the heterogeneity of ADHD samples by including children comorbid for other disorders would impair interpretation of research findings as argued elsewhere (e.g., Vaessen and Van der Meere 1990). All selected children met criteria for ADHD-Combined Type and were attending general education elementary school classrooms, although several received concurrent special education services.

Experimental design and procedures

A double-blind, placebo-controlled, within-subject (crossover) experimental design was used. Children with ADHD received a placebo and each of four active immediate-release MPH doses following baseline assessment. Order of dose administration was counterbalanced and determined by random assignment such that an equal number of children received each dose during a given week of the study. MPH was prescribed by each child's physician in the following doses: placebo, 5 mg (range = .10 to 0.26 mg/kg), 10 mg (range = 0.20 to 0.52 mg/kg), 15 mg (range = 0.29 to 0.79 mg/kg) and 20 mg (range = 0.39 to 1.1 mg/kg). Fixed doses were used to reflect typical pediatric practice because response to MPH is independent of body mass (Rapport and Denney 1997; Swanson et al. 1991). MPH and placebo doses were packaged in colored gelatin capsules by the clinic's pharmacist to avoid detection of dose and taste. Capsules were sealed in individual, daily envelopes to help control for accurate administration.

After baseline data collection (first week), parents were given one week of medication in predated envelopes at a single dose level (i.e., placebo, 5 mg, 10 mg, 15 mg, or 20 mg). Single morning doses (as opposed to twice per day) were administered to maintain experimental control, as it was not possible to ensure that medication would be appropriately administered at school at an established time during the day. This procedure continued until each child received every dose for 6 consecutive days. All weekly dose changes occurred on Sundays (i.e., no capsules were administered on Saturdays) to allow for "washout" and to control for possible rebound/carryover effects. Parents were instructed to give their child a capsule each morning, 30 minutes before breakfast. Both used and unused envelopes were returned on a weekly basis to assess medication compliance. Medication was properly administered nearly 100% of the time.

Behavioral and physical complaint items were adapted from the National Institute of Mental Health Subject's Treatment Emergent Symptoms Scale (STESS; Guy 1976). The STESS was initially devised for adult raters and consists of questions concerning the occurrence and severity of a broad range of possible physical and behavioral complaints and emergent symptoms associated with pharmacotherapy. A child version was created using the same items, but reworded to ask children (1) whether they had experienced a particular problem within the past three days, and (2) if so, the degree of severity using the original version's 4-point response format ("not at all," "just a little," "pretty much," "very much"). Additional details of the development of the child version are reported in Rapport et al. (2002). The revised child version has been shown to be sensitive to medication status and dosage changes (Rapport et al. 2002).

Parents were asked to respond to each item during each weekly visit throughout the study. Children were administered the items during each weekly visit by trained graduate research assistants who read each item aloud to the child and recorded their verbal response. Parents and children were asked about the presence and severity of each symptom during the preceding three days. Graduate assistants were blind to children's medication status. Completed questionnaires reflected physical and behavioral complaints experienced by children within the past three days and associated with a single experimental condition (baseline, placebo, or one of the four MPH conditions).

Items were judged to fall into one of three categories using an empirically-driven rational approach (Clark and Watson 1995). Four independent judges reviewed the empirical literature described above and determined whether each item reflected behavioral/physical complaints that (1) may mimic core and secondary features of ADHD (Ahman et al. 1993; Barkley et al. 1990; Beidel et al. 1991; APA 2000); (2) are common to pediatric age children (Belmaker et al. 1985; Campo and Fritsch 1994; Garber et al. 1991), including unmedicated children with ADHD (Egger et al. 1999; Mitchell et al. 1987); or (3) do not fit into the preceding categories and are associated with psychostimulant treatment (e.g., nausea/upset stomach, dry mouth, decreased appetite). Intraclass correlation and Fleiss' kappa were computed to test the

reliability of the revised scale categories (Nunnally and Bernstein 1994). Intraclass correlation was computed using the Shrout and Fleiss (1979; Case 2) method to determine the generalizability of the four judges' item categorization to the larger population of potential judges (i.e., others that have reviewed the treatment emergent and physical complaints literatures), ICC(2, 4) = .95, $p < .0005$. Fleiss' kappa for more than two raters (Siegel and Castellan 1988) was computed using SPSS syntax (King 2004), and provided further evidence of reliability, $\kappa = .86$. Individual disagreements were discussed and resolved based on empirical literature. Items judged to belong to each category are shown in Tables 1 and 2.

Results

All tests were two-tailed with alpha level set at .05. A three-tier data analytic strategy was used to examine the study's two primary hypotheses: (Tier I) that adult raters confuse some features of ADHD with drug-related side effects; and (Tier II) that baseline/placebo measures reflect normal levels of physical and behavioral complaints for boys in general including unmedicated children with ADHD. Tier III analyzed endorsement of remaining emergent symptoms associated with psychostimulants to determine whether previously reported unexpected effects remain evident after removing ADHD-like and common behavior and physical complaints. Mean severity and percentage of parents and children endorsing each symptom are shown in Tables 1 and 2.

Tier I analysis: Rater confusion hypothesis

Parental report of physical and behavioral complaints that may mimic core/secondary features of ADHD were analyzed using a repeated measures ANOVA (conditions: baseline, placebo, 5 mg, 10 mg, 15 mg, 20 mg). The analysis examines the hypothesis that adult raters confuse ADHD core/secondary features as MPH side effects. The main effect for drug condition was significant, $F(5, 640) = 16.34$, $p < .001$. Tukey post hoc analysis revealed that parent endorsement of physical and behavioral complaints that mimic core/secondary ADHD features under baseline were significantly higher than complaints endorsed under placebo and all active medication conditions (all $p < .05$). Additionally, behavioral complaints were significantly higher in the placebo condition relative to the four MPH conditions (all $p < .05$). No significant differences emerged among the four MPH doses (see Fig. 1).

Analysis of trend was performed to examine the shape of the relationship between parent ratings of physical/behavioral complaints and MPH dose. Parent endorsements under baseline and active medication conditions were examined in the initial analysis (i.e., the placebo condition was excluded). The ensuing analysis was conducted using placebo and active drug conditions with baseline excluded.[1] The proportion of treatment variance (R^2_{trend}) was computed for each significant trend to determine the relative contribution of each trend component (e.g., linear, cubic, quadratic) when more than one component reached statistical significance (Keppel 1991).

Trend analysis of parent endorsement of physical and behavioral complaints excluding the placebo condition (i.e., baseline, 5 mg, 10 mg, 15 mg, 20 mg) revealed significant linear $F(4, 256) = 37.83$, $p < .001$, quadratic $F(4, 256) = 20.77$, $p < .001$, and cubic $F(4, 256) = 9.31$, $p < .001$ trends. The linear trend accounted for the greatest proportion of variance (15%), whereas 6% and 3% of unique variance was accounted for by the two higher-order trends, respectively. This finding indicates that parental report of physical and behavioral complaints that mimic core/secondary features of the disorder evince a moderately abrupt decrease between baseline and MPH 5-mg, with minimal variation in frequency under higher dose conditions (see Fig. 1). Only the linear trend was significant for the placebo-active drug trend analysis $F(4, 256) = 12.35$, $p < .001$, and the small proportion of variance accounted for by the model (5%) indicates that the primary change in complaint frequency results from changes between baseline and active drug conditions.

Collectively, the preceding analyses indicate a significant reduction in parental report of physical and behavioral complaints that mimic core/secondary ADHD features under placebo relative to baseline, and under active MPH conditions relative to both baseline and placebo, with no significant variation in complaint frequency among active drug conditions. These findings are consistent with the hypothesis that adult raters confuse some features of ADHD with drug-related side effects.

Tier II analysis: Preexisting/normal level hypothesis

Parent and child reports of physical and behavioral complaints common to pediatric age children were analyzed using a 2 (child and parent raters) × 6 (conditions: baseline, placebo, 5 mg, 10 mg, 15 mg, 20 mg) mixed-model ANOVA to examine the preexisting/normal level hypothesis. This hypothesis posits that the base rate of physical and behavioral complaints commonly reported by children (including unmedicated children with ADHD) must be accounted for by examining baseline frequencies to separate them from actual treatment emergent symptoms associated with MPH.

The main effect for drug condition was significant, $F(5, 640) = 4.42$, $p < .001$. Examination of Fig. 2 suggests that the significant decrease in endorsements from baseline to placebo ($p < .05$) and all active MPH conditions (all p-values $< .05$) is related primarily to decreased child endorsements. However, neither the main effect for rater, $F(1, 128) = 2.84$, *ns*, nor the rater by drug condition interaction, $F(5, 640) = 2.22$, *ns*, was significant.

Tier III analysis: Side effects commonly attributed to psychostimulant treatment

Parent and child reports of physical and behavioral complaints commonly attributed to psychostimulant therapy (true emergent symptoms) were analyzed using a 2 (child and parents raters) × 6 (conditions: baseline, placebo, 5 mg, 10 mg, 15 mg, 20 mg) Mixed-model ANOVA. The rater by drug interaction, $F(5, 640) = 2.94$, $p < .05$, and main effect for drug were significant, $F(5, 640) = 10.66$, $p < .001$. There was no significant main effect for rater, $F(1, 128) = .099$, *ns*.

Tukey post hoc analysis indicated that children endorsed

[1] A basic assumption of trend analysis is that "levels" of experimental conditions be of similar magnitude, which precludes simultaneous use of baseline and placebo in the same analysis.

Table 1. Mean Severity and Percentage of Participants Endorsing Each Behavioral and Physical Symptom under Baseline, Placebo, and Active Methylphenidate Conditions—Child Ratings

	Behavioral/Physical Complaints[1]	*Baseline*	*Placebo*	*5 mg*	*10 mg*	*15 mg*	*20 mg*
Core/secondary symptoms of ADHD	Difficulty sitting still	.47(25%)	.16(6.6%)	.15(8.2%)	.21(9.5%)	.20(7.8%)	.06(3.2%)
	Difficulty sleeping	.86(39.1%)	.24(12.9%)	.25(14.1%)	.27(14.1%)	.33(14.1%)	.24(9.7%)
	Decreased sleep	.26(18.5%)	.21(9.7%)	.34(12.5%)	.22(10.9%)	.11(4.7%)	.13(6.7%)
	Crying	.17(7.7%)	.16(6.5%)	.05(1.5%)	.08(3.2%)	.08(3.1%)	.00(0.0%)
	Difficulty with attention	.41(15.9%)	.25(11.5%)	.10(4.8%)	.16(6.3%)	.09(6.3%)	.02(1.7%)
	More talkative	.98(44.4%)	.37(15%)	.44(18%)	.41(17.5%)	.27(12.7%)	.36(13.1%)
	Difficulty with sports	.25(10.8%)	.08(3.3%)	.05(1.6%)	.03(1.6%)	.05(1.6%)	.03(1.6%)
	Difficulty with parent relationships	.13(9.4%)	.21(11.1%)	.09(6.2%)	.13(6.3%)	.03(3.1%)	.03(3.3%)
	Difficulty with peer relationships	.53(25%)	.24(12.7%)	.18(8.1%)	.16(6.3%)	.21(8.2%)	.13(6.5%)
	Anger	.54(24.6%)	.13(6.5%)	.08(3.1%)	.17(6.3%)	.20(11.1%)	.10(4.8%)
Complaints common to all children	Stomach aches	.46(33.8%)	.21(11.3%)	.23(13.8%)	.25(14.1%)	.25(15.9%)	.25(12.7%)
	Cramps	.31(20%)	.18(9.8%)	.18(6.5%)	.13(6.3%)	.16(9.7%)	.23(9.7%)
	Headaches	.50(23.4%)	.18(9.7%)	.18(9.2%)	.38(18.8%)	.25(14.1%)	.21(11.1%)
	Dizziness	.23(13.8%)	.11(6.6%)	.02(1.6%)	.08(4.7%)	.02(1.6%)	.16(9.7%)
	Tiredness/fatigue	.60(32.3%)	.37(16.1%)	.33(17.2%)	.38(15.6%)	.36(18.8%)	.18(11.5%)
	Muscle aches	.34(25%)	.09(6.3%)	.06(4.6%)	.06(3.1%)	.09(6.2%)	.12(6.2%)
Emergent symptoms	Less eating	.23(20%)	.20(10%)	.11(4.8%)	.30(10.9%)	.16(6.3%)	.14(7.9%)
	More drinking	1.22(53.1%)	.32(11.7%)	.21(9.7%)	.27(9.4%)	.32(12.7%)	.26(11.3%)
	Dry mouth	.59(35.9%)	.37(14.5%)	.31(13.8%)	.20(10.9%)	.27(14.1%)	.21(11.5%)
	More bowel movements	.09(6.3%)	.12(6.7%)	.11(4.7%)	.17(6.3%)	.05(1.6%)	.03(3.3%)
	Fewer bowel movements	.36(21.9%)	.31(13.1%)	.20(7.8%)	.17(7.9%)	.19(7.8%)	.12(5.0%)
	Harder bowel movements	.05(4.9%)	.11(4.8%)	.11(4.8%)	.05(1.6%)	.00(0.0%)	.02(1.7%)
	Softer bowel movements	.40(21.7%)	.24(12.9%)	.11(4.8%)	.36(12.5%)	.19(6.3%)	.15(6.8%)
	Sick to stomach	.36(25%)	.21(11.3%)	.18(9.2%)	.27(14.1%)	.25(12.7%)	.23(9.7%)
	Throw up	.19(14.3%)	.10(4.8%)	.02(1.6%)	.08(3.1%)	.13(6.3%)	.03(3.2%)
	More bedwetting	.11(4.7%)	.11(4.8%)	.08(3.1%)	.11(4.7%)	.11(4.7%)	.06(3.2%)
	Polyurea	.25(12.3%)	.11(6.6%)	.09(4.7%)	.11(4.7%)	.00(0.0%)	.07(3.3%)
	Decreased urine	.31(23.1%)	.23(8.2%)	.15(7.7%)	.19(6.3%)	.16(7.9%)	.13(6.6%)
	Painful urination	.08(4.6%)	.10(6.5%)	.00(0.0%)	.06(3.2%)	.06(3.1%)	.00(0.0%)
	Skin itching	.41(28.1%)	.25(9.8%)	.20(7.8%)	.28(12.5%)	.19(12.5%)	.18(6.5%)
	Rash	.12(9.2%)	.11(5.0%)	.11(6.3%)	.11(6.3%)	.10(6.5%)	.06(3.2%)
	Difficulty with harder words	.22(11.1%)	.13(8.2%)	.00(0.0%)	.00(0.0%)	.05(1.6%)	.00(0.0%)
	More shaky	.17(9.4%)	.11(4.9%)	.06(3.1%)	.16(6.3%)	.02(1.6%)	.13(8.3%)
	Harder to do things with hands	.08(7.7%)	.16(8.1%)	.11(4.9%)	.09(4.7%)	.05(1.6%)	.07(6.6%)
	More bad dreams	.22(10.8%)	.10(4.8%)	.15(6.2%)	.06(3.1%)	.05(1.6%)	.11(4.8%)
	More energy	1.24(55.6%)	1.18(48.4%)	.82(36.1%)	.76(27.4%)	.78(32.8%)	.89(32.8%)
	Unhappy	.20(10.8%)	.06(3.2%)	.16(6.3%)	.10(4.8%)	.05(1.6%)	.00(0.0%)
	Feeling "worse"	.04(3.8%)	.06(3.2%)	.14(7.9%)	.08(4.8%)	.02(1.6%)	.03(3.2%)

Note: Values in each column reflect symptom mean severity score. Values in parentheses reflect percentage of participants endorsing symptom

[1]Moderate increases in parent or child ratings of select emergent symptoms were reported for some children under the two highest doses (15 mg and 20 mg): feeling sick to stomach, $n = 11$; itchy skin, $n = 10$; dry mouth, $n = 9$; and reduced appetite, $n = 6$).

ADHD, attention-deficit/hyperactivity disorder.

Table 2. Mean Severity and Percentage of Participants Endorsing Each Behavioral and Physical Symptom under Baseline, Placebo, and Active Methylphenidate Conditions—Parent Ratings

	Behavioral/Physical Complaints[1]	*Baseline*	*Placebo*	*5 mg*	*10 mg*	*15 mg*	*20 mg*
Core/secondary symptoms of ADHD	Clumsiness	.21(15%)	.15(11.3%)	.00(0.0%)	.03(3.3%)	.13(7.9%)	.00(0.0%)
	Difficulty sleeping	.08(4.7%)	.13(11.3%)	.06(6.2%)	.27(20.6%)	.10(10.2%)	.13(8.3%)
	Decreased sleep	.17(14.1%)	.14(11.1%)	.08(7.7%)	.16(14.8%)	.13(11.5%)	.15(15.3%)
	Crying	.46(34.9%)	.26(19.4%)	.28(23.1%)	.32(21.7%)	.35(23.8%)	.28(21.7%)
	Daydreaming	.23(19.4%)	.11(9.8%)	.09(9.4%)	.02(1.7%)	.07(5.0%)	.11(6.6%)
	Difficulty with attention	.87(46.8%)	.83(45.0%)	.42(29.2%)	.31(21.3%)	.23(14.8%)	.24(13.6%)
	More talkative	.63(36.5%)	.60(38.7%)	.43(29.2%)	.58(33.3%)	.48(30.6%)	.37(27.1%)
	Difficulty with sports	.25(12.3%)	.17(7.8%)	.05(4.9%)	.00(0.0%)	.08(4.8%)	.05(3.2%)
	Difficulty with parent relationships	.91(56.3%)	.67(43.8%)	.53(40%)	.45(32.3%)	.43(25.4%)	.48(33.9%)
	Difficulty with peer relationships	1.12(61.5%)	.70(42.2%)	.49(34.4%)	.48(33.9%)	.44(25.4%)	.40(29%)
	Anger	1.29(69.2%)	.69(48.4%)	.60(41.9%)	.47(38.7%)	.54(33.3%)	.47(29%)
Complaints common to all children	Stomach aches	.33(26.6%)	.27(18.8%)	.20(18.8%)	.30(25.4%)	.22(17.5%)	.32(27.4%)
	Cramps	.05(4.8%)	.08(4.8%)	.12(9.2%)	.05(4.8%)	.02(1.6%)	.08(4.8%)
	Headaches	.39(37.5%)	.19(18.8%)	.25(20%)	.24(17.5%)	.17(14.1%)	.19(14.5%)
	Dizziness	.00(0.0%)	.05(3.2%)	.00(0.0%)	.03(3.2%)	.03(1.6%)	.11(8.1%)
	Tiredness/fatigue	.15(10.8%)	.05(4.8%)	.20(18.8%)	.16(16.1%)	.20(15%)	.21(17.7%)
	Muscle aches	.09(7.8%)	.06(3.1%)	.05(4.8%)	.03(3.2%)	.00(0.0%)	.15(8.1%)
Emergent symptoms	Less eating	.12(10.8%)	.17(15.9%)	.25(20%)	.30(22.2%)	.37(23.8%)	.38(27%)
	More drinking	.14(10.8%)	.13(9.5%)	.22(15.6%)	.15(11.5%)	.27(22.2%)	.16(11.5%)
	Dry mouth	.05(4.9%)	.10(9.8%)	.15(11.7%)	.08(6.5%)	.10(6.8%)	.13(10%)
	Constipation	.05(4.7%)	.02(1.6%)	.00(0.0%)	.03(3.2%)	.03(3.2%)	.00(0.0%)
	Diarrhea	.09(9.4%)	.11(7.9%)	.11(7.9%)	.16(11.3%)	.10(4.8%)	.08(6.3%)
	Nausea	.03(1.6%)	.08(6.3%)	.05(4.6%)	.06(4.8%)	.08(6.3%)	.16(11.3%)
	Bedwetting	.17(10.8%)	.11(7.9%)	.00(0.0%)	.10(4.8%)	.11(7.8%)	.05(3.2%)
	Polyurea	.08(6.3%)	.00(0.0%)	.10(7.9%)	.07(5%)	.08(4.9%)	.08(6.6%)
	Decreased urine	.02(1.6%)	.00(0.0%)	.00(0.0%)	.05(3.3%)	.00(0.0%)	.00(0.0%)
	Painful urination	.00(0.0%)	.02(1.6%)	.00(0.0%)	.00(0.0%)	.02(1.6%)	.02(1.6%)
	Skin itching	.09(6.3%)	.19(14.3%)	.09(7.7%)	.10(9.7%)	.16(14.1%)	.15(14.5%)
	Rash	.03(3.1%)	.05(3.1%)	.06(6.2%)	.03(3.2%)	.13(9.4%)	.10(8.1%)
	Light sensitivity	.05(4.8%)	.06(6.5%)	.05(4.9%)	.07(4.9%)	.05(4.9%)	.05(3.5%)
	Difficulty with balance	.18(11.5%)	.08(6.5%)	.03(3.2%)	.03(3.3%)	.06(3.2%)	.02(1.7%)
	Difficulty with speech	.09(6.3%)	.08(6.3%)	.05(4.7%)	.02(1.6%)	.06(3.2%)	.03(3.3%)
	Shaky hands	.03(3.1%)	.03(3.3%)	.00(0.0%)	.02(1.7%)	.05(3.2%)	.05(3.3%)
	More bad dreams	.02(1.6%)	.05(4.9%)	.05(3.2%)	.05(4.9%)	.03(3.2%)	.07(4.9%)
	Difficult to please	.58(35.4%)	.48(38.1%)	.34(29.2%)	.37(24.2%)	.27(21%)	.18(16.4%)
	More serious	.26(25.8%)	.30(25%)	.39(37.5%)	.38(28.6%)	.48(34.4%)	.48(33.9%)
	Silliness	.73(50.8%)	.48(32.8%)	.31(24.6%)	.49(33.3%)	.39(29.7%)	.30(27.9%)
	More energy	.69(36.9%)	.60(39.7%)	.35(24.6%)	.50(30.6%)	.29(20.6%)	.26(16.4%)
	Less Energy	.02(1.6%)	.06(4.8%)	.22(15.4%)	.18(13.1%)	.22(14.3%)	.26(21%)
	More withdrawn	.06(6.2%)	.05(4.8%)	.06(6.2%)	.03(3.3%)	.15(9.7%)	.16(11.3%)
	Unhappy	.41(32.8%)	.24(17.5%)	.16(15.6%)	.18(12.9%)	.21(14.3%)	.16(16.1%)
	Happiness	.52(31.3%)	.44(26.2%)	.37(26.2%)	.47(32.2%)	.44(31.7%)	.33(23.3%)
	More repetitive behaviors	.44(25.8%)	.23(17.7%)	.09(6.3%)	.18(16.4%)	.08(8.1%)	.17(8.3%)
	More self-harm behaviors	.03(1.5%)	.00(0.0%)	.00(0.0%)	.00(0.0%)	.03(1.6%)	.00(0.0%)
	Feeling "worse"	.44(20.6%)	.58(33.9%)	.25(20.6%)	.23(16.4%)	.22(13.3%)	.16(10.5%)

Note: Values in each column reflect symptom mean severity score. Values in parentheses reflect percentage of participants endorsing symptom

[1]Moderate increases in parent or child ratings of select emergent symptoms were reported for some children under the two highest doses (15 mg and 20 mg): feeling sick to stomach, $n = 11$; itchy skin, $n = 10$; dry mouth, $n = 9$; and reduced appetite, $n = 6$).

ADHD, attention-deficit/hyperactivity disorder.

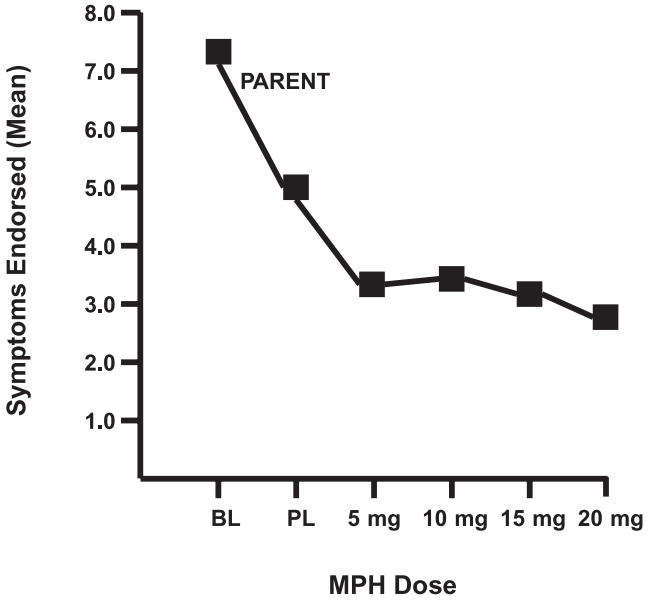

FIG. 1. Mean number of physical and behavioral symptoms endorsed by parents that may reflect core or secondary features of attention-deficit/hyperactivity disorder under baseline, placebo, and active methylphenidate (MPH) conditions.

significantly more physical and behavioral complaints commonly attributed to psychostimulants under baseline relative to placebo and all four active MPH conditions (all $p < .05$), and under placebo relative to 5 mg, 15 mg, and 20 mg conditions (all $p < .05$). No significant differences emerged among the active MPH conditions (see Fig. 3). Parent endorsements showed a similar pattern of results—significantly more physical and behavioral complaints were reported under baseline relative to 5 mg and 20 mg MPH (both $p < .05$). No other contrasts were significant.

Collectively, these results indicate that the significant interaction effect was due to initially higher child relative to adult complaint endorsements under baseline, coupled with lower complaint frequency under the MPH conditions. Trend analysis reveals that child ratings are best characterized by a linear decrease in physical and behavioral complaints, with the largest decrease occurring between baseline and active medication conditions. Parent ratings are best characterized by a cubic decrease in complaints that accounts for less than 2% of change—indicating minimal change across the experimental conditions.

Group-level analysis was supplemented by examination of individual child rating scale results, and revealed moderate increases in select emergent symptoms for some children (e.g., feeling sick to stomach, $n = 11$; itchy skin, $n = 10$; dry mouth, $n = 9$; and reduced appetite, $n = 6$) under the two highest doses (15 mg and 20 mg).

Discussion

The present study examined competing hypotheses regarding past reports of unexpected reductions in physical and behavioral complaints associated with MPH therapy for children with ADHD. Symptoms on the child version of the STESS side effect rating scale (Rapport et al. 2002) were separated into specific categories using an empirically-driven rational approach to investigate predictions that some physical and behavioral complaints represent ADHD primary/secondary features, some reflect non-medication-related complaints reported by children in general, and others are true emergent symptoms specific to psychostimulant treatment.

Child endorsements of both common physical complaints and true emergent symptoms showed significant reductions from baseline to active immediate-release MPH conditions, and were of a sufficient magnitude to be considered clinically meaningful (range = 27% to 62% reduction). Significant reductions in symptom endorsements were also observed between placebo and active MPH conditions for parent ratings that reflect ADHD core/secondary features (e.g., sitting still, difficult peer relationships), and for child symptom ratings specific to MPH treatment (e.g., stomachaches, reduced appetite). These changes were smaller in magnitude than those observed for the baseline-MPH contrasts, and suggest that part of the observed effect is associated with expectancy, "cry for help," regression to the mean, or other factors related to placebo phenomena. No significant differences emerged among the four active MPH doses for child and parent endorsements across the three categories.

Our results are consistent with those reported in past studies that included baseline measures of psychostimulant effects. For example, Ahman and colleagues (1993) reported reduced frequencies in four behavioral symptoms assessed by the Stimulant Drug Side Effects Rating Scale (Barkley 2006) under their high dose MPH condition (dose range = .3 mg/kg to .6 mg/kg). Efron and colleagues (1997) reported

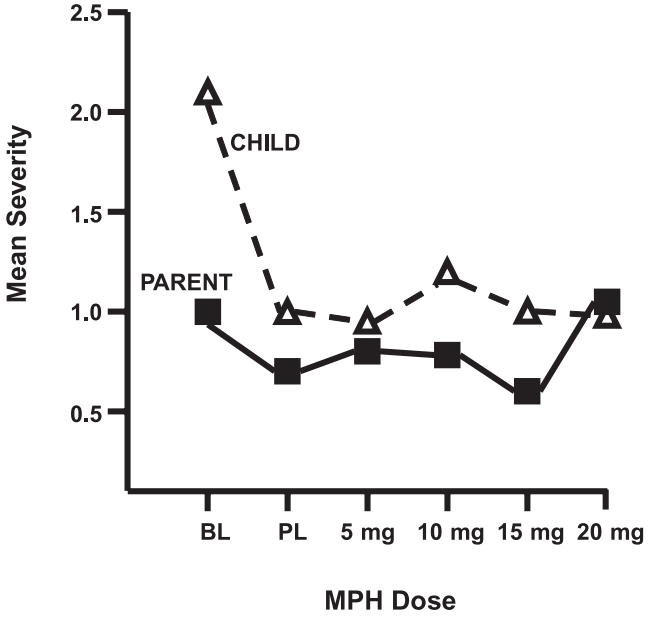

FIG. 2. Mean severity ratings of parent and child endorsements of physical and behavioral complaints commonly reported by children (including those with attention-deficit/hyperactivity disorder) in the general population. MPH = methylphenidate; BL = baseline; PL = placebo.

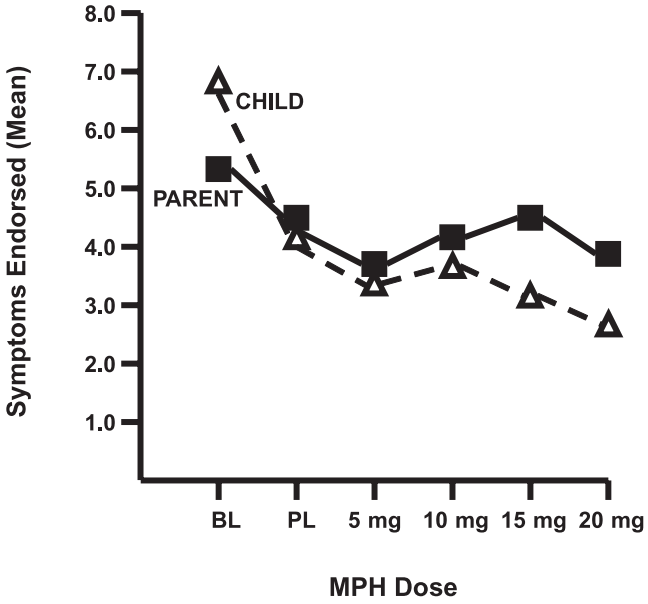

FIG. 3. Mean number of physical and behavioral symptoms endorsed by parents and children that are commonly attributed to methylphenidate (MPH) therapy (true side effects).

similar results—a decrease in frequency and severity of side effects relative to baseline when comparing MPH to dexamphetamine at .3 mg/kg and .15 mg/kg, respectively. Placebo-controlled dose-response investigations without baseline measures report similar findings (e.g., Firestone et al. 1998; Fischer and Newby 1991; Short et al. 2004). Collectively, these findings suggest that several items included on emergent rating scales likely reflect phenotypical, behavioral features of ADHD rather than true emergent symptoms related to MPH therapy. Parent and teacher ratings of these scale items have previously been attributed to rater confusion. However, an equally plausible explanation is that raters are accurately reflecting observed behavior changes in children consistent with the vast literature on psychostimulant response, and investigators have misinterpreted these ratings by relying on total rather than item or factor scale scores. This explanation also holds for scales developed specifically to monitor emergent symptoms associated with psychostimulant therapy, such as the Stimulant Drug Side Effects Rating Scale (Barkley 2006), which contains multiple items that mirror core and secondary features of ADHD (e.g., trouble sleeping, proneness to crying, daydreams).

Children's complaints of physical discomfort on a weekly and reoccurring basis are well documented in the literature (Egger et al. 1999; DuPaul et al. 1996; Mitchell et al. 1987). Our results corroborate extant research in demonstrating that children with ADHD share this propensity for experiencing weekly discomfort such as headaches, feeling tired, muscle aches, stomachaches, and occasional dizziness under no-medication conditions. The results provide a compelling rationale for recognizing that children, like adults, regularly experience physical discomfort that must be recognized and accounted for prior to initiating a medication trial. An unexpected result, however, was the significant decrease in these complaints under placebo and MPH conditions relative to baseline by child endorsements. Mean child complaint severity decreased between 44% and 56% from baseline to active MPH conditions. A proportion of this change appears to be related to expectancy effects associated with placebo phenomena in child ratings (i.e., changes from baseline to placebo for child ratings was 52%). These effects are traditionally attributed to a person's belief in a treatment's potential efficacy, but may also be mediated by changes in emotional state, perception, and behavioral improvement (Stewart-Williams 2004).

Placebo effects, however, only partially account for the significant reductions in complaints from baseline to MPH. A halo effect may explain the similar magnitude reductions from placebo to active medication conditions across all three symptom categories. In other words, active medication reduces impairing symptoms (reflected in the Tier I analyses), which may result in parents viewing their children as healthier in general (as reflected in the Tiers II and III analyses). The reduction in children's endorsements may also reflect improvement in associated areas of daily functioning, such as improved attention, academic performance, and classroom conduct associated with both placebo and active medication conditions (e.g., DuPaul and Rapport 1993; MTA Cooperative Group 1999; Pelham et al. 1990). This potential halo effect merits consideration and requires a carefully designed protocol to determine whether improved behavioral and/or academic functioning serve as significant mediators for children's emergent symptoms (Greenhill et al. 2001b).

Similar results were found when examining child endorsement of symptoms highly specific to psychostimulant medication. Children endorsed a significantly higher severity of complaints for this category under baseline relative to placebo (a 34% decrease) and all four active MPH conditions (decreases between 43% and 59%); and under placebo relative to 5mg (25% decrease), 15-mg (31% decrease), and 20-mg (38% decrease) conditions. Parent endorsements showed fewer significant contrasts, with higher severity of physical and behavioral complaints reported under baseline relative to 5mg (28% decrease) and 20mg (27% decrease) MPH conditions only. Idiographic examination revealed moderate increases for some children in nausea ($n = 11$), itchy skin ($n = 10$), dry mouth ($n = 9$), and reduced appetite ($n = 6$) under the two highest doses (15mg and 20 mg).

Limitations

Although all three classes of potential emergent symptoms showed significant decreases from baseline, several caveats merit consideration. Increased frequency and/or severity of emergent symptoms reported by or observed in children receiving psychostimulant therapy are probable to the extent that dosing regimens differ from the parameters reported herein, particularly in those symptoms highly specific to MPH. That is, children receiving multiple doses per day, single doses exceeding 20 mg, different MPH formulations, and MPH over a longer duration of time are likely to experience a higher frequency and/or severity of emergent symptoms (Gadow and Sverd 2006). The immediate-release MPH formulary is currently used less frequently than newer formulations, and the generalizability of the present findings to long-duration, sustained-release, and other variants is unknown. Preschool children with ADHD (Connor 2002;

Kollins 2004), and those whose presentation includes other clinical features such as developmental delays (Aman et al. 1991; Handen et al. 1992), may also experience a higher frequency and/or severity of psychostimulant-related emergent symptoms. Because baseline assessments necessarily preceded placebo and active medication conditions, and no age-matched control group was included, the influence of halo, order, or regression to the mean effects on the significant decreases in symptom severity between baseline and placebo cannot be entirely eliminated. However, the pattern of symptom reductions from the counterbalanced placebo to active medication conditions was similar to the pattern shown from baseline (albeit smaller magnitude). Carryover effects are unlikely due to counterbalancing and the inclusion of a "washout" day between all conditions. In addition, four days elapsed between the administration of the preceding week's final dosage and symptom ratings for the current dosage. A final caveat involves the applicability of group-level results for titrating and monitoring psychostimulant regimens for individual children. Generalization can never be assumed, and is always limited by the highly idiosyncratic treatment response observed within and across behavioral, cognitive, and emergent symptom domains in children with ADHD (Rapport and Kelly 1991).

Conclusions

Collectively, our findings point to a clear need to develop psychometrically sound treatment emergent symptom rating scales for purposes of monitoring physical and behavioral complaints in children treated with psychostimulants (Greenhill et al. 2001b). Special care is warranted in wording scale items to ensure that their content differentiates between emergent symptoms and core/secondary symptoms of the disorder. This can be accomplished through extensive item refinement and submitting items to expert judges for review (see Clark and Watson 1995). The development of a separate factor scale that contains typical daily complaints endorsed by children based on extant research may also be desirable. Separating these complaints from drug-related emergent symptoms affords practitioners improved ability to assess the extent of a child's usual complaint frequency and severity, and to determine whether it changes with treatment as evidenced herein. Including items that help differentiate improved attention from staring or constricted attention are also desirable. Finally, the administration of treatment emergent scales prior to initiating therapy must be considered a *de rigueur* component of clinical management for establishing a true baseline of child complaints (Barkley et al. 1990; Greenhill et al. 2001a).

Disclosures

Drs. Rapport and Coiro and Mr. Kofler, Mr. Raiker, Mr. Alderson, and Mr. Sarver have no financial, corporate, or commercial relationships to disclose.

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