PHYSICAL AND BEHAVIORAL COMPLAINTS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): PARADOXICAL EFFECTS OF METHYLPHENIDATE

by

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ABSTRACT

Hypotheses concerning paradoxical, psychostimulant-related side effects experienced by ADHD children were examined in the context of a double-blind, placebo-controlled, within subject (crossover) experimental design. Results revealed that behavioral and physical complaints were significantly higher under baseline relative to placebo and the four methylphenidate (MPH) conditions (5-mg, 10-mg, 15-mg, 20-mg) across three symptom categories: ADHD core/secondary symptoms, symptoms common to all children, and symptoms highly specific to MPH. No significant differences were found among active drug conditions. Implications of these findings for assessing and monitoring potential treatment emergent symptoms in children are discussed.

This is dedicated to the loving memory of my beloved father. A man who truly valued education, he helped create a home, family, and life filled with love and all things great. Along with God's grace, what he gave to me: the memories, teachings, and words etched in my mind, and the love that resides in my heart, have provided me the fortitude and endurance to persevere through this journey.

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CHAPTER ONE: INTRODUCTION AND LITERATURE REVIEW

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 (DSM-IV, 1994), and are hypothesized to affect behavioral and cognitive functioning to the extent that the latter are dependent upon the former for successful execution (Rapport, Chung, Shore, & Issacs, 2001).

Treatment of attention deficits traditionally involves using behavior or pharmacological therapy alone or in combination (for reviews, see Conners, Epstein, & March, 2001; Jensen, 1999; Pelham et al., 1998; Swanson, McBurnett, Christian, & Wigal, 1995). 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 (Douglas, Barr, O'Neil, & Britton, 1985; DuPaul & Eckert, 1997; Gittelman-Klein & Klein, 1976; MTA Cooperative Group, 1999). Methylphenidate (MPH) is by far the most commonly prescribed pharmacological treatment for ADHD (Faraone, Biederman, & Roe, 2002; Grcevich, Rowane, Marcellino, & Sullivan-Hurst, 2001; Jensen et al., 1999; Swanson & Volkow, 2002), and its reputation is well deserved based on traditional benchmarks such as the breadth of effectiveness and overall response rate among affected individuals.

Beneficial effects are observed across multiple domains of functioning based on direct observations of children's attention, behavior and academic performance (Barkley, 1977; Cunningham, Seigel, & Offord, 1985; Douglas, Barr, O'Neil, & Britton, 1985; DuPaul &

Rapport, 1993; Rapport, Denney, DuPaul, & Gardner, 1994), parent and teacher ratings of social deportment (DuPaul et al., 1993; Fischer & Newby, 1991; Musten, Firestone, Pisterman, Bennett, & Mercer, 1997; MTA Cooperative Group, 1999), and objective performance indices associated with a wide range of clinic-based neurocognitive tests, tasks, and paradigms (for reviews, see Denney & Rapport, 2001; Losier, McGrath, & Klein, 1996; Rapport & Kelley, 1991). Peer relationships and interpersonal behavior (Barkley, Karlsson, Pollard, & Murphy, 1985; Cunningham, Seigel, & Offord, 1991; Cunningham et al., 1985; Humphries, Kinsbourne, & Swanson, 1978; Smith et al., 1998; Whalen et al., 1989), and even performance during extracurricular activities such as playing baseball (Pelham et al., 1990), may improve as a function of treatment. Treatment response rates are remarkable and estimated to range between 50% and 96% depending on the stringency with which positive response is defined and the nature of the targeted outcome variable (Barkley, 1997; Denney & Rapport, 2001). 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 most fall 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 & Moffitt, 2002). Investigations of psychostimulant related physical and behavioral complaints, however, have generated renewed interest owing to the paradoxical effects reported in recent, better-controlled studies. For example, higher mean severity ratings of physical and behavioral complaints were reported by teachers for children under placebo relative to children under low MPH doses (Barkley,

McMurray, Edelbrock, & Robbins, 1990; DuPaul, Anastopoulos, Kwasnick, Barkley, & McMurray, 1996; Fischer & Newby, 1991). Parents also report that their children experience fewer physical and behavioral complaints such as daydreaming, irritability, anxiety and nail biting under MPH than placebo (Ahman et al., 1993).

Two hypotheses have been proposed to account for the paradoxical findings: (a) that adult raters (parents, teachers) confuse some symptoms of the disorder such as daydreaming and staring with drug-related side effects (Fine & Johnson, 1993; Firestone, Monteiro Munsten, Pisterman, Mercer, & Bennett, 1998); and (b) that ratings under no medication conditions (i.e., baseline, placebo) reflect normal levels of physical and behavioral complaints for boys in general, or boys with ADHD in particular, that may occur less frequently as a function of treatment (Rapport, Moffitt, & Randall, 2002). Both hypotheses are possibly owing to the non-specific nature of side effect rating scales. Most 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. Treatment related decreases in only those physical and behavioral complaints that mimic core or 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) lends empirical support to the rater confusion hypothesis. Juxtaposition of the psychostimulant emergent symptom literature with extant literature concerning the occurrence of physical and behavioral complaints in samples of non-referred and clinically diagnosed children is needed to examine the latter hypothesis.

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 3rd through 12th grade reported at least one physical symptom during the preceding two weeks (Garber, Walker, & Zeman, 1991), with the highest frequency of complaints involving headaches (25%), low energy (23%), sore muscle (21%), and abdominal discomfort (17%). Literature reviews confirm that headaches represent the most commonly reported painful physical and behavioral symptom, and occur in 10% to 30% of community samples of children on at least a weekly basis (Campo & Fritsch, 1994). Epidemiological studies corroborate these findings, wherein 50% to 80% of children report some type of headache within the past year (Barea, Tannhauser, & Rotta, 1996), and upwards to 15% experience headaches of a migrainous nature (Abu-Arefeh & Russell, 1995). Recurrent abdominal pain is also common (i.e., 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, 1991). Other physical and behavioral complaints commonly reported by children include musculoskeletal pain, back pain, and dizziness (Campo & Fritsch, 1994).

Physical and behavioral complaints in children are not limited to Western culture (cf. Belmaker, Espinoza, & Pogrund, 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 headache, limb pain, and polysymptomatic somatization in general increases with age (Achenbach, 1989).

Psychiatric disability confers additional risk for physical and behavioral complaints. Twenty to 69% of children and adolescents with at least one psychiatric diagnosis experience physical and behavioral complaints (Egger, Costelo, & Angold, 1999; Masi, Favilla, Millepiedi, & Mucci,

2000; Taylor, Szatmari, Boyle, & Offord, 1996), particularly children with anxiety disorders. Children with panic disorder and separation anxiety are significantly more likely to complain of physical and behavioral symptoms than children with other primary anxiety diagnoses or depression (Last, 1991); however, physical and behavioral complaints are also prominent in children with depression (Carlson & Kashani, 1998, Pine, 2002; Ryan, Puig-Antich, Ambrosini, & Rabinovich, 1987). Children with externalizing disorder 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 ADHD is associated with more frequent complaints of stomach aches (Egger et al., 1999), polydypsia, and polyuria (Mitchell, Aman, Turbott, & Manku, 1987) relative to non-psychiatrically disabled children.

Collectively, the physical and behavioral complaint literature indicates that moderate to elevated physical and behavioral complaints consisting of headache, 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 potentially 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 physical and behavioral complaints with those reported under placebo and active medication conditions. A stable or decreasing frequency of complaints under placebo and active medication conditions relative to baseline levels supports 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 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.

The purpose of the present study was to examine several factors that may account for reported reductions in physical and behavioral complaints in children with ADHD as a function of psychostimulant therapy. Rival hypotheses concerning paradoxical effects associated with psychostimulant therapy and physical and behavioral complaint occurrence in children with ADHD were examined using a large sample of children with ADHD, and evaluated in the context of a double-blind, placebo-controlled, within subject (crossover) experimental design.

CHAPTER TWO: METHODOLOGY

Participants

One hundred thirty-four children were screened for inclusion in the study based on referrals from psychiatrists, pediatricians, and school personnel over a 5-year period. All children and their parents participated in a detailed, semi-structured clinical interview with the clinic's supervising psychologist (M.D.R.). The interview was adapted from the Schedule for Affective Disorders and Schizophrenia for School-Age Children (Kaufman et al., 1997) and reviewed symptoms associated with disorders usually evident in childhood and adolescence as outlined in the DSM-III (American Psychiatric Association, 1980). Children were required to meet the following inclusion criteria: (1) an independent diagnosis by the child's referring physician and the Children's Learning Clinic (CLC) clinical psychologist (M.D.R.) using DSM-III criteria for ADDH; (2) a maternal report of a developmental history consistent with ADDH and problems in at least 50% of the situations on Barkley's (1990) Home Situations Questionnaire; (3) a maternal rating of at least 2 standard deviations above the mean for the child's age on the Werry-Weiss-Peters Activity Scale (Routh, Schroeder, & O'Tauma, 1974); (4) a teacher rating of at least 2 standard deviations above the mean on the Abbreviated Conners Teacher Rating Scale (ACTRS) (Conners, 1990); and (b) absence of any gross neurological, sensory, or motor impairment as determined by pediatric examination.

Sixty-five children (58 boys, 7 girls) met criteria and participated in the study after written informed consent was obtained from their parent. Selected children were between 6 and 11 years of age (mean age = 8.56) and fell within the average range of intelligence (mean = 102.8; SD =

10) based on the Peabody Picture Vocabulary Test–Revised, Form L (Dunn & Dunn, 1981). All participants were Caucasian and from families of low to middle socioeconomic status (Hollingshead, 1975). Eight had experienced brief trials of psychostimulant within the past 4 years.

All children were considered pervasively hyperactive as judged by clinical interview and rating scale scores. A systematic review using current diagnostic nomenclature indicated that each of the 65 children would currently be classified as meeting criteria defining ADHD combined type, as detailed in the DSM-IV (American Psychiatric Association, 1994). The clinical outcome of these children has been reported elsewhere (Rapport et al., 1994) and the ADHD moniker will be used throughout this report.

Many of the children showed symptoms of but did not meet formal criteria for mood and anxiety disorders. As a result, findings of this study may not generalize to children comorbid for ADHD and anxiety or affective disorders. Comorbidity for oppositional defiant disorder was not assessed because of the controversial nature of the disorder at the time the study was initiated. All selected children were attending regular elementary school classrooms, although several received concurrent special education services. Learning disabilities were not specifically assessed.

Thirty-one of the 69 nonparticipating children met criteria and were enrolled in an abbreviated placebo-controlled medication trial (5 to 15 mg of MPH) during the first year of the clinic's operation and are not reported here. Insufficient data were available for 2 children because of school conflicts, and 1 child moved out of state before completing the study. Side effect ratings were not obtained for the first 11 children participating in the 5-20 mg medication trials because the procedure was implemented late in the second year of the clinic's operation.

The remaining 24 children scored within the established range for inclusion on the various rating scales, but their developmental histories were inconsistent with DSM-III criteria (i.e., onset of symptoms later than age 7 and/or duration less than 6 months). Fourteen of these children met criteria for conduct disorder, seven showed symptoms of anxiety disorder (1 social phobia, 6 separation anxiety disorder), one had an eating disorder, and two were referred for neurological evaluation because there was evidence of a seizure disorder.

Experimental Design and Procedures

Drug administration. A double-blind, placebo-controlled, within-subject (crossover) experimental design was used in which ADHD children received a placebo and each of four active MPH doses after 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 and because response to MPH is independent of body mass (Rapport & Denney, 1997; Swanson, Cantwell, Lerner, & McBurnett, and Hanna, 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 1 week's 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 effects. Parents were instructed to give their child a capsule each morning, one half hour before breakfast. Both used and unused envelopes were returned on a weekly basis to control for medication compliance. Medication was properly administered nearly 100% of the time. "Makeup" observation days were scheduled in 4 cases when compliance was not obtained.

Procedures

Parents and children completed the Subjective Treatment Emergent Symptoms Scale (STESS; Guy, 1976) during baseline, placebo, and each of the MPH conditions. 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 (exceptions noted below), but reworded to ask children whether they had experienced a particular problem within the past three days, and 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"). The original format of the STESS included several potential physical and behavioral complaints that would be difficult to interpret in terms of directionality, such as whether a child experienced problems with eating, drinking, or bowel movements (i.e., it would be unclear whether the child was eating more or

less, drinking more or less, or having more or fewer bowel movements). To reduce ambiguity, these items were reworded to include a directional outcome (e.g., During the past three days did you feel more thirsty?). The revised child version included a total of 63 questions.

Parents were asked to complete the scale during each weekly visit throughout the study. The outcome reflected the physical and behavioral symptoms for the preceding week. Children were administered the scale during each weekly visit by trained graduate research assistants who read each item aloud to the child and recorded their verbal response. Graduate assistants were blind concerning 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).

Table 1: Summary of symptoms included in STESS scale that may reflect Core/Secondary symptoms of ADHD.

Parent
Clumsiness
Difficulty sitting still
Difficulty sleeping
Decreased sleep
Crying
Daydreaming
Difficulty with attention
More talkative
Difficulty with sports
Difficulty with parent relationships
Difficulty with peer relationships
Anger

Table 2: Summary of most common symptoms found in the general population and in children with ADHD

Parent	Child
Stomachaches	Stomachaches
Cramps	Cramps
Headaches	Headaches
Dizziness	Dizziness
Tiredness/fatigue	Tiredness/fatigue
Muscle aches	Muscle aches

Table 3: STESS scale items considered emergent symptoms or true side effects

Parent	Child
Less Eating	Less Eating
More drinking	More drinking
Dry mouth	Dry mouth
----	More bowel movements
Constipation	Fewer bowel movements
---	Harder bowel movements
Diarrhea	Softer bowel movements
Nausea	Sick to stomach
----	Throw up
Bedwetting	More bedwetting
Polyurea	Polyurea
Decreased urine	Decreased urine
Painful urination	Painful urination
Skin itching	Skin itching
Rash	Rash
Light sensitivity	---
Difficulty with balance	---
Difficulty with speech	Difficulty with harder words

Table 3 (continued)

Parent	Child
Shaky hands	More shaky
---	Harder to do things with hands
More bad dreams	More bad dreams
Difficult to please	---
More serious	---
Silliness	---
More energy	More energy
Less Energy	---
More withdrawn	---
Unhappy	Unhappy
Happiness	---
More repetitive behaviors	---
More self-harm behaviors	---
Feeling “worse”	Feeling “worse”

Note. Dashes indicate item was not included in the questionnaire.

CHAPTER THREE: RESULTS

A three-tier data analytic strategy was used to examine the study's two primary hypotheses: (a) rater confusion (i.e., that adult raters confuse some features of ADHD with drug related side effects); and (b) that baseline/placebo measures reflect normal levels of physical and behavioral complaints for boys in general or children with ADHD in particular. Children and parents completed the Subjective Treatment Emergent Symptoms Scale (STESS; Guy, 1976) during baseline, placebo, and each of the MPH conditions. All data was grouped into the following physical and behavioral complaint categories: (a) descriptions of physical and behavioral complaints related to core and secondary features of ADHD (Ahman, et al., 1993; Barkley et al., 1990; Beidel et al., 1991; DSM-IV, 1994) (see Table 1); (b) descriptions of physical and behavioral complaints common to pediatric age children (Belmaker et al., 1985; Campo et al., 1994; Garber et al., 1991), including those frequently reported by children with ADHD not receiving psychostimulant therapy (Egger et al., 1999; Mitchell et al., 1987) (see table 2); and (c) physical and behavioral complaints commonly reported in children receiving MPH treatment (e.g., nausea/upset stomach, dry mouth, decreased appetite) (see Table 3).

Tier I Analysis: Rater Confusion Hypothesis

Parent reports of physical and behavioral complaints in the symptom category that mimics core/secondary features of ADHD were analyzed using a within subjects (parents) x 6 (conditions: baseline, placebo, 5 mg, 10 mg, 15 mg, 20 mg) repeated measures analysis of variance (ANOVA). The analysis examines the hypothesis that adult raters confuse ADHD core/secondary features as MPH side effects. A *p*-value of .05 was used to evaluate significance for all analyses. The main effect for drug condition was significant [F (5, 640) = 16.34, p<.001]. Post hoc analysis using Tukey's HSD revealed that parent endorsement of physical and behavioral complaints that mimic secondary/core ADHD features under baseline were significantly higher than complaints endorsed under placebo and all active medication conditions (all *p*-values<.05). Significant differences were also found between placebo and the four MPH conditions (all *p*-values<.05). No significant differences emerged among the four MPH doses (see Figure 1).

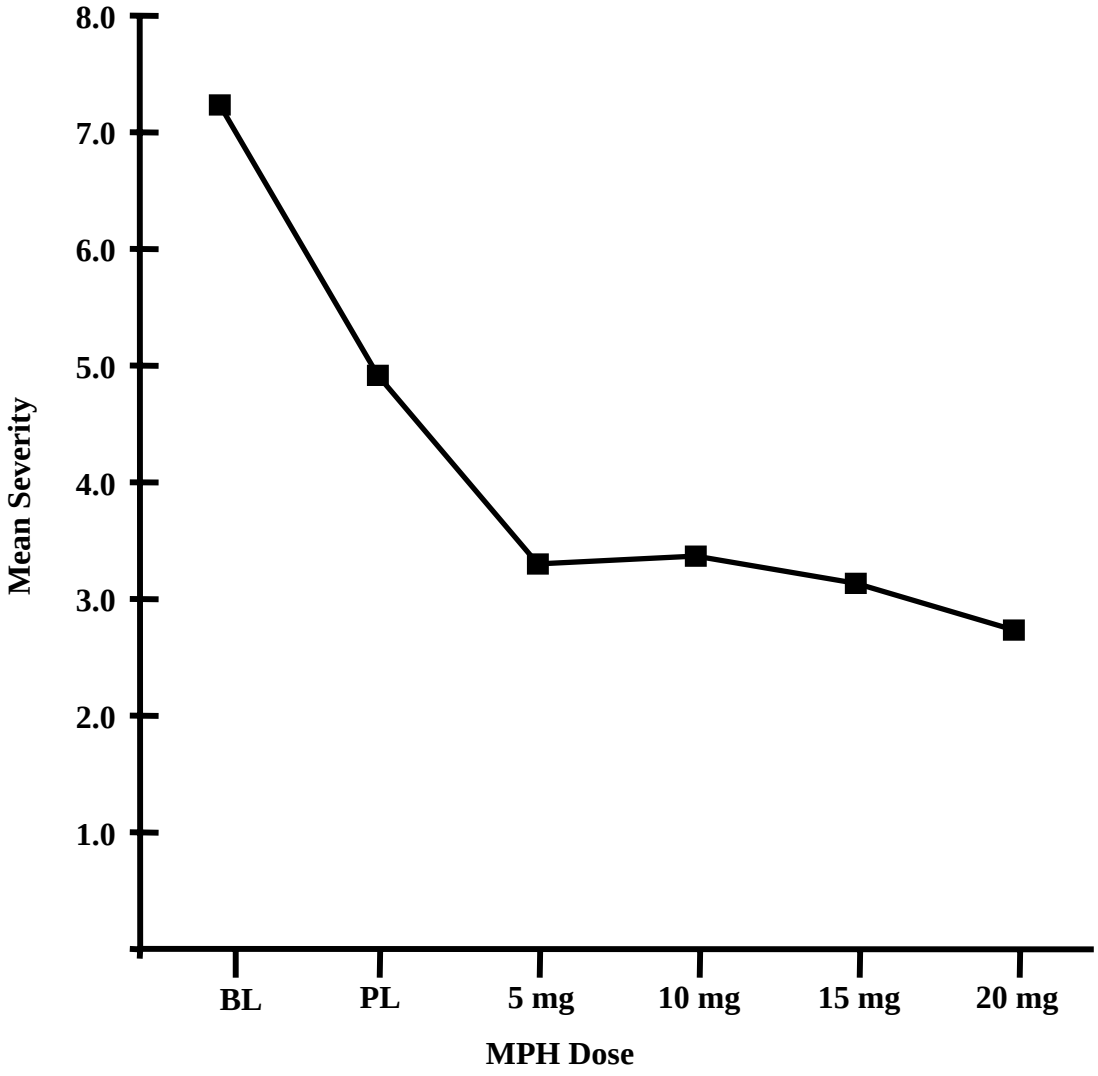

Figure 1: Mean severity ratings of physical and behavioral complaints in core and secondary features of ADHD category endorsed by parents under baseline, placebo, and methylphenidate conditions.

Analysis of trend was performed to examine the shape of the relationship between parent ratings of physical and 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. (Note: a basic assumption of trend analysis is that "level" of experimental conditions be of similar magnitude, which precludes simultaneous use of baseline and placebo in the same analysis). 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 reaches statistical significance (Keppel, 1991).

Table 4: Trend Analysis for Symptoms Found in the Core Symptom Category

	F_{Linear}	R^2_{Linear}	$F_{Quadratic}$	$R^2_{Quadratic}$	F_{Cubic}	R^2_{Cubic}
Base-MPH	37.83**	0.15	20.77**	0.06	9.31*	0.00
Placebo-MPH	12.35*	0.05	2.36	0.01	2.05	0.01

Note. Base = baseline (no drug condition). MPH = methylphenidate. Base-MPH = trend analysis using baseline and active methylphenidate conditions. PL-MPH = trend analysis using placebo and active methylphenidate conditions. R^2 = proportion of variance accounted for by trend components. * = $p < .05$; ** = $p < .001$.

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 variance was accounted for by the two higher-order trends (see Table 4 for R^2 values). This finding indicates that physical and behavioral complaints reported by parents that mimic core/secondary features of the disorder evidence a moderately abrupt decrease between baseline and MPH 5-mg, with minimal variation in frequency under higher dose conditions (see Figure 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 (5%) indicates that the primary change in complaint frequency results from changes between baseline and active drug conditions.

Collectively, the preceding analysis indicates a significant reduction in parent reports 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 as 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 parents raters) x 6 (conditions: baseline, placebo, 5 mg, 10 mg, 15 mg, 20 mg) repeated measures analysis of variance (ANOVA) to examine the preexisting/normal level hypothesis. This hypothesis posits that the myriad everyday physical and behavioral complaints commonly reported by children (including those with ADHD) must be accounted for by examining baseline frequency/severity rates to separate them from actual treatment emergent symptoms associated with MPH.

The rater by drug condition interaction [F (5, 640) = 2.22, *ns*] and main effect for rater [F (1, 128) = 2.84, *ns*] were not significant, however, the main effect for drug condition was significant [F (5, 640) = 4.42, p<.001]. The decrease in endorsements from baseline to placebo (p<.05) and all active MPH conditions (all p-values <.05) is due primarily to decreased child endorsements albeit insufficient to produce a rater main effect or interaction. Mean child and parent endorsements of physical and behavioral complaints common to children under baseline, placebo, and the four MPH conditions are depicted in Figure 2.

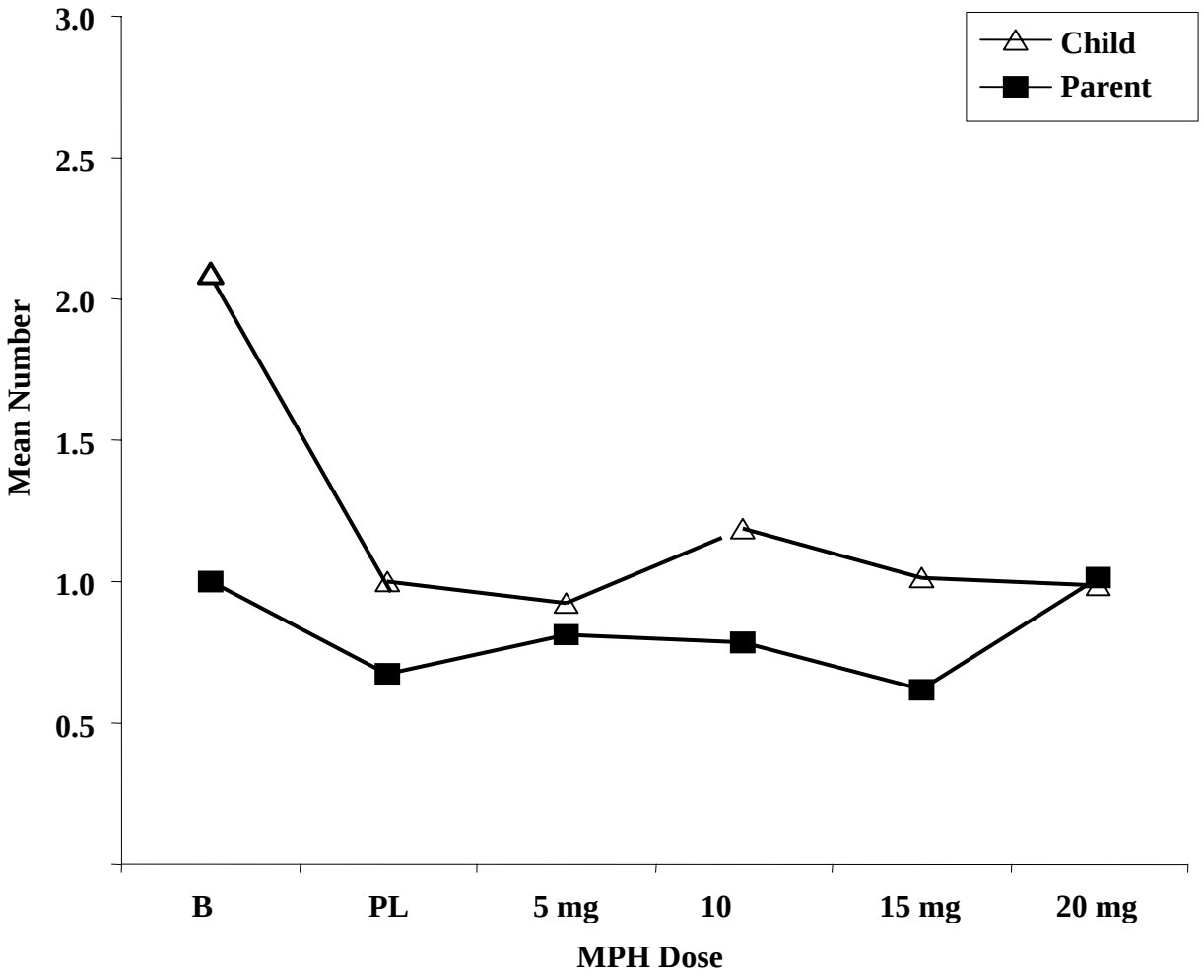

Figure 2: Mean severity ratings parent and child endorsements of physical and behavioral complaints commonly reported by children (including those with ADHD) in the general population.

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) x 6 (conditions: baseline, placebo, 5 mg, 10 mg, 15 mg, 20 mg) repeated measures analysis of variance (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 rater main effect [F (1, 128) = .099, *ns*].

Post hoc analysis using Tukey's HSD indicated that children endorsed significantly higher severity rates of physical and behavioral complaints commonly attributed to psychostimulants under baseline relative to placebo and all four active MPH conditions (all-p values < .05), and under placebo relative to 5-mg, 15-mg, and 20-mg conditions (p<.05). No significant differences emerged among the active MPH conditions. 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 (all p-values<.05). No other contrasts were significant.

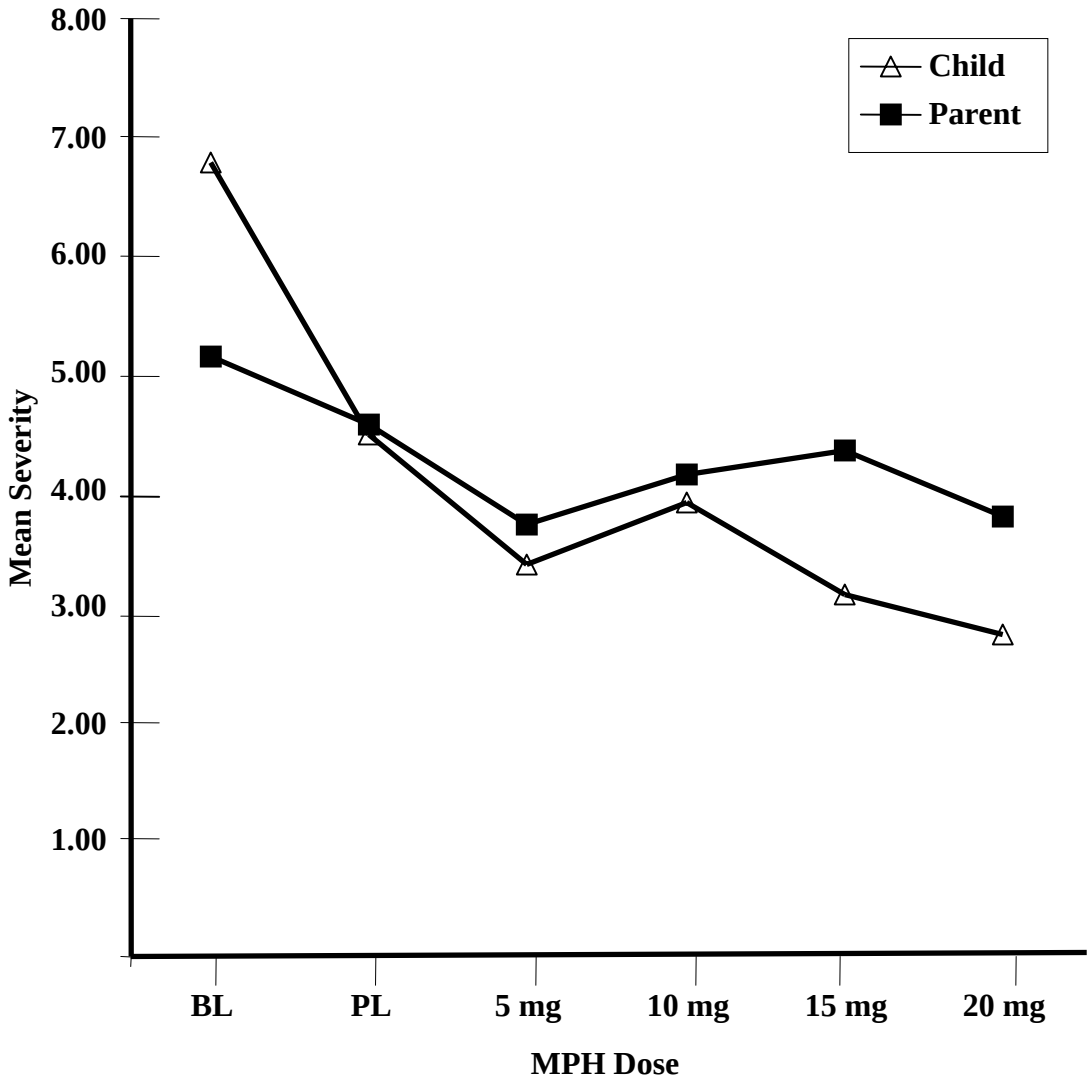

Figure 3: Mean severity ratings of parent and child endorsements of physical and behavioral complaints in the category of emergent symptoms commonly attributed to methylphenidate therapy (true side effects).

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 severity under higher doses. Trend analysis results are summarized in Table 5 and reveal 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.

Table 5: Trend Analysis for Symptoms that are considered "Emergent" or True Side Effects of Medication.

	F_{Linear}	R^2_{Linear}	$F_{Quadratic}$	$R^2_{Quadratic}$	F_{Cubic}	R^2_{Cubic}
Child						
Base-MPH	26.82**	0.11	6.23*	0.03	8.94*	0.02
Placebo-MPH	6.25*	0.03	0.02	0.00	1.42	0.00
Parent						
Base-MPH	2.57	0.01	1.27	0.00	4.05*	0.02
Placebo-MPH	0.56	0.00	0.11	0.00	2.28	0.01

Note. Base = baseline (no drug condition). MPH = methylphenidate. Base-MPH = Trend analysis using baseline and active methylphenidate conditions. PL-MPH = Trend analysis using placebo and active methylphenidate conditions. R^2 = proportion of variance accounted for by trend components. * = $p < .05$; ** = $p < .001$.

CHAPTER FIVE: CONCLUSION

The present study examined competing hypotheses that may help explain past reports of paradoxical reductions in physical and behavioral complaints associated with MPH therapy in children with ADHD. Symptoms on the STESS side effect rating scale were separated into specific categories to investigate predictions that some physical and behavioral complaints represent ADHD primary/secondary features, whereas others reflect non-medication related complaints reported by children in general, or true emergent symptoms specific to psychostimulant treatment.

Parent and child endorsements of physical and behavioral complaints showed significant reductions from baseline to active MPH conditions for all three categories, and were of a sufficient magnitude to be considered clinically meaningful (i.e., range = 27% to 62%). 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 indicate that part of the observed effect is associated with expectancy 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, 2005) under their high dose MPH condition (dose range = .3 mg/kg to .6

mg/kg). Efron, Jarman, and Barker (1997) reported 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 & Newby, 1991). Collectively, these findings suggest that several items included on emergent rating scales likely reflect behavioral phenotypical 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 the 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 holds even for scales developed specifically to monitor emergent symptoms associated with psychostimulant therapy, such as the Stimulant Drug Side Effects Rating Scale (Barkley, 2005), 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 (Eggers 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, experience daily 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 44% to 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. The additional reduction in children's endorsements may reflect improvement in associated areas of daily functioning, such as improved attention, academic performance, and classroom conduct (e.g., DuPaul & Rapport, 1993; MTA Cooperative Group, 1999; Pelham et al., 1990). This explanation 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.

Similar results were evidenced 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 5-mg (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 5-mg (28% decrease) and 20-mg (27% decrease) MPH conditions only. 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; skin itching, n = 11; dry mouth, n =8; less

urination, n = 8; appetite reduction, n =7, and less bowel movements, n = 7) under the two highest doses (i.e., 15-mg and 20-mg).

Although all three classes of potential emergent symptoms showed significant decreases from baseline levels, 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 the symptom category highly specific to MPH. That is, children receiving multiple doses per day, single doses exceeding 20-mg, and over a longer duration of time are likely to experience a higher frequency and/or severity of emergent symptoms (Gadow, 1986). Preschool children with ADHD (Connor, 2002; Kollins, 2004), and those whose presentation includes other clinical features such as developmental delays (Aman, Marks, Tubott, Wilsher, & Merry, 1991; Handen et al., 1992), may also experience a higher frequency and/or severity of psychostimulant related emergent symptoms. 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 owing to the highly idiosyncratic treatment response observed within and across behavioral, cognitive, and emergent symptom domains in children with ADHD (Rapport & Kelly, 1991).

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. 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 & 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 they change with treatment as evidenced herein. Inclusion of items that help differentiate improved attention from staring or constricted attention are also desirable (for a discussion of over-focused phenomena associated with psychostimulants, see Denny & Rapport, 2001). Finally, the administration of treatment emergent scales prior to initiating therapy must be considered a *de rigueur* component of clinical management for determining a true baseline picture of child complaints.

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