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Tina K. Head
Western Michigan University

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EVALUATION OF MEDICATION EFFECTS ON ACADEMIC PERFORMANCE, SLEEP, AND CORE ADHD SYMPTOMS IN CHILDREN

by

Tina K. Head

A Dissertation
Submitted to the
Faculty of The Graduate College
in partial fulfillment of the
requirements for the
Degree of Doctor of Philosophy
Department of Psychology
Advisor: Galen Alessi, Ph.D.

Western Michigan University
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EVALUATION OF MEDICATION EFFECTS ON ACADEMIC PERFORMANCE, SLEEP, AND CORE ADHD SYMPTOMS IN CHILDREN

Tina K. Head, Ph.D.
Western Michigan University, 2010

Idiosyncratic effects of Vyvanse™ (lisdexamfetamine dimesylate) and placebo were evaluated in a double-blind alternating treatments experimental design in this 4-week study. Direct, objective measures were combined with traditional behavior ratings to provide data sets to assess whether or not the prescribed stimulant medication showed detectable therapeutic effects for a child whose positive response to medication was not obvious via traditional subjective methods. Effects of medication on core ADHD symptoms, academic performance, and sleep in four children ages 10-12 with attention-deficit/hyperactivity disorder. Potential side effects were also measured. Daily measures included parent rating scales, side effects checklist, sleep journal and sleep questionnaires. Weekly data collection of objective measures included a computerized a continuous performance task, 1-minute reading and math tests, and youth self-report instruments. Brief daily school interval data and teacher ratings were collected for one child who was enrolled during the school year. A local pediatrician followed standard clinical practice to provide dose titration and clinical supervision.

All children were referred for clarification of effects or dose titration of Vyvanse. Data sets provided copious and sometimes conflicting information between parent ratings and objective measures. The ability to conceptualize medication effects from both parent
responses and direct measures enabled the physician to alter the child’s course of
treatment. Attention and motion data from the M–MAT offered information not
otherwise available, allowed a behind-the-scene look at effects of less-obvious processes
(e.g. processing speed, patterns of attendant responses, subtle hyperactivity), a process
that supports clinical experience and judgment. Daily monitoring of side effects and
weekly visits with a physician provided for closer monitoring for potential adverse
events. Data plotted over time (parent ratings) or condition (objective measures) painted a
different clinical picture for each child. Responses common to all participants included
minimal side effects and no discernable effects on sleep. Medication effects were fairly
straightforward for two participants, while a more enigmatic picture presented for the
final two children.
ACKNOWLEDGMENTS

Acknowledgments and accolades for patience go to my committee for helping me navigate the convoluted river of research that eventually deposited me on the banks of graduation.

Tina K. Head
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CHAPTER I
INTRODUCTION
Attention-Deficit/Hyperactivity Disorder

Associated Characteristics

Children with attention-deficit/hyperactivity disorder (ADHD) are often impulsive, inattentive, overactive, have a low frustration tolerance, and have difficulty delaying gratification (American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 2000; DSM-IV-TR). This persistent pattern of inattention and/or hyperactive and impulsive behavior significantly impairs academic functioning or peer and family relations during childhood (DSM-IV-TR). Some authors assert the core symptoms of ADHD — inattentiveness, hyperactivity and impulsivity — hinders the ability of children to perform normative developmental tasks as a result of impairment in functioning in academic (Barkley, 2006) and social domains (Deater-Dekard, 2001). The majority of children with ADHD will continue to experience symptoms into adolescence (Barkley, Fischer, Edelbrock, & Smallish, 1990; Biederman et al., 1996) and adulthood (Kessler et al., 2006) with the impairment negatively impacting job performance (Kessler et al., 2005).

Prevalence

The American Psychiatric Association (DSM-IV-TR, 2000) reports ADHD prevalence rates at 3% to 7% for American school-age children. The Centers for Disease Control’s (CDC) 2003 National Survey of Children’s Health estimated the prevalence rate to be 7.8% of the U.S. population under 17 years of age. Incongruent with the ongoing concern of overdiagnosis and increase in prescribing of stimulants, the CDC
survey found only half of the 4.4 million children who had symptoms consistent with a diagnosis of ADHD were taking medication. Efficacious treatments for ADHD include pharmacological and/or behavior therapy (e.g., Multimodal Treatment Study of Children with ADHD Cooperative Group, MTA; 1999; Barkley, 2006). Pharmacological treatment with stimulant medication is the most common treatment for the disorder, with methylphenidate being the most frequently researched (Barkley, 2006). It is estimated that around 75% of children with this disorder respond to initial treatment with stimulant medication with reduced symptom severity in one or more core symptom domains (e.g. Barkley, 1979; Barkley, DuPaul, & Connor, 1999; Pelham, 1993). As a group, these children show clinically significant improvement with stimulant treatment in sustained attention, decreases in motor activity, impulsivity, on-task performance, social interactions, and/or behavioral compliance.

Comorbidity

Comorbidity is a significant problem for a majority of children and adults with ADHD. Jensen and his associates (1997) estimated that up to 80% of children with ADHD have comorbid conditions, with prognoses declining with multiple diagnoses. He noted children exhibiting externalizing symptoms such as hyperactivity and conduct problems benefited usually from pharmacological treatment with stimulant medications; whereas children with ADHD who also have internalizing diagnoses (e.g. anxiety disorders, depression and/or other mood disorders) improved more often from antidepressant medications. The APA (2000) and others (Barkley, 2006; Milberger, Biederman, Faraone, Murphy, & Tsuang, 1995) estimate half of the children with a diagnosis of ADHD also meet criteria for oppositional defiance disorder (ODD) or
conduct disorder, one-quarter have an anxiety disorder, around one-fifth have a learning
disability that is independent of inattentiveness, approximately 15% experience
significant depressive symptoms, and 11% have a diagnosis of bi-polar disorder.

Lifetime of Symptoms

Contrary to early research findings that children “outgrow” ADHD symptoms,
hyperactivity and/or inattentiveness continue at a lower, but still significant degree into
adolescence for 70–80% of the children (Barkley, Anastopoulos, Guevremont, &
Fletcher, 1991; Barkley, Fischer, Edelbrock, & Smallish, 1990; Biederman et al., 1996).
Other follow-up studies; found symptoms persist into adulthood for 50% to 65% of
diagnosed children (Kessler et al., 2006; Klein & Mannuzza, 1991). The results of these
outcome studies are somber, noting poorer academic outcomes, including high dropout
rates (Barkley et al., 1990), social relations problems (Weiss & Hechtman, 1993), low
self-esteem (Weiss, & Hechtman, 1993; Hechtman, Weiss, & Perlman, 1980) and much
higher rates of driver-related car crashes and injury, and license suspension (Barkley,

Pharmacological Treatment of ADHD Symptoms

Stimulants: Rates of use, efficacy

Stimulants have been shown to be efficacious short-term treatment of core
symptoms and some associated characteristics of ADHD in more than 200 clinical trials
(Barkley et al., 1991; MTA, 1999; Pelham, 1993; Swanson, Sandman, Deutsch, &
Barren, 1983). Methylphenidate is the most frequently prescribed and researched
stimulant-class medication for the disorder (Barkley, 2006; Pelham, 1993; Purdie, Hattie,
& Carroll, 2002). In the late 1960’s, efficacy of stimulant medications for treatment of
ADHD began to be widely reported (e.g., Conners & Eisenberg, 1963; Knights & Hinton, 1969) and became physicians' first-line treatment for the disorder (Chatfield, 2002). Later, a longitudinal study found young adults with ADHD who received long-term stimulant treatment as children had better social skills and self-esteem, fewer car accidents and committed fewer delinquent behaviors compared to same-age young adults with ADHD who did not receive treatment (Hechtman et al., 1984).

**MTA study**

Pharmacological treatments alone and in combination with intensive behavioral interventions are effective in reducing behavioral problems associated with ADHD, according to conclusions drawn from traditional group statistical analysis and the most publicized outcome from the Multimodal Treatment Study of ADHD (MTA, 1999). The landmark MTA study compared the effectiveness of medication (well-titrated with an algorithm), intensive behavioral school and parent training interventions, the combination of these two treatments, and treatments typically available within the community. Although all four groups showed improvement over time results from the preliminary analysis of this large 14-month study showed that children in the medication management treatments yielded the most improvement on core ADHD symptoms. Oppositional and/or aggressive behaviors, internalizing symptoms, social skills, parent-child relations, and reading achievement demonstrated moderate advantages for children in the combined treatment group. While combined medication and behavioral treatments were not statistically superior to medication management alone, on average children receiving combined treatments needed lower doses of medication. It is also noteworthy that although two-thirds of the community (treatment of usual) group received medication, the
medication management group with carefully controlled titration procedures had superior symptom outcome compared to participants in the community comparison group. MTA authors emphasized that to evaluate clinical significance, one must consider that combined treatments had the best outcome on 12 of 19 measures. Treatment recommendations from the study seem contradictory, wherein the MTA authors note optimal treatment may differ, depending upon which treatment is used as a comparison (1999):

If one assumes that a behavioral intervention should always be used as the first-line ADHD treatment (often the preference for many parents, and the practice in many European countries), and that the possibly greater benefits of combined treatment should be determined, then combined treatment seems to offer a great deal of benefit over behavioral treatment alone. But if one provides carefully monitored medication treatment similar to that used in this study as the first line of treatment, our results suggest that many treated children may not require intensive (emphasis added) behavioral interventions. (p. 1081)

Swanson, Kraemer, and Hinshaw (2002) published a secondary analysis of the MTA data that evaluated the study results for clinical relevance of the treatments. In contrast to the primary analysis by the MTA group, Swanson and his colleagues did not look for significant differential changes over time via paired comparisons of overall group means. To reduce measurement variance and increase analytical power, Swanson and his associates compared collapsed end-of-treatment parent and teacher rating scores into a total “severity” measure. These orthogonal comparisons were evaluated as binominal “success” and “failure” categories. “Success” was defined as 1.0 or less on the
parent rating scale, a score at which the participant would no longer meet DSM-IV criteria. Swanson’s group also emphasized effect size as a measure of clinical relevance. Results of the reanalysis found variation was significantly reduced by the use of condensed severity scores resulting in a more powerful analysis. Employment of an algorithm contrast of combined and medication management groups vs. behavioral and community groups confirmed significant medication effects as found in the primary analysis, with a large effect size (Cohen $d = 0.59$). To evaluate whether the combined treatment was superior to medication management or behavioral treatments, average end-treatment measures across domains and summary scores were compared. Findings for the secondary analysis confirmed advantages for the combination treatment, with a statistically significant, but small to moderate effect size of 0.26. The most illuminating analysis was the conversion of summary rating scores to “success” measures: Sixty-eight percent of the participants in the combined treatment group were no longer clinically symptomatic; 56% of the medication management group did not meet DSM-IV criteria; and 25% of the community care group were also indistinguishable from the same-age and gender nonclinical populations.

Inconsistent with the original 14-month findings, the 3-year follow-up of children in the MTA study did not find differences between any of the groups (Jensen et al., 2007). Participants were released from the medication-algorithm protocol after 24-months, then families were free to alter their child’s treatment. The authors speculated that earlier advantages were no longer evident due to some children in the medication algorithm and combined treatments group stopped taking medication, while some children in the behavioral intervention group began pharmacological treatment. They
additionally discussed loss of treatment intensity as another factor contributing to the lack of differences between treatment groups.

Although controversy over the outcome of the MTA study continues, it is clear that effective pharmacological treatment as part of a total treatment package is a vital consideration for clinicians and their clients.

Stimulant Mechanism of Action

Following decades of research on the efficacy of stimulant medications for treatment of ADHD symptoms, advances in neuroimaging and neurochemical techniques drew research attention to investigate the mechanism of action of these drugs (Bradley & Golden, 2001). Although the exact mechanism of action of stimulant medications has not been definitively identified, they are believed to ameliorate ADHD symptoms by blocking reuptake of dopamine and norepinephrine into presynaptic neurons. Blocking reuptake of the two neurotransmitters increases availability of dopamine and norepinephrine in the extraneuronal space (e.g., Arnsten, 2000; Biederman & Spencer, 1999) in both prefrontal cortex and subcortical areas of the striatum and nucleus accumbens (Biederman & Spender, 1999; Bymaster, et al., 2000). The origin of the central norepinephrine system is primarily in the locus coeruleus, which consists of noradrenergic neurons that project from its location in the reticular formation to the cerebral cortex, midbrain, and spinal cord. Animal research has shown that the locus coeruleus has a significant impact on attention (Aston-Jones, Rajkowski, & Cohen, 1999). Dorsolateral and dorsomedial prefrontal cortex appear to be the only afferent norepinephrine neurons to the locus coeruleus, leading to speculation that dysfunction in either the locus coeruleus or prefrontal cortex may affect regulation in reciprocal relation
Signal-to-noise ratios for afferent neurons increase when locus coeruleus neurons release norepinephrine, and postsynaptic cortical activity is decreased (Pliszka, Mcracken, & Maas, 1996). Norepinephrine enhanced signal-to-noise ratios facilitate information processing by reducing spontaneous or low activity simultaneously, while increasing responses to specific synaptic inputs (e.g., Ashton-Jones, et al., 1999; Berridge, Arnsten, & Foote, 1993). It is believed that the signal-to-noise ratio function of norepinephrine is a key mechanism for its effect on attention and results in a state in which forebrain circuits have the most efficient discrimination between optimal and non-optimal inputs (Aston-Jones, et al.; Pliska, et al.). Other animal researchers have noted that the locus coeruleus is relatively inactive during repetitive, habituated activities such as grooming, but is stimulated during activities requiring discrimination and other attention-demanding tasks (Ashton-Jones, et al.; Pliszka, et al.). Further, these researchers found stimulation of the locus coeruleus during tasks requiring attention results in activation of the anterior attention system in the forebrain.

Elucidation of attentional processes at a neurobiological level has evolved, paralleling advances in neuroimaging techniques. Attentional processes in humans and primates have been shown to be distributed over multiple areas of the brain, performing distinct functions (Pliska, et al.). The vision-activated attention system is considered to be “broadly divided” into anterior and posterior systems (Pliska, et al.).

**Posterior Attention System**

Norepinephrine neurons prime posterior attentional components to respond to the presence of novel stimuli (Pliszka, et al.). When a new stimulus appears in the visual field, the posterior attention system is activated, first chiefly in the right superior parietal
area. Current research indicates the right superior parietal then disengages from the current stimulus, followed by diversion of the focus of attention to the new stimulus by activation of the superior colliculi (Pliszka, et al.). Finally, the pulvinar engages attention on the new stimulus. Pliszka, et al. Concluded that “norepinephrine primes the posterior attention system, which orients to and engages new stimuli ... for efficient attentional functioning, there must be a clean ‘hand off’ to the anterior system, which coordinates the frontal lobe functions.”

Anterior Attention System

The anterior cingulated gyrus and its projections to the prefrontal cortex comprise the anterior attentional system (Pliszka, et al.). The anterior cingulated gyrus, which is innervated by both noradrenergic and dopamine neurons, is activated during tasks requiring mental manipulation of information and a response (Pliszka, et al.). The anterior cingulated is especially active during tasks requiring inhibition of responses or divided attention.

Prefrontal Cortex

In prefrontal cortex neurons, norepinephrine appears to decrease unrestrained activity, but increase these neurons’ response to specific input (Pliszka, et al.). Current understanding of prefrontal cortical function to some extent has been extrapolated from animal model research and assessments of cognitive function in patients with brain damage. Research with primates demonstrates support for working memory function in the prefrontal cortex: Performance on delayed-response tasks declines dramatically with only small ablations to the prefrontal cortex (Arnsten et al., 1996). Lesions in humans in the dorsolateral area have been observed to impair attention to details, restrict response
alternatives, and induce perseveration (Pliszka, et al). Conversely, medio-orbital lesions generally result in poor inhibitory control — a hallmark of ADHD symptomatology that manifest as impulsivity, emotional liability, and social functioning deficits (Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001).

Dopamine

Dopamine, like norepinephrine, decreases spontaneous activity in prefrontal cortex neurons, but in contrast it decreases the responsiveness of cortical neurons to new input, locking out new information to prepare the organism to respond (Pliszka, et al.). Investigations of dopamine and norepinephrine on primate prefrontal neuronal activity during a delayed-response task showed that dopamine augmented activity of prefrontal neurons active in integration of visual cues and motor performance based on spatial short-term memory. During this delayed-response task, norepinephrine appeared to modulate activity of prefrontal neurons involved in visual reception and behavioral states or activity levels (Arnsten, et al., 1996). Additionally, it is well understood that a critical function of dopamine is preparing animals for motor action (Pliszka, et al.).

Increased dopamine availability in subcortical regions (basal ganglia and limbic areas such as the nucleus accumbens) is likely responsible for psychotomimetic effects, euphoria, reinforcement and abuse potential of stimulants (Arnsten, 2000). Additionally, increased dopamine availability in the striatum may be responsible for both inducing hyperactive motor behaviors in non-hyperactive subjects and reducing hyperactive motor behaviors in patients with ADHD (e.g., Arnsten, 2000; Bymaster, et al.; Pliszka, et al.).

Maximal effects of stimulants are seen within 2 hours of ingestion, at the time when there is an acute release of these neurotransmitters, leading Zametkin and Rapoport
(1987) to conclude that stimulant effects on dopaminergic and noradrenergic projections occur via an increase in inhibition of prefrontal cortex activity on subcortical structures. Indeed, Zametkin, et al. (1985) reported the effects of dextroamphetamine reuptake blockage norepinephrine lead to long-term decrease in locus coeruleus firing; hence, stimulants may “reset” the locus coeruleus to a lower level of activity to there can be a more robust response to external stimuli. Imaging studies of patients with ADHD with hyperactivity show decreased activity in prefrontal cortex and striatum and increased activity in posterior sensory/motor cortex. These levels of activity are reversed with stimulants (Pliszka, et al.).

*Extended-Release Stimulants*

Studies evaluating the effects of methylphenidate conducted prior to 2000 were immediate-release formulas that reached peak plasma levels 1.5 to 2 hours post-administration (Physicians Desk Reference, PDR, 2002). Peak plasma levels are known to coincide with maximum therapeutic effects of the drug, and two or three doses every 4 hours are required to maintain effectiveness throughout the day (Swanson, Kinsbourne, Roberts, & Zucker, 1978).

In 2000, the Food and Drug Administration (FDA) approved 8- and 12-hour extended-release formulations of methylphenidate. Concerta was designed to produce effects for 12 hours. Information supplied by its pharmaceutical manufacturer shows plasma-level concentrations reach an initial peak of methylphenidate between 1 to 2 hours after ingestion, with a gradual increase until the drug reaches a maximal peak around 6 to 8 hours post ingestion after which plasma levels gradually decline (ALZA Pharmaceuticals, 2003). Concerta has been shown to have equivalent effects to three-
dose daily administrations of immediate-release methylphenidate, without peak and trough concentrations seen with three-dose administration. In clinical efficacy trials, Concerta was compared to Metadate CD, an 8-hour extended-release methylphenidate product, in a double-blind, crossover design (Swanson, et al., 2004). Results showed superior attention and behavior performance was achieved by the formula with the highest plasma concentration post administration: Metadate > Concerta 1 to 5 hours; Metadate ~ Concerta 5 to 8 hours; Concerta > Metadate 8 to 12 hours. The authors report that Concerta caplets were overencapsulated with a gelatin capsule to blinding. Swanson and his associates reported they completed in vitro dissolution testing of the materials, and were able to confirm the absence of a detectable effect of the overencapsulation on the release of active agents in the Concerta tablets.

Limitations and Adverse Effects of Stimulant Treatment

Finally, while most criticisms of stimulant medications are unfounded, there are inherent complications, the most frequent and problematic of which are side effects. The most common side effects of stimulant medications are loss of appetite and insomnia, which usually do not dissipate with repeated administration (Pelham, 1993). Nausea, nervousness, dizziness, stomachaches, headaches, tachycardia, skin rashes, and drowsiness are also frequently reported. Insomnia and lack of appetite are two of the main reasons that stimulant medications are typically not given in the evening. When medication is not in effect after school hours, beneficial effects are usually not realized (Pelham, 1993). These commonly occurring side effects may be a major factor in noncompliance with pharmacotherapy (Rapport & Moffitt, 2002).
Inadequate titration resulting in doses that are too high can cause what critics have named the “zombie effect,” which is cognitive over-focusing, blunting, and social withdrawal (Pelham & Milich, 1991; National Institutes of Mental Health, 1994). In rare instances, stimulant medication taken by children with ADHD can exacerbate or precipitate tics. There are a few isolated cases in which stimulants are suspected of acting as a catalyst in producing Tourette’s syndrome (NIMH, 1994; Pelham, 1993).

In a review by Rapport and Moffitt (2002), 8 of 11 studies that evaluated height and weight gain found lower than expected rates of growth; however, follow-up reports showed that for many children, initial growth reductions appear to dose related and may be diminished by suspending drug treatment during the summer. The authors noted studies with follow-up reports for a period of 4 years or more did not show significant differences in expected height and weight gain. Rapport et al. concluded cardiovascular effects, although statistically significant, were not considered of clinical concern.

Paradoxically, somatic complaints were found to decrease with methylphenidate treatment in comparison with placebo in several of the studies reviewed. Rapport, et al. (2002) observed somatic complaints decreased in correspondence to reduction in distress associated with improvement in core ADHD symptoms and academic performance; however, the authors noted stimulant treatment exacerbated somatic symptoms for some children with comorbid internalizing symptoms.

Despite beneficial influence on attention, in-seat completion and cognitive performance, stimulants alone do not normalize academic achievement for approximately half of the children with ADHD (Abikoff & Gittelman, 1985; Pelham, 1993; Swanson, et al., 1978). As discussed previously, reanalysis of the MTA data (Swanson, et al., 2002)
only 56% of the children on well-titrated medication regimens showed significant symptom remission.

Concern for medicated children’s self-esteem has been expressed by some advocacy organizations (e.g., Children and Adults with Attention Deficit Disorders) and others (e.g., Bugental, Whalen, & Henker, 1977; Rosen, O’Leary, & Conway, 1985) when improvements in behavior and academic performance are attributed to the drug. Contrary to these detrimental predictions, several studies found long-term stimulant treatment did not have a deleterious effect on behavioral attributions of children with ADHD (Ingram, 2001; Milich, Licht, Murphy, & Pelham, 1989; and Ohan & Johnson, 1999).

Controversy over the abuse potential of methylphenidate and an increased risk of substance abuse among ADHD population treated with stimulants surfaced during Congressional hearings in the 1970s (Barkley, 1998) and has continued to be a topic of debate in the legislature. Drug Enforcement Agency (DEA) officials’ testimony before a House Education subcommittee (Woodworth, 2000) warned abuse of methylphenidate has increased significantly since 1990 and the drug’s pharmacokinetic similarity to cocaine greatly increases methylphenidate’s abuse potential. The report was based on poison control, emergency room, and pharmacy and school theft data. Although the DEA strongly criticized school administrators for lack of control storing and administering methylphenidate and other prescription medications, the Government Accountability Office (formerly the General Accounting Office; 2001) in its investigation of medication administration in U.S. schools found few incidences of diversion or abuse, and reported 96% of the schools dispensed stimulant medications with appropriate safeguards.
Conversely, high risk of substance abuse among adolescents and adults who have had long-term treatment with stimulants have not been borne out. A 16-year prospective follow-up study found no differences between children treated with methylphenidate and normal comparisons for substance abuse disorders or dependence (Mannuzza, Klein, & Moulton, 2003). Further a review by Hechtman and Greenfield (2003) of long-term prospective follow-up studies also did not find that methylphenidate treatment increased the risk of substance abuse. Sustained-release methylphenidate appears to have a much lower abuse potential than the original immediate-release formulation, which is likely due to sustained-release's slow and stable rate of onset (Kollins, Rush, Pazzaglia, & Ali, 1998).

Finally, comorbid anxiety and/or depression may predict poor response to stimulants (DuPaul, Barkley, & McMurry, 1994; Pliszka, 1989), and may be better treated with bupropion, tricyclic or other types of antidepressants (Barkley, 1998; Biederman et al., 1989).

Effects of Stimulant Treatment on Academic Performance

Nearly all clinic-referred children with ADHD have significant problems at school, with 20% having a diagnosis of a specific or general learning disability (Barkley, 2006). A review of the literature of academic performance reflect that up to half of the children with an ADHD diagnosis have academic difficulty that warrants intervention (e.g., Barkley, Fischer, Edelbrock, & Smallish, 1990; Weiss et al., 1993). In a 13-year follow-up study of school-age children (Barkley, Fischer, Smallish, & Fletcher, 2006), young adults from the hyperactive group were significantly more likely to have been retained at least for one grade, and suspended from school than the control group. In this
outcome study, 32% of the hyperactive group failed to graduate from high school, compared to none of the control group.

Following several instrumental studies in the 1960s, it was widely accepted that stimulants have beneficial effects on core symptom reduction (Conners, 2002). Subsequent studies have shown significant reduction of out-of-seat and off-task behaviors and increased academic productivity (e.g. Abikoff & Gittleman, 1985a; Douglas, Barr, O’Neill, & Britton, 1985; Evans et al., 2001). Laboratory measures of cognitive performance also readily showed improved performance on attention, error reduction, reduced variability in responses, and less impulsive responding (e.g. Douglas et al., 1985; Greenberg & Waldman, 1993). Additionally, research that evaluated the reliability/translatability of laboratory and clinic measures to classroom performance found decreases in continuous performance task (CPT) omission error scores, which approximate increases in classroom attention (Rapport, DuPaul, Stoner, & Jones, 1986). Predictions that these short-term gains would readily translate into increased grade point averages and fewer classes failed were not confirmed. In earlier reviews of studies evaluating stimulant drug effects on classroom behavior, Barkley (1979) and others (O’Leary, 1980; Whalen & Henker, 1976) concluded there was not sufficient evidence that stimulants positively affected either short- or long-term academic performance; Pelham (1993) speculated that methodological problems failed to detect statistically or clinically significant effects. He and other researchers argued that broad, gross measures such as end-of-term grades, and some broad achievement measures such as Wide Range Achievement Test, may be insensitive to stimulant effects. Carlson and Bunner (1993) asserted direct measures of academic progress can be achieved with workbook
assignments of consistent length and difficulty. Subsequent studies have shown better long-term outcomes for graduation rates, grade retention, reading achievement, and less absenteeism (Barbaresi, Katusic, Colligan, Weaver, & Jacobsen, 2007). Additionally, a preponderance of evidence of short-term, clinically significant improvements has been found with stimulant treatment. Carlson and Bunner’s review (1993) and a meta-analysis by Kavale (1982) of 135 stimulant efficacy trials showed consistent short-term clinically significant effects on academic performance.

Conversely, support for improvement in academic performance for a period of 6 months or longer is scarce, with one of the few notable outcomes only recently seen for reading, but not math or spelling (MTA, 1999). In a discussion of their 5-year study on long-term effects of stimulants on academic performance, Frankenberger and Cannon (1999) discuss infrequent reporting of concurrent behavioral interventions in academic performance studies. It was this discussion within the research community that undoubtedly served as a catalyst for the MTA study discussed earlier.

Methylphenidate improved word and nonword decoding, and rapid naming in a study in boys with ADHD and comorbid reading disability (Bental & Tirosh, 2008). In this sample, all participants had confirmed decoding deficits and slower naming fluency. The authors asserted that effortful processing is involved in these tasks, and improvement with stimulant treatment was accounted for via better attention, but not improved reading skill deficits. Marzocchi et al. (2008) evaluated the impact of executive functioning on reading in children with ADHD who did not have a reading disability. The authors found ADHD children had impaired interference control, but not response suppression. This group also showed deficits in visual working memory, planning, cognitive flexibility, and
phonetic fluency. Comparison children with a reading disability, but not an ADHD, diagnosis exhibited deficits in phonetic fluency and almost as much impairment in visual working memory as the ADHD group. The authors noted these findings and a lack of significant difference between ADHD children and normal controls on measures of cognitive inhibition suggest inhibition problems in ADHD children are indicative of a generalized deficit in attention, rather than a function specifically related to executive functions.

Sprague and Sleator's (1977) early work on differential dose effects of methylphenidate on cognitive functions and hyperactivity appeared to show low to moderate doses optimally aided learning and higher doses likewise decreased hyperactivity, but also decreased cognitive performance. As further studies were published, this conclusion appeared to be overly simplistic. Rapport and Kelly (1991, p. 78) reviewed 84 studies that investigated methylphenidate dose-response effects on learning and concluded, “Low doses of MPH were not reported as significantly superior to high does in enhancing cognitive performance in a single study reviewed. Rather, performance tended to be superior under high-dose conditions as a function of task difficulty and complexity.” The reviewers found 38% to 43% of the studies demonstrated significant between-dose differences on academic tasks, all of which favored the high-dose condition. Group data further revealed repetitive, automatic response tasks such as those measured by CPT are optimized with low doses of methylphenidate, assignments, requiring relatively equal application of vigilance and inhibition are optimized with mid-dose range, and effortful academic work also requiring behavioral inhibition is generally optimal with higher dosages. A further observation from Rapport at al., has been recently
confirmed by the MTA study: Behavioral intervention appears to interact with stimulant treatment in a manner that less medication is required for optimal performance. A final note regarding dose-effect analysis of methylphenidate: Several studies (e.g. Rapport et al., 1988; Rapport, DuPaul, Stoner, & Jones, 1986; Vyse & Rapport, 1989) have discussed the misleading nature of generalizing group analyses due to idiosyncratic and task-specific response. In fact, Vyse et al., found 31% of children in their study had a linear dose-response function, as has been widely found in-group analyses. Around 27% had a quadratic dose-response profile.

While new research continues to be published on the topic of long-term effects on academic performance, double-blind placebo trials may be difficult to execute due to removal of pharmacological treatment during placebo conditions. There is an increased risk of the participant being off-task, inattentive, hyperactive, impulsive, and exhibiting rule-breaking behavior during the placebo condition, which may affect the child’s academic performance, including testing. In her dissertation completed at Western Michigan University, Thompson (1994) evaluated the effects of methylphenidate and placebo on on-task behavior in elementary students with ADHD, using the interval observation method contained in this protocol. Thompson found participants were off-task 6% more of the time when they were on placebo, than when they had taken their medication.

Research evaluating effects of mediation on grades, test scores, and other measures of academic performance have not led to a clear understanding of this topic, with many studies showing little or no improvement over placebo. Some authors speculate that no significant differences were found for studies that looked at end-of-term
grades and standardized achievement measures, because long-term measures are insensitive to medication effects. The landmark MTA study (1999) found a small but significant improvement for participants for reading, but not for math or spelling. Although the literature measuring stimulant effects on learning predominately shows short-term benefits of medication over placebo, these results have been mixed and occasionally contradictory, depending upon the domain being evaluated, comorbid conditions, dosage, and academic measures used (i.e. Aman & Werry, 1982; Abikoff & Gittleman, 1985).

Sleep in Children with ADHD

Sleep Problems

Excessive movements during sleep was listed as a diagnostic criteria for hyperactive children in earlier editions of the DSM, but was dropped in the DSM-III-R edition (APA, 1987). Gruber, Sadeh, and Raviv (2000) noted sleep difficulties were appropriately excluded from current editions due to its low specificity. Despite the fact that sleep problems are not a hallmark of ADHD, a majority of studies examining sleep problems in children with the disorder have shown parts report higher incidences of sleep-related problems compared to parents of control children (LeBourgeois, Avis, Mixon, Olmi, & Harsh, 2004; Crabtree, Ivanenko, O’Brien, Gozal, 2003; Ring, et al., 1998; Sung, Hiscock, Sciberras, & Efron, 2008).

In a review of sleep problems in the ADHD pediatric population, Lecendreux and Cortese, (2007) echoed concerns voiced in the 1950’s (Laufer & Denoff, as cited in Lecendrux et al.) that sleep problems greatly overshadowed daytime behavior problems. The reviewers agreed that sleep disturbances significantly decreased quality of life for the
children and their families, and that sleep should be a primary target of intervention. Since poor sleep quality (inadequate duration and/or fragmented sleep) frequently impacts children’s mood, attention, and ability to inhibit behavior, daytime symptoms may be greatly reduced with improved sleep quality (Lecedrux et al.).

Some studies that examined the influence of comorbid oppositional/conduct disorders and stimulant medications found medication and comorbid externalizing behaviors were more strongly associated with parental reports of sleep disturbances than ADHD diagnosis alone (Mick, et al., 2000; Corkum, Moldofsky, Hoff-Johnson, Humphries, & Tannock, 1999). A recent trial (Hvolby, Jorgensen, & Bilenberg, 2008) that used actigraphy to compare non-medicated children with ADHD to non-medicated children with ADHD and comorbid ODD did not find significant differences in sleep onset. Although Dagan, et al. (1997) did not find differences between diagnosed and control groups for sleep problems via parental reports, objective measures of sleep within this study showed less time asleep after lights out until waking in morning, and more restless sleep for children with ADHD, compared to controls. Conversely, Hvolvy and associates found significant differences in sleep onset latency between children with ADHD, comparison children with psychiatric diagnoses, and healthy controls. These authors also found parents overestimated sleep latency when dairies were compared to actigraph records.

In contrast to the Dagan et al. findings, parent report of sleep problems were not substantiated by other studies that used both subjective and objective measures of sleep within the same study (Corkum, et al., 2001; Greenhill, Puig-Antich, Goetz, Hanlon, & Davies, 1983; O’Brien et al., 2003). Interestingly, Gruber and associates (2000) actigraph
study also did not find sleep differences between medication naive ADHD boys without comorbid learning or oppositional/conduct disorders and controls when mean sleep variables were compared. Gruber and his associates looked more closely at their data and examined instability of sleep patterns via night-to-night standard deviations, group differences were significant. Controls had much more stable sleep behaviors than did children in the ADHD group, leading the researchers to posit instability of the sleep-wake system is a common characteristic of children with ADHD. A more recent study by Gruber and Sadah (2004) supported these initial instability findings.

*Objective Measures of Sleep*

*Polysomnography*

Three measures of sleep used in studies reviewed here can be considered objective: Cardiorespiratory polysomnography, actigraph, and behavioral observation. Polysomnography is considered the “gold standard” for laboratory sleep disorder diagnoses (Penzel, et al., 2002) and has been used to detect sleep-related breathing and other sleep problems, as well as to evaluate the effect of stimulants on sleep. The core variable of polysomnography is electroencephalographic (EEG) activity, which measures electrical brain fluctuation (Ondze, Espa, Dauvilliers, Billiard, & Besset, 2003). Up to 10 electrodes were reported used in these studies, as well as gauges held be straps to measure respiratory muscle movement and/or nasal sensors that detect changes in exhalation temperatures and the movement of air. Additionally, control and ADHD children had indwelling intravenous catheters inserted during the second night of one study (Greenhill, et al., 1983). Although periodic blood sampling yielding oxygenation levels of these children, it was unclear which, if any dependent variables from the blood
monitoring were used for analyses. Dependent variables commonly reported for these studies included measures of breathing problems (e.g. apnea), periods of awakenings, periodic leg movements, rapid eye movement (REM) and non-rapid eye movement (NREM) sleep period durations, latency to sleep, sleep efficiency and/or duration of sleep. Since it is currently unclear how REM and NREM sleep processes effect the quality of sleep, or how rested one feels the following morning, REM and NREM and other sleep-state phenomena will not be discussed here.

While polysomnography is touted as the gold standard in diagnostic sleep paraphernalia, the procedure is usually carried out in sleep clinics' unfamiliar environments. Worse, some labs are located on inpatient hospital wards that intrinsically harbor sleep disruptive events, such as late admissions, phones ringing, and staff discussions in hallways (Penzel, et al., 2003).

**Actigraphy**

An actigraph is a noninvasive wrist- or belt-worn device that records fluctuations in minute-to-minute activity and reliably differentiates between sleep and awake state based on movement (Acebo, et al., 1999). Actigraphy has been validated with polysomnography in measures of sleep-wake identification, with a correlation of .90 (Sadeh, Sharkey, & Carskadon, 1994). The system, which quantifies levels of activity during the day or night, has been used to accurately detect hyperactivity, agitation, or psychomotor retardation associated with depression, seasonal affective disorder, and bipolar disorder (Teicher, 1995).
Alertness and Arousal

The quality of one’s sleep is a clinically relevant issue largely due to its impact on cognitive alertness and arousal the following day. Gruber and Sadeh (2004) compared actigraph variables of sleep to vigilance, which is one dimension of cognitive alertness. Vigilance is considered a gauge of responsiveness of the central nervous system and is often measured by signal detection response latency (Ondze, espa, Dauvilliers, Billiard, & Besset, 2003). Although control children’s sleep quality (absence of restless sleep) and quantity significantly impacted performance on neurobehavioral evaluations (continuous performance task measures of omission, commission, and response time, digit span and symbol-digit tasks) no correlation was found for non-medicated ADHD children. Gruber and associates noted significant variability in sleep parameters for the ADHD group account for not finding a significant relationship between sleep and alertness. A follow-up study by Gruber et al. (2007) did not find medication effects on sleep; however, children with ADHD who had severe sleep problems had significantly improved CPT scores when they were on medication and not on placebo. Conversely, CPT performance declined for medicated children with ADHD who had few sleep problems.

The multiple sleep latency test (MSLT) like polysomnography is often used to evaluate sleepiness (Besst, 2003a). Two studies that used MSLT suggested non-medicated ADHD children in the control group due to significantly shorter sleep latencies (Lecendreux, et al., 2000; Golan, Sharhar, Ravid, & Pillar, 2004).

Restless Sleep

Increased incidence of reports of restless sleep appears to include two types of sleep problems, tossing and turning due to longer periods of awakenings between sleep
stages, or periodic limb movement (PLM). PLM is a diagnosable condition that parents may describe as “kicking” or “thrashing” that occurs approximately every 30 seconds for brief periods. PLMs occur in 80% of patients with restless legs syndrome (RLS; Montplaisir, 2004). During wakefulness, patients with RLS experience a severe motor restlessness (usually in one’s legs) frequently described as an irresistible urge to move, crawling sensation, or tension that is partially relieved by movement. Although PLMs commonly co-occur with RLS, excessive movement during sleep may occur in isolation and may reduce sleep quality when the movements evoke arousals. PLMs are also associated with a variety of other sleep disorders (e.g. insomnia, hypersomnia, apnea). Gruber, et al. (2004), who evaluated sleep variability described earlier, speculated PLM may be related to sleep variability.

Stimulant Effects on Sleep

In studies that utilized objective measures to evaluate stimulant effects on sleep, two polysomnography studies (O’Brien, et al., 2003; Lecedreux, et al., 2000), one actigraph study (Dagan, et al., 1997), and one in-hospital behavioral observation study (Kent, Blader, Koplewicz, Abikoff, & Foley, 1995) did not find differences in sleep onset or efficiency. Study results for duration of sleep, however, have been contradictory: Three studies found no differences (Dagan; Kent; Lecedreux), one study found children had shorter sleep duration (O’Brien), but Greenhill and his associates (1983) reported children slept longer. In fact, Greenhill’s within-subject polysomnography study found ADHD children had significantly longer latency to sleep onset, and lower sleep quality due to more frequent awakenings when they took stimulant medication than when they did not. Conversely, several studies that evaluated stimulant effects on sleep found
significant problems via parental report (e.g., Corkum, et al., 1999; Mick, et al., 2000; Ring, et al., 1998; Stein, 1999).

A 2006 study compared effects of methylphenidate and non-stimulant atomoxetine on sleep in children with ADHD (Sangal et al.). Actigraph and polysomnography data showed three doses of immediate-release methylphenidate delayed sleep onset more than three times than did atomoxetine.

Stress Experienced by Parents of Children with ADHD

Early research on parent-child behavior (Danforth, Barkley, & Stokes, 1991). Bell (1971) was the first to speculate that child behavior shapes parental repertoires. In families with hyperactive and/or aggressive children, Bell postulated that undesired child behaviors evoked higher-level parenting responses, including reasoning, giving or removing rewards, restraint, reprimands, or corporal punishment. Children from the Fels Longitudinal Study (Battle & Lacey, 1972), were observed interacting with their mothers biannually for 6 years. Hyperactive children in the cohort were described as aggressive, noncompliant, and attention seeking, while their mothers were reported as responding in critical, disapproving, and punishing manners. Researchers involved with the study speculated that hyperactivity evoked negative responses from their mothers.

Patterson (1984) posited that aggressive and antisocial children’s behavior is shaped via a coercive family process, in which the negative reinforcement process strengthens child coercion and parent withdrawal of command. Patterson’s behavioral observation of hundreds of parent-child dyads supported his assertions that escape/avoidance learning escalates the intensity of coercive family interactions.
Cunningham and Barkley (1979) applied Patterson’s analysis to children with ADHD due to the high level of aversive behaviors emitted by hyperactive, inattentive, impulsive children. Additionally, half of the children with ADHD had significant oppositional and conduct problems, which frequently involve aggressive behaviors. Cunningham, et al. Compared interactions of mother-child dyads in two groups, hyperactive and normal boys. During free-play and task-oriented activities, mothers of hyperactive children issued twice as many commands as mothers of control-group boys. Correspondingly, normal boys were 57% more compliant to instructions than hyperactive boys during free play, and 35% more compliant during structured task completion. Mothers of non-hyperactive boys also provided contingent rewards twice as often and were more likely to give differential attention for positive behaviors as did mothers of hyperactive children.

Mash and Johnston (1983) found mothers of hyperactive boys reported clinically significant elevated levels of stress when compared to mothers of typically developing boys. The authors found stress was highly associated with their child’s distractibility and demand characteristics, as well as feelings of self-blame, social isolation, and lack of confidence in parenting skills. These mothers also reported higher incidence of depressive symptoms. Likewise, Breen and Barkley (1988) found mothers of hyperactive girls with ADHD reported no differences in child-evoked stress responses than mothers of hyperactive boys with ADHD. Mothers of boys, but not girls in this study were found to have higher incidences of depression and marital discord.

Later studies that differentiated effects of stress related to oppositional/conduct behaviors versus hyperactivity, found oppositional problems uniquely contributed to the
majority of parental stress, rather than severity of ADHD symptoms or hyperactivity (e.g., Anastopoulos, Guevremont, Shelton, & DuPaul, 1992; Barkley, Fischer, Edelbrock, and Smallish, 1991; Podolski & Nigg, 2001). Minority parents of children with ADHD reported higher levels of child related stress than parents of children with chronic medical conditions (Gupta, 2007), which supports earlier findings discussed above in studies that looked at parent-child interactions in predominately white, middle class parents.

**Effects of Child Stimulant Treatment on Parental Behavior**

A counterpart to the Cunningham and Barkley (1979) study discussed earlier, was observation of free-play and structured-task interactions between mothers and their hyperactive sons under triple-blind crossover placebo and drug conditions (Barkley & Cunningham, 1979). Compared to placebo, in response to maternal requests, children were more frequently compliant and for longer periods following consumption of a titrated dose of methylphenidate. In the drug condition, mothers were less demanding and more attentive to their son’s compliant responses, which prompted the authors to speculate that with medication, the behavior of the boys was more acceptable to the mothers, who responded by reducing their control demandingness over the children.

A component of the MTA study (1999) measured parent-child relations via power assertion by the child’s parent(s) and personal closeness with two composite questionnaires. Improvement on parental power assertions was reported for all treatment conditions. Conversely, personal closeness was reported to increase for the combined, behavioral, and community control groups, but declined for the medication-only group. Owens and her associates (2003) who analyzed the MTA data found lower rates of “excellent response” to treatment for children in the medication-only and combined
groups when parents reported significant depressive symptoms and their child had a high severity rating at baseline. A recent look at stress experienced by parents of preschoolers with ADHD did not find differences between medication and placebo groups as measured by the Parent Stress Index (PSI; Abidin, 1995); however, the Preschoolers with ADHD Treatment Study (Abikoff, et al., 2007) did find effects varied by informant and outcome measure.

Medication Effects

While the vast majority of patients with ADHD benefit from pharmacotherapy, predicting which medication will effectively reduce symptoms with tolerable side effects for specific individuals has not been successful (Kent, Cambfield, & Camfield, 1999). Physicians customarily use a “medication trial” to determine effectiveness. Nikles and her colleagues (2006) assert bias can occur as a result of this clinical practice, especially expectancy effects and regression toward the mean. Nikles modified the “n-of-1” trials (within-subject, double-blind, crossover) with randomized, multiple crossovers, basically creating an A-B-A-B-A withdrawal evaluation for clinical practice. This process was used to evaluate the effectiveness of stimulant treatment for 86 pediatric ADHD patients. Data was based on daily reports and exit interviews. Authors determined the process was valuable for clarifying idiosyncratic treatment effects. A commentary on single-subject design by Newcombe (2008) cautioned that while results cannot be generalized, the method is warranted for atypical patients and for populations for which clinical trials have not been published (e.g. use of a medication for patients with comorbid conditions). Newcombe adds the process is also valuable for cases where a physician speculates at least one medication can be discontinued for a patient who is on multiple medications.
Subjective reports (e.g., parent and teacher reports) are an essential, but often-insufficient method of detecting behavior change. In a 1994 study by Thompson, classroom behavioral observations detected marked improvement in attentiveness and activity levels for participants in the methylphenidate condition, whereas teacher reports did not. Studies such as these illustrate the importance of objective measures for detecting efficacy in pharmacological treatments of ADHD symptoms. This proposed study combines objective efficacy measures with traditional behavior ratings by the children’s parents and teachers.

**Clinical Pharmacology of Lisdexamfetamine Dimesylate**

The FDA approved the Vyvanse (lisdexamfetamine dimesylate) for treatment of ADHD symptoms in children in June, 2007. Vyvanse was shown to be effective for the treatment of ADHD symptoms in children ages 6 to 12 years for up to 12 hours in two clinical trials. Pharmacodynamic studies show the parent component, lisdexamfetamine dimesylate, has a half-life of less than 1 hour, with the average half-life of converted dexamphetamine at 10 hours (The Medical Letter, 2007). Lisdexamfetamine dimesylate is therapeutically inactive until it is metabolized and converted to dextroamphetamine within the digestive system (Cowles, 2009). Gradual release of d-amphetamine occurs as lisdexamfetamine is hydrolyzed following oral ingestion into l-lysine, a naturally occurring amino acid, which is therapeutically inactive. Dexamphetamine is gradually released as l-lysine is enzymatically cleaved as it first is processed by the liver and/or during intestinal digestive metabolism. The process of rate-limited hydrolysis transformation is understood to limit dose-related adverse effects and abuse potential (Cowles). Unlike all other stimulant extended release formulas, which are achieved via
manufactured processes, lisdexamfetamine’s unique biotransformation produces steady release of the active metabolites. Dexamphetamine is broken down, excreted by the body and is no longer in the patient’s bloodstream around 48-50 hours after oral administration. Dextroamphetamine is a psychomotor stimulant that has been used to treat symptoms of inattention for more than 70 years.

Adverse Effects of Stimulant Medications

Research that presents more than minimal risk for children may be approved under 45 CFR 46.405 if the research may benefit the participant. Unlike clinical trials that use a group design (one group receives the medication and one group receives a placebo), the alternating treatments experimental design employed in this study ensures each participant is able to compare the effects of the ADHD medication under study with placebo. Additionally, more than attention and activity levels are measured: The effects of the medication and placebo are measured on each child’s reported compliance behavior, sleep, and academic performance.

Concern for medicated children’s self-esteem has been expressed by some advocacy organizations (e.g., Children and Adults with Attention Deficit Disorders) and others (e.g., Bugental, Whalen, & Henker, 1977; Rosen, O'Leary, & Conway, 1985) when improvements in behavior and academic performance are attributed to pharmacotherapy. Contrary to these detrimental predictions, however, several studies found long-term stimulant treatment did not have a deleterious effect on behavioral attributions of children with ADHD (Ingram, 2001; Milich, Licht, Murphy, & Pelham, 1989; and Ohan, & Johnston, 1999).
Stimulants have been used to treat ADHD since the 1940s (Feldman, Meyer, & Quenzer, 1997). Efficacy and safety information on these stimulant medications have been extensively documented (Elia, Easley, & Kirkpatrick, 2007). In 2006, following multiple reviews, FDA’s Pediatric Advisory Committee declined to recommend a black box warning (FDA’s strongest advisory warning), instead suggesting problems be added to the warning section of medication labeling. The American Academy of Pediatrics (Sullivan, 2006) reminded the public and practitioners that “A black box warning is not a contraindication. It does not mean that physicians should refrain from using a medication when it is indicated” (p. 4). Adderall XR’s medication label has a black box warning stating, “Misuse of amphetamine may cause sudden death and serious cardiovascular adverse events.” Label warnings include reports of heart-related problems: sudden death in patients who have heart problems or heart defects; stroke and heart attack in adults; and increased blood pressure and heart rate. Mental (Psychiatric) problems: New or worse behavior and thought problems; new or worse bipolar illness; new or worse aggressive behavior or hostility. Children and Teenagers: New psychotic symptoms (such as hearing voices, believing things that are not true, are suspicious) or new manic symptoms. Observations from clinical practice have also shown that children may exhibit irritability as the medication is wearing off (Sloane, personal communication, 2005). Although medication is the most common treatment for ADHD (Barkley, 1998), it is only part of an effective multimodal treatment package that includes psycho-education and behavior management (MTA, 1999). Despite the beneficial influence on attention, staying in-seat and enhanced cognitive performance, stimulants alone do not normalize academic achievement for approximately half of the children with ADHD (Abikoff &
Gittelman, 1985; Pelham, 1993; Swanson et al., 1978). As discussed previously, reanalysis of the MTA data (Swanson et al., 2002) only 56% of the children on well-titrated medication regimens showed significant symptom remission.

Side Effects for Stimulant Medications

Typical stimulant side effects include appetite suppression, slower weight gains, insomnia, and transient headache and stomachache (see Table 1). In one study, 2% of children reported development of tics, which are repeated motor movements or vocal sound. Additionally, mild increases in blood pressure and heart rate have been observed in children and adolescents during clinical trials. The manufacturer noted the long-term consequences of these short-term observations are unknown (“FDA PAC March 06 Briefing Document,” 2006). There have been rare reports of visual disturbances, including blurring of vision with stimulant medications.

Several studies (reviewed by Rapport & Moffitt, 2002) have shown slower weight and height gains for children who take stimulant medications. Although researchers (Klein & Mannuzza, 1988; Spencer et al., 1996) have found no differences in weight and height gains in follow-up studies, it is recommended that children’s growth be monitored. A recent meta-analysis of 13 trials of methylphenidate (Spencer et al., 2005) showed children on the medication for two years or more had “minimal effect” on participants’ height and weight. These researchers notice that children who were the smallest had the most gains, whereas the tallest children had slightly less height gains than expected. Four-week trials of Vyvanse showed higher doses were associated with more initial
weight loss (Shire US, 2007a). Adolescents lost between 1.1 and 2.8 pounds during the first 4 weeks of treatment.

**Table 1.**

*Increased Risk* of Side effects for Stimulant Medication

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Adderall</th>
<th>Concerta</th>
<th>Daytrana</th>
<th>Focalin</th>
<th>Metadate</th>
<th>Ritalin LA</th>
<th>Vyvanse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>4%</td>
<td>—</td>
<td>—</td>
<td>6%</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cough</td>
<td>—</td>
<td>2%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Lability</td>
<td>7%</td>
<td>—</td>
<td>6%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2%</td>
<td>2%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>5%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>5%</td>
</tr>
<tr>
<td>Headache</td>
<td>—</td>
<td>4%</td>
<td>—</td>
<td>14%</td>
<td>4%</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>15%</td>
<td>3%</td>
<td>8%</td>
<td>—</td>
<td>3%</td>
<td>3%</td>
<td>16%</td>
</tr>
<tr>
<td>Infection</td>
<td>2%</td>
<td>3%</td>
<td>3%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Anorexia</td>
<td>20%</td>
<td>4%</td>
<td>21%</td>
<td>21%</td>
<td>7%</td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>—</td>
<td>1%</td>
<td>3%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Psychiatric Disorder</td>
<td>—</td>
<td>—</td>
<td>6%</td>
<td>11%</td>
<td>—</td>
<td>—</td>
<td>10%</td>
</tr>
<tr>
<td>Rash</td>
<td>—</td>
<td>—</td>
<td>6%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3%</td>
</tr>
<tr>
<td>Sinusitus</td>
<td>—</td>
<td>3%</td>
<td>5%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Stomachache</td>
<td>4%</td>
<td>6%</td>
<td>10%</td>
<td>4%</td>
<td>3%</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3%</td>
<td>1%</td>
<td>10%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>5%</td>
</tr>
</tbody>
</table>

* increased occurrence of side effects in comparison to placebo.

**Abuse Potential**

Controversy over the abuse potential of stimulants and an increased risk of substance abuse among ADHD population treated with methylphenidate surfaced during Congressional hearings in the 1970s (Barkley, 1998), and has continued to be a topic of debate in the legislature. Drug Enforcement Agency (DEA) officials testimony before a
House Education subcommittee (Woodworth, 2000) warned that abuse of stimulants intended to treat ADHD symptoms has increased significantly since 1990.

Abuse potential increases significantly if taken via rapid administration (e.g. snorting, injecting), which increases drug intensity and duration (Feldman, Meyer, & Quenzer, 1997). Vyvanse (lisdexamfetamine dimesylate) is therapeutically inactive until it is metabolized into dexamphetamine (Shire, 2007a). In two drug abuse studies, the reinforcing effects of Vyvanse lisdexamfetamine dimesylate were rated significantly lower when compared to both inhaled and intravenously administered d-amphetamine (Shire).

Additionally, increased risk of substance abuse among adolescents and adults who have had long-term treatment with stimulants have not been borne out. Two studies (Fischer & Barkley, 2003; Wilens, 2004) found early and appropriate treatment of ADHD significantly reduced the rate of substance abuse in adolescence. Also, a 16-year prospective follow-up study found no differences between children treated with stimulant and normal comparisons for substance abuse disorders or dependence (Mannuzza, Klein, & Moulton, 2003). Further, a review by Hechtman and Greenfield (2003), of long-term prospective follow-up studies also did not find that stimulant treatment increases risk of substance abuse.

Single-Subject Research

Single-Subject Analyses as a Clinical Instrument

Since the early 1980s, single-subject repeated measures experimental withdrawal design — referred to as “n = 1” or “n of 1” trials in medical references — has been discussed as a pharmacological evaluative instrument that can serve to bridge the gap
between research and clinical practice (Conners & Wells, 1982). The inability to predict which patients will be responders to specific medications is largely due to reliance on large, randomized clinical trials, which statistical methods obscures individual differences in response (Kent, Camfield, & Camfield, 1999). Pharmacological clinical trials are acknowledged as necessary in the drug evaluation process (Conners et al., 1982). Kazdin (1982) noted that both group and single-subject experimental designs serve disparate, yet complementary functions. To eliminate problems with confounding variables, randomized group pharmacological trials almost always exclude participants with comorbid diagnoses and low average cognitive function. Questions often remain when characteristics of the sample research population do not match individual patients (Cook, 1996). Conners and Wells asserted other concerns remain to be addressed for individuals following clinical studies: Consistency of symptom reduction; optimal range of dosages; and characteristics of responders. Others have cited inherent problems, including: observation and/or outcome bias (Miller & Corner, 1999; Sheldon, Guyatt, & Haines, 1998); high within-group variance ("Randomised Controlled Trials," 1998); regression toward the mean (Mahon, Laupacis, Donner, & Wood, 1996; Nikles, Mitchell, Del Mar, Clavarino, & McNairn, 2006); placebo effect (Mahon et al., 1996; Nikles, Clavarino, & Del Mar, 2005; Miller et al., 1999), social desirability (Miller et al.), and maturation/spontaneous recovery (Miller et al.; Whyte, 1994).

When pharmacotherapy is warranted, standard pediatric practice typically involves a medication trial based on research and physicians’ experience (Newcombe, 2005; Nikles et al., 2006). Frequently trials of medication are successful in producing effective symptom reduction; however, some authors speculate that this common practice
yields a high risk of a false positive result, likely resulting in over-prescription of medications with unsubstantiated efficacy (Guyatt, Keller, Jaeschke, Rosenbloom, Adachi, & Newhouse, 1990; Miller & Corner, 1999).

Cook (1996) advocated for use of single-subject trials within standard clinical practice for instances when an open medication trial is inconclusive, a clinician is doubtful about a treatment on which the patient insists, side effects may be causing secondary symptoms, or the optimal dosage is not evident. She discussed several considerations pertinent to initiating single-subject evaluations, of which the most crucial may be patient/parent ability and willingness to consistently fill out diaries and/or rating forms. Cook asserted this comprehensive medication assessment procedure was feasible under certain conditions: rapid onset and brief washout period; operational definition of outcome measures, including side effects; sufficient duration of trials to establish valid, interpretable results; and pharmacist who will blind medications and create placebos (if not available from manufacturer).

Nikles and her colleagues (2006) provided a long-distance “n-of-1 trial service” to evaluate response and side effects for children 5 to 16 years of age with ADHD in Australia. Pharmacological therapy with methylphenidate or dexamphetamine was assessed in single-subject, randomized, double-blind, three-phase, crossover trials. Children for whom a blinded, non-placebo comparison trial was deemed appropriate, data collection occurred throughout a 6-week period. Shorter single-medication/placebo trials of 3 weeks were implemented to reduce attrition. Monitoring was conducted with local physicians and data was collected from parents, teachers, and adolescents via mail or telephone. The authors found 63% of participants and their physicians used trial results to
guide prescription management, and 28% of the participants ceased stimulant treatment. The authors concluded this type of study resulted in rational and cost-effective prescribing practices. They speculated that long-term benefits may include improved academic and occupational outcomes.

This research project compared symptom reduction of FDA approved extended-release stimulant medication to placebo. Additionally, a qualitative evaluation of the protocol is discussed with regard to the social acceptability and feasibility of incorporation of objective measures within pediatric clinical practice.

*Single-Subject Research Questions*

- Is the child’s ADHD stimulant medication more effective than placebo in reducing core ADHD symptoms?
- Is the child’s ADHD stimulant medication more effective than placebo in reducing oppositional behavior at home?
- Does the participant’s ADHD medication reduce core symptoms at home?
- How does the child’s ADHD stimulant medication affect math and reading fluency in comparison with placebo?
- Does the child’s ADHD stimulant medication interfere with sleep?
- How do the side effects of the child’s ADHD stimulant medication compare to placebo? Were side effects of the medication tolerable?
- For children on polypharmacological therapy, does the ADHD medication under evaluation enhance symptom reduction of the child’s pharmacological regimen?
Social Validity and Feasibility Questions

Acceptability and feasibility of the procedures were evaluated by requesting parents and participants complete survey questionnaire (Appendix U) after their participation in the study concluded. Acceptability/satisfaction ratings included:

- Time and effort required
- Interactions with team members
- Evaluation session and consent procedures
- Lab session procedures
- Medication delivery
- Feedback from others (e.g. peers, teachers)
- Whether teachers felt classroom observations disrupted class
- Participant comfort/discomfort with observations
- Safety procedures

Survey feasibility questions included:

- Evaluation of procedure (e.g. are components practical), discussion of problems
- Compliance in filling out daily forms
CHAPTER II

METHODS

Participants

Characteristics of Participant Population

Three boys and one girl ages 10-12, who had a physician diagnosis of attention-deficit/hyperactivity disorder (any subtype) and with parents who chose pharmacotherapy as part of the treatment for the disorder were recruited. Participants had a symptom severity T-score of 65 or higher on a DSM-IV or Conners Index of the Conners’ Parent Rating Scale–Revised (CPRS–R; Conners, 1997). T–scores of 65 or higher places children in the 90th percentile for diagnosable symptoms. As with previous studies on ADHD medications (e.g., Biederman et al., 2002; Michelson et al., 2001), participants’ intelligence was within the normal range. One child endorsed slightly elevated mood symptomatology on the Beck Youth Inventories (Beck, Beck, Jolly & Steer, 2005) during his eligibility session. All of his subsequent T-scores were in the average range.

Recruitment of Participants

Recruitment efforts focused on local pediatricians and general physician practitioners in the Kalamazoo area. Ten pediatric practices in the region were personally contacted by the Student Investigator, which resulted in presentations at three of the practices. Pediatric specialists from related fields, psychologists, other health care professionals, and the local chapter of CHADD (ADHD support group) were also contacted. Recruitment flyers (Appendix H) were posted around campus and other local establishments. A newspaper advertisement (Appendix J) resulted in 12 inquiries; 4 families were sent brochures (Appendix I), but declined to proceed after receiving
information; two children were not appropriate for the study due to age or taking medication that excluded the child from the study.

Procedures

Protocol Development Background

Original proposal was to evaluate medication effects of atomoxetine, a non-ADHD medication in a cross-over experimental design that was approved by the dissertation committee and WMU’s Human Subjects Institutional Review Board (HSIRB). Attempts to fund this large project via grants and research scholarships was not successful, and subsequent endeavors to obtain financial sponsorship for other new ADHD medications were unproductive. The project was scaled down to evaluate effects of medication with single-subject design and received protocol approval from WMU’s HSIRB (Appendix O) and from the Industrial Review Board at Bronson Methodist Hospital (Appendix V) to evaluate effects of lisdexamfetamine dimesylate. Revisions to the protocol to allow for titration within the protocol and evaluation of other extended-release stimulant ADHD medication was approved by both boards and was the procedure followed in this research project.

Independent Variables and Experimental Design

The effects of Participants’ ADHD medication and placebo were evaluated with a double-blind alternating treatments experimental design (see Table 2). Effects of participants’ ADHD medication and placebo were repeatedly measured over a 4-week period via daily measures, including, parent and teacher rating scales, side effects checklist, and sleep measures. Brief daily school interval data was taken for Participant 1 who was enrolled during the school year; other children were recruited during the
summer during school break. Weekly measures included administration of a continuous performance task, academic measures, and youth self-report instruments.

Dosage protocol for the medication followed standard clinical practice. The physician titrated the dosage for each participant.

Table 2.

*Alternating Treatment Schedule*

<table>
<thead>
<tr>
<th>Week</th>
<th>Sunday</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>U</td>
<td>U</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>B</td>
<td>A</td>
<td>A</td>
<td>A</td>
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<td>A</td>
</tr>
<tr>
<td>5</td>
<td>B</td>
<td>B</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
</tr>
</tbody>
</table>

A=medication, B=placebo, U=unblinded (no data collection).

*Medication Blinding Protocol*

Medications were blinded under the supervision of Alan Poling, Ph.D., who is licensed to handle Schedule II medications. The medications were packaged and labeled according to prescription and alternating treatment schedule by Andy Reeves, R.Ph., pharmacist at the Unified Clinics Pharmacy, 1000 Oakland Dr., Kalamazoo. Medication instructions and pharmacy label were attached to the pharmacy bag.

All persons collecting or recording data were blind to drug conditions, including participants, research assistants, teachers, and parents. The supervising physician, the principal investigators, and the administrative assistant were not blinded and did not collect or record data.
Location of Data Collection

The Center for Behavioral Pediatrics, located at 700 Mall Drive, Portage, Suite C, was the site for assessment and weekly research sessions. All medical supervision and prescriptions for participants were provided by the supervising physician according to standard clinical practice and HSIRB- and IRB approved protocols. The supervising physician completed a medical assessment (see Appendix A) and monitored each child’s medical progress and weight during the study (see Appendix F). The physician determined whether each child is appropriate for the study using standard clinical practice and HSIRB-approved protocols.

Consent, Assent, and Eligibility Sessions

Parent consent (Appendix O) and child assent (Appendix Q) were obtained during a session prior to the eligibility assessment session, which required a brief washout period. Parent(s) were given a copy of the signed consent and assent forms, the Informed Consent Handout (Appendix C), Consent for Release of Confidential Information (Appendix P), and the brochure (see Appendix I). Parent(s) who scheduled an eligibility session were given an information packet that included a letter of explanation (see Appendix K) and Sleep Questionnaire and Medical History Form to complete at home and bring to the session (see Appendix L), and the Conner’s Parent Rating Scale–Revised long version (Conners, 1997).

During the eligibility assessment session the parent(s) filled out the Eyberg Child Behavior Inventory (ECBI; Eyberg & Pincus, 1999), and the Parent Stress Index (PSI; Abidin, 1995). After child assent was confirmed, a research assistant administered the M–MAT continuous performance task, one-minute math test, one-minute reading tests
(Good & Kaminski, 2002), and Beck Youth Inventories (Beck, Beck, Jolly & Steer, 2005). The child's weight and vital statistics, were taken by the supervising physician and recorded on the vital signs portion of the medical history form (see Appendix L). The physician then meet with the child and his/her parent(s) and recorded clinical data on the eligibility/screening worksheet (see Appendix A). The physician documented his admission decision on the routing portion of the first page of the screening worksheet. All four children who were assessed in an eligibility session were admitted to the study.

![Figure 1. Eligibility Assessment Sessions Flow Chart](image-url)
Several logistical events preceded the start of each child’s data collection phase: medication/placebo preparation and dispensation; scheduling of lab sessions, coordination of brief daily contact; notification of enrollment to the child’s physician; and when applicable, coordination of school observations and teacher reports. Medication organization was the most complex. Children were required to end their course of previous ADHD medication for washout purposes 2 days prior to the start of their participation in the study. The Unified Clinics Pharmacist was given the medication key, which was used to fill the prescription in cold-seal bubble packs that were labeled by the student investigator. Three out of four parents chose to have their child’s medications delivered. The student investigator also sent letters (Appendix B) to the child’s primary care physician to consult on the possible participation of the child in the study. Parents were required to closely supervise their children while taking the medications at the same time each morning.

Parents were offered their choice of phone or e-mail for brief daily contact, all of whom selected telephone calls. These intervention integrity checks were completed by the student investigator who randomly sampled a score from any of the four forms, e.g. “What was your answer for number 3 on the Conner’s form today?” This contact usually took 5 minutes or less, although occasionally parents would comment on their child’s behavior, or confirm their upcoming lab session. Parent(s) turned in their daily forms during lab sessions. Parents were required to complete four instruments (5-10 minutes): Eyberg Child Behavior Inventory (Eyberg & Pinkus, 1999), Conners’ Parent Rating Scale—Revised: Short version (Conners, 1997), Daily Sleep Questionnaire and Diary (Appendix D), and the Side Effects Questionnaire (Appendix E) each evening.
As discussed above, Participant 1 was the only child to be in school while enrolled in the study. Permission for interval observation and research participation in school was granted by his principal. Two of this participant’s teachers agreed to allow observations and shared responsibility for completing daily forms (see teacher agreement form Appendix R); Conners' Teacher Rating Scale–Revised: Short Version (CTRS–R:S; Conners, 1997). Participant 1’s teacher(s) identified three “comparison child” candidates of the same gender who represented a typical child in the classroom. For each observation period, one of these three children were selected by the student investigator based on proximity and the students’ faces being within the research assistant’s line of sight. The previous day’s forms were picked up on a daily basis.

Lab Sessions

Continuous performance task and other objective data were collected during lab sessions that included measures on the M-MAT (see Objective Measures, pp. 52-55), and brief timed math and reading tests. Anger and depressive symptoms were monitored with the Beck Youth Inventories (Beck, et al, 2005). Research assistants were responsible for confirming the child took their pill that morning and inspecting and the medication bubble packaging. They confirmed child assent before testing, without parent(s) present. The child’s vital statistics were taken by the supervising physician. pulse, weight, and record these in the child’s vital signs chart (Appendix F).

Academic performance tests, the M-MAT continuous performance task, and the Beck Youth Depression and Anger Inventories (Beck, et al., 2005), were administered in random order by a research assistant. The physician consulted briefly with the student investigator to review the side effect questionnaires and other data from the week. After
the child completed testing, the participant and his parent(s) met with the physician who took and recorded vital statistics. The physician adjusted the medication dosage, if in his clinical judgment it was appropriate to do so. Upon completion of the session, parents were given the following week’s forms to be filled out and arrangements were made for them to pick up or have medication delivered.

Figure 2. Lab Sessions Flow Chart.
Feedback Session

Feedback sessions were held with the participants' parents 2 to 3 weeks after the child's final session. A brief summary was prepared by the student investigator and reviewed by the advisor for the parents. Effects of each medication on their child's attention, activity levels, academic performance, sleep, and compliance were and side effects and severity for each condition was reviewed. At the conclusion of the feedback session, parents and participants filled out the social validity surveys (Appendix U).

Protection/Safety Procedures

Parents were read the Adverse Reaction/Severe Side Effects Hierarchy flyer (see Appendix M) that detailed what they had to do under certain conditions. They will discussed the most appropriate place to post the flyer for easy access (e.g., by telephone, on refrigerator). The student investigator was on 24-hour on-call status with the study cell phone and medication key (see sample Appendix N) so that physicians or emergency personnel had immediate access to each child's medication record.

As noted in the methods section, the Side Effects Questionnaire (see Appendix E) was reviewed weekly by the physician. Reports of side effects with a rating of 3 (often) or higher (4=frequently; 5=severe) were monitored, and the dosage was adjusted if in the physician's clinical judgment was appropriate to do so.

Research assistants completed job aid/checklists (see Appendix G) for each lab session, which were reviewed at the end of the lab session by the student investigator to monitor protocol integrity.
Dependent Variables

Parent Rating Scales

Conner's Rating Scales–Revised

The Conners' Rating Scales–Revised for parents and teachers are some of the most widely used instruments for assessment of children's externalizing behaviors (Christophersen & Mortweet, 2002), and have been used in hundreds of research projects (Wainwright et al., 1996). The Conners Parent Rating Scale–Revised: Long Version (CPRS–R:L; Conners, 1997), used during the eligibility/screening session, was a broadband assessment instrument used extensively as a diagnostic component to assess for ADHD and internalizing and externalizing comorbid conditions such as oppositional behaviors, anxiety, and emotional lability. Reviews published in the 14th Mental Measurements Yearbook (2001), rated it as a top instrument for psychometric integrity and utility (Knoff, 2001, Review 2 of 2, ¶ 1). A large standardization sample of 2,500 children was used to develop the revised edition. Caution appears to be warranted in making comparisons to the norming data: Racial distribution of the norming population does not match U.S. and Canada ethnic demographics (Knoff, 2001). Although the 2002 U.S. census shows Caucasians make up 76% of the population, 83% of the students rated were white. Use of the CPRS–R:L for this study will be for confirmatory assessment purposes since inclusion criteria requires a physician diagnosis of ADHD. Additionally, norming data should not cause skewed evaluations for our purpose due to the fact that within subjects research design uses differences between repeated measures of each participants’ scores, allowing a within-subject comparison.
While the long version was used for assessment purposes, instructions on the abbreviated version were altered so that parents would consider only behaviors for that day. The Conners Parent Rating Scale–Revised: Short Version (CPRS–R:S; Conners, 1997) is a 27-item instrument that consisted of the most relevant items as indicated by factor analysis for cognitive problems/inattention, hyperactivity, and ADHD Index subscales from the CPRS–R long version. Conners (1997) reported there were no significant differences between long and short version standardized subscale scores. Indeed, correlations between the long and short versions ranged from $r=.96$ to $r=.98$.

**Eyberg Child Behavior Inventory**

The Eyberg Child Behavior Inventory (ECBI; Eyberg & Pincus, 1999) was a parental report rating scale that assessed externalizing behavior problems with a focus on compliance behaviors. The Intensity Scale summarized the frequency of 36 problem behaviors on a scale of 1 to 7 (1 = never occurs, 2 and 3 = seldom, 4 = sometimes, 5 and 6 = often, 7 = always). A Yes-No Problem Scale identified whether the behavior was incommmodious for the parent. The authors reported several studies that established the ECBI's sensitivity to treatment in diagnosed and normal populations (both Intensity and Problem Scale scores declined significantly following treatment).

**Side Effects Questionnaire**

The Side Effects Questionnaire was devised to assess side effects of the drugs (Appendix E). Items were inclusive of previously commonly occurring side effects, and also included runny nose, sore throat, vomiting, cough increased, rash, nausea, fever,
weakness or loss of strength, infection, and severe itching. Two "red herring" items (ringing in ears and craving sugar) were also added.

Parent Stress Index

A gauge of parental stress was taken via the full-length version of the third edition of the Parenting Stress Index (PSI; Abidin, 1995). The full-length version was a 120-item measure that was developed to identify stress levels in parent-child relationships in clinical and research settings. The full-length version divided parental responses into two domains: parent and child, and yielded a "life stress" score, which was a measure of external or other stressors felt by the parent. Parent and child domains were further divided into 13 subscales, providing a systematic overview of parent-child relations. The Life Stress scale that evaluated significant life events (e.g. divorce, finances, job loss) was not used since it was considered too personal and not relevant to the study. The instrument's validity was supported by several published studies, including research investigating: hyperactive children (Beck, Young, & Tarnowski, 1990); hyperactivity, stress, and self-esteem (Mash & Johnston, 1983); conduct disorder (Kazdin, 1990); and child conduct problems and maternal depression (Webster-Stratton, 1988). Internal consistency was reported as strong for each of the domains (Abidin, 1995) with reliability coefficients ranging from 0.90-0.95. Test-retest reliability for 1–3 months was $r = 0.96$.

Daily Sleep Evaluation Questionnaire and Diary

Information from the Sleep Evaluation Questionnaire (Appendix D) was used for descriptive purposes. Current daytime symptoms assessed subjective reports of ease/difficulty awakening and daytime sleepiness, which reflect items of interest in the Schuh (Taylor, 2004) study. The questionnaire consisted of 10 items which were rated on
a five-point likert scale: never, not often (less than 1 day a week), sometimes (1 to 2 days a week), often (3 to 5 times a week), always (6 to 7 days a week), and “do not know.” Parents logged the time their child went to bed, fell asleep, got up in the morning, and the number of wakenings in the Sleep Diary (Appendix X). To aid parents in accurate reporting of the time their child fell asleep, parents were provided nursery monitors and recorded the time their child ceased movement (rustling sounds). Parents were able to carry the portable sound unit with them, then mark tic marks on the Sleep Latency Form (Appendix T) to record when they heard their child make noise. As per approved protocol, parents turned off the monitor when they went to bed, whether or not their child was asleep.

**Teacher Ratings**

*Conners’ Teacher Rating Scale—Revised: Short form*

The Conners’ Teacher Rating Scale—Revised: Short Form (Conners, 1997) consisted of 28 of the highest factorial-loading items from the full-length teacher version, grouped into four subscales: Oppositional, Cognitive problems/Inattention, Hyperactivity, and ADHD indices. Conners (1997) reported there were no significant differences between long and short version standardized subscale scores.

**Objective Measures**

*McLean Motion and Attention Test (M-MAT)*

The M-MAT, a continuous performance task (CPT) that quantified a child’s ability to sit still and focus on the task at hand, was used to provide objective measures of activity, impulsivity, and inattention. The M-MAT system consisted of a computer with CPT software, and used an infrared motion camera that tracked and recorded children’s
movement while taking the computerized test (see Figure 3). The infrared camera
detected a tiny light beam that bounced back from a reflector ball attached to the back of
a sports headband worn by the child. The M-MAT was used in clinics nationwide as an
assessment tool for differential diagnosis of ADHD, assessment of symptom severity, and
for medication titration. Since the conclusion of the data collection phase, the system was
updated and marketed as the Quotient ADHD system. This new version of was the first
FDA-cleared test and used a front-mounted camera system that reads a reflector device
on a child’s forehead.

The M-MAT CPT was a demanding, but boring, task that required children to
discriminate between moving visual stimuli flashed on the computer screen at a rate of
100 milliseconds every 2 seconds, while sitting as still as they were able during the 15-
minute session. Participants were to push the space bar on the computer keyboard when
they saw the eight-pointed star, but not when they saw the five-pointed star (see
Figure 4).

The M-MAT, which was normed by gender and age on children ages 7–12, has
high measures of sensitivity (0.89) and specificity (1.0; M. Teicher, personal
communication, May 17, 2001) in a small sample. M-MAT successfully discriminated 16
of 18 non-medicated children with a DSM-IV ADHD diagnosis from all 11 healthy
controls. Test-retest reliability coefficients were also high, ranging from $r = 0.77$ to $r =
0.95$ (Teicher, Ito, Glod, & Barber, 1996). Teicher, Anderson, Polcari, Glod, Maas, and
Renshaw (2000) later validated M-MAT behavior ratings with findings from functional
The M-MAT unit used an infrared camera to track motion while the child focused on the task on the computer screen.

*Figure 3.* The M-MAT Continuous Performance Task.

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*Figure 4.* The M-MAT Computer Instruction Screen.
magnetic resonance imaging (fMRI) relaxometry measures of brain activity, which were highly correlated with M-MAT measures of inattentiveness $r = 0.75$ and hyperactivity $r = 0.80$. The T2 relaxometry is a new fMRI procedure that evaluates steady-state blood flow in specific regions in the brain (Teicher et al., 2000).

Results were sent to and retrieved from the M-MAT server at McLean Hospital in Massachusetts for analysis via an internet connection. M-MAT reports yielded 12 measures of attention and motor activity, with activity patterns graphed in 5-minute segments (see sample Appendix Y). The test was further divided into 30-second epochs that were categorized as: attentive, impulsive, distracted, contrary (higher response to non-targets and missed targets than would be expected by chance), minimal, or random responding. Teicher et al. (2004) found M-MAT's shifts in 30-second epochs provide more robust sensitivity and specificity than traditional measures of CPT error rates. The percent of epochs spent in impulsive, distracted, and random response states are not correlated, and can be used to quantify medication effects, which differentially effect these states (Teicher et al., 2004). Healthy controls averaged 5.4 quantitative attention shifts, whereas children with ADHD averaged 12.8 shifts. These new measures were significantly affected by methylphenidate, which produced a 77% increase in the amount of time ADHD participants were on-task.

**Academic Performance Tests**

**DIBELS.** The reading fluency portion of the academic performance tasks employed grade- and age-appropriate measures of the Dynamic Indicators of Basic Early Literacy Skills (DIBELS; Good & Kaminski, 2002). DIBELS is a standardized set of one-minute fluency measures designed to monitor the development of early reading skills.
(Good & Kaminski, 2002). The measures have been found to be reliable and valid measures of phonological awareness, alphabetic understanding, and automaticity and fluency, as determined by reports of the National Reading Panel (2000) and the National Research Council (1998).

The oral reading portion of DIBELS measured participant performance by having the children read a passage aloud for one minute. Words omitted, substituted or misread, and hesitations of more than three seconds were scored as errors. Words self-corrected within three seconds were scored as accurate. The number of correct words from the passage determined the oral reading fluency rate.

Math minute. One-minute, grade-appropriate addition and subtraction math tests were used to evaluate participants’ academic performance. A different version of each grade-appropriate test was created (see Appendix Y), which consisted of the same problems in different order. Children had one minute to complete as many math problems as they could, as accurately as they were able.

Daily Classroom Observations

Research assistants recorded occurrences of a participant’s and a comparison child’s off-task inattentive, off-task gross motor, and on-task behaviors during daily 15-minute classroom interval observation periods (see Appendix S). Each 10-second interval consisted of an 8-second observation period and 2-second recording period. Classroom behavior codes included: (a) off-task inattentive, (b) off-task gross motor, and (c) on-task behaviors. Inattentive off-task behaviors were defined by the absence of expected and necessary behaviors required for the current task, (e.g., daydreaming, staring blankly for more than three seconds; looking away from desk/teacher for more than three seconds).
Hyperactive off-task behaviors were noted by the presence of inappropriate gross motor behavior (e.g., out of seat; passing notes, using work materials inappropriately, and inappropriate vocalization). On-task was coded when no off-task behaviors occurred. All observations were completed during academic periods requiring in-seat or group work.

Three teacher-nominated, typically developing students of the same-gender were observed simultaneously for comparative purposes. Prior to the daily observation, one of the three comparison children were selected by the student investigator based on proximity to the participant and unobstructed view of both student’s faces. Comparison children’s identities were kept anonymous by denoting them as “CC” on the observation form. The “comparison child’s” behavior was coded simultaneously with the participant’s.

Undergraduate research assistants trained to > 80% interrater reliability before collecting data. They trained weekly throughout two semesters via didactics, readings, practice during videotaped vignettes, and finally completed behavioral observations for local school psychologists. Interrater reliability was checked during videotaped, real-life practice, and data collection sessions.

Assistant recorded observations of the participant and a comparison child for 15 minutes each available school day during the data collection period. Interrater reliability, collected data for 31% of the observation sessions, was generally high. Since off-task (target) behaviors rarely occurred, reliability was calculated using the occurrence-agreement and non-occurrence-agreement method (Poling, Methot, & LeSage, 1995, p. 75; see Table 3) in which number of intervals that were in agreement that an off-task behavior occurred is divided by the number of intervals in agreement plus the number of
intervals that do not agree an off-task behavior occurred \([A/A+D(100)]\). The same formula is used counting the number of intervals in which behaviors did not occur (non-occurrence).

<table>
<thead>
<tr>
<th>Type</th>
<th>IOA 1 (V)</th>
<th>IOA 2 (P)</th>
<th>IOA 3 (V)</th>
<th>IOA 4 (V)</th>
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</thead>
<tbody>
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<td></td>
<td>Occur</td>
<td>Non-Occur</td>
<td>Occur</td>
<td>Non-Occur</td>
</tr>
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<td>100%</td>
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<td>P1</td>
<td>100%</td>
<td>100%</td>
<td>75%</td>
<td>97.8%</td>
</tr>
<tr>
<td>CC</td>
<td>87.5%</td>
<td>96.9%</td>
<td>100%</td>
<td>92.5%</td>
</tr>
</tbody>
</table>

Interobserver agreements were generally high for these rare-occurring events. Top row shows statistics for interobserver occurrence and non-occurrence for Participant 1 (P1). Likewise, percent of agreement is shown for the comparison child (CC).

**Self-Ratings**

**Beck Youth Inventories**

Self-report measures of depressive symptoms, anxiety, and anger were taken for each participant during the assessment session. The Beck Youth Inventories (Beck, et al., 2005) consisted of five instruments that yielded acceptable test-retest reliability \((r=.74 \text{ to } r=.90)\) and internal consistency coefficients of \(r=.74 \text{ to } r=.93\). These 20-question instruments were developed for both clinical assessments and school screening had a second-grade reading level. The depression and anger inventories were administered during each lab session to monitor for depressive symptoms, suicidal ideation, and aggressive behavior.
CHAPTER III

RESULTS

Individual Protocol Findings for Participant 1

Social History and Background

Participant 1 was an 11-year-old white male who lived with his biological parents and two siblings: a 17-year-old brother and 13-year-old sister. His parents noticed hyperactive and inattentive behavior around age 4 and was diagnosed with ADHD at age 6 by his pediatrician. Subsequent to an evaluation in first grade, his school psychologist recommended classroom and program modifications under Federal regulation Section 504 of the Rehabilitation Act for symptoms consistent with ADHD. He received pharmacological treatment in conjunction with behavioral interventions at home (e.g. structured routine, response-cost, reinforcers). Participant 1 did not experience significant learning problems, but struggled with organization and task completion. His parents reported occasional, mild problems with noncompliant behavior. Participant 1’s parents described their son’s social skills as age-appropriate; however, they desired less verbal conflict with his siblings. They reported he experienced problems falling asleep and going back to sleep after wakening, which was treated with a hypnotic (8 mg Rozerem). Participant 1 denied problems with anxiety, depressive mood, suicidal/homicidal ideation, self-injurious behavior, aggression, or strange thoughts.

Parents’ scores on the Parent Stress Index indicated significant levels of stress that were disproportionately high for areas related to emotional response to their child’s behavior. Elevated Child Domain scores in relation to Parent Domain scores are indicative of the child’s behavior being a major source of stress. The only elevated score
on the parent domain was the Health Index, which reflected chronic illness experienced by this participant’s mother. As per protocol, the couple was counseled and given referrals to local mental health service providers. They agreed their stress was significantly high, but felt they were coping well and declined services.

Participant 1’s math and language arts teachers alternated responsibility for filling out the daily CTRS. This student’s math teacher was a long-term substitute who was filling in during maternity leave for Participant 1’s regular math teacher and had taught the participant for four weeks prior to the start of the protocol.

Referral Source and Reason for Enrollment

Participant 1 was referred to the study by his pediatrician to investigate whether Vyvanse would be effective in reducing ADHD symptoms without problematic side effects. This participant had a history of adverse side effects to first-line ADHD medications methylphenidate (Concerta) and amphetamine/dextroamphetamine (Adderall), most notable of which were loss of appetite, failure to gain weight at a developmentally appropriate rate, and exacerbation of sleep problems. Environmental allergies were managed with Allegra (60 mg. 2/x day), and Rozerem (8 mg) was taken to reduce insomnia. His parents reported he took these medications consistently throughout the study. His pediatrician referred him to the study with a prescription dose of 70 mg Vyvanse. (Note: After this child completed his data collection phase the HSIRB and IRB granted a request for protocol change to allow for dose titration.)

Protocol Findings for Participant 1

Weekly medication checks for compliance and parent report showed Participant 1 took his medication according to protocol. This participant’s parents were compliant with
the research protocol, including brief daily communication. His parents reported completing appropriate forms on a daily basis. Lab sessions for placebo conditions were on the 12th and 19th days of the protocol, the first of which was the third consecutive “dose” of placebo. The second placebo lab session was on the first day of the next placebo condition. This participant remained on his pediatrician’s prescribed dose of 70 mg throughout the entire protocol. Effects of Vyvanse were measured lab sessions on the 6th and 26th days of the protocol, with the first lab session occurring on the 6th consecutive day of the medication condition and the second lab session being held on the 5th consecutive day in the final medication condition. No school-based scores were available for 16 of the protocol days due to various reasons: weekends (8), school spring break (5), sick days (2), missing data (1).

**M-MAT**

Participant 1’s overt behavior during M-MAT testing sessions was cooperative and generally engaging. This participant appeared to put effort into his responses, returning his attention to the computer after brief periods of distraction.

**M-MAT attention and impulsivity.** Participant 1 performed within the normal range for all conditions (no pill, Vyvanse, and placebo) for missed targets (omission), and incorrect targets (commission; see Table 4). Accuracy declined during the first placebo trial with all other trials showing average performance. He made the most impulsivity (commission) errors during baseline testing; however the percentage of responses to incorrect targets was within the normal range (see Table 4). He committed fewer commission errors (responses to nontargets) than during both medication conditions, with
no significant differences between commission errors on medication compared to errors shown when he took placebos.

Table 4.

*M-MAT Measures of Attention and Impulsivity for Participant 1*

<table>
<thead>
<tr>
<th>Protocol Day</th>
<th>Condition</th>
<th>Accuracy Normal Range</th>
<th>Omission Normal Range</th>
<th>Commission Normal Range</th>
</tr>
</thead>
<tbody>
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<td>Baseline</td>
<td>No Pill</td>
<td>89.3</td>
<td>5.0</td>
<td>17.0</td>
</tr>
<tr>
<td>6</td>
<td>70 mg</td>
<td>94.9</td>
<td>3.4</td>
<td>7.0</td>
</tr>
<tr>
<td>12</td>
<td>Placebo</td>
<td>88.4 L</td>
<td>10.9</td>
<td>12.0</td>
</tr>
<tr>
<td>19</td>
<td>Placebo</td>
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<td>11.1</td>
</tr>
<tr>
<td>26</td>
<td>70 mg</td>
<td>97.8</td>
<td>0.8</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Accuracy scores are percentage of correct responses. Percentage of omission errors or missed target stimuli are considered to be a measure of inattention. Commission errors are percent of incorrect responses to a nontarget stimuli and considered to be an estimate of impulsivity.

*M-MAT latency and variance.* Participant 1's latency scores were within the normal range for all conditions (see Figure 5). His response speed was just slightly faster for both medication condition scores (448 ms, 430 ms) compared to response latency to targets on placebo (506, 491) and when he did not take a pill for baseline measures.

M-MAT measures of variance (standard deviation, $s_x$) indicated Participant 1’s response to targets varied significantly during non-medication conditions ($P1 = 197$, $P2 = 163$; see Figure 6) with his baseline score falling just outside the normal range (151). Standard deviation data showed this participant displayed more consistent performance during medication conditions ($V1 = 91$, $V2 = 82$) with scores in the low end of the normal range.
Participant 1’s speed was in the normal range for all conditions. Latency scores measures the amount of time between presentation of target stimuli and response to target (press of spacebar) in milliseconds. Lower scores indicate faster response to the target. Normal range is 356-531 and is shown in grey area.

*Figure 5. M-MAT Response Latency Scores for Participant 1.*

Participant 1 showed significantly more variance during days he took placebo than when he took medication. His baseline score was slightly elevated. M-MAT variability scores ($s_x$) represent standard deviation in response time latency on the M-MAT. Higher scores show greater inconsistency. Normal range is 77-195 and is shown in grey.

*Figure 6. M-MAT Variability Scores for Participant 1.*
**M-MAT activity.** Participant 1 demonstrated an ability to sit still (Immobility, see Figure 7; Movements, see Table 5) that was within the normal range when he was on placebo. His immobility scores showed he sat still longer during the medication condition (V1 = 1.24, V2 = 0.66; see Figure 7); however, both elevated medication immobility scores indicated average time the participant sat motionless was longer than expected for children who do not have ADHD. Results for both placebo trials (P1 = 0.253, P2 = 0.147) showed his duration of immobility was within normal limits.

This child spent significantly more time holding still than typically developing children when he was on medication. He had difficulty sitting still during baseline, but not during placebo trials. Immobility duration measure on the M-MAT reflects the average amount of time spent sitting still. Children in the control group were able to sit still for an average of 0.11–0.29 of the 15-minute task (shown in grey). Low numbers reflect more movement (e.g., fidgeting).

*Figure 7. M-MAT Immobility Duration Scores for Participant 1.*

In contrast to immobility duration scores, the extent of activity (temporal scaling) was significantly different for each condition for this child: Within normal range for no pill, low for Vyvanse, and high for placebo (see Figure 8). Participant 1 spent less than 25 percent of the 15-minute testing period sitting still on days he took placebo (P1 = 0.79, P2 = 0.76), with baseline performance (B = 0.57) just outside the normal range. The
child’s M-MAT Temporal Scaling score taken on the 6th consecutive day during the first medication phase (V1 = 0.184) showed he spent less time moving than other children his age. His subsequent medication score, which was taken on the fifth consecutive day during the final medication phase (V2 = 0.374) reflected the amount of time moving was in the normal range.

![Temporal Scaling Graph]

Participant 1 spent significantly more time sitting still during medication conditions, with his baseline measurement on the high border of the normal range. Temporal Scaling scores on the M-MAT measure the extent to which the child is active with 0 indicating lack of movement to 1 showing incessant movement. Normal range (shown in grey) is considered to be between 0.31 and 0.56.

**Figure 8.** M-MAT Temporal Scaling Scores for Participant 1.

Participant was able to sit very still for the first 5-minutes, but became increasingly active as the test went on. This pattern indicates problems with sustained attention.
Hypoactivity shown as the participant spent increasing time immobile and less time active. He made fewer position changes than expected and moved within a narrow area.

Position changes, distance moved, and temporal scaling were within normal limits. Participant 1 spent increasing amount of time immobile, moving within a very narrow area (<30 cm²) indicating possible hypoactivity or activity in the low end of the normal range.

Displacement and temporal scaling scores were elevated; however, position changes, area, and immobility measurements were within normal range. Low movement area indicated subtle pattern of mild hyperactivity that would be difficult to detect via observation.

M-MAT scores recorded during the second placebo condition showed the same pattern of subtle hyperactivity as the first placebo trial.

Figure 9. M-MAT Pictorial Representations of Movement in 5-Minute Segments for Participant 1.
On one measure of spatial movement (displacement), Participant 1 performed within the normal range when on medication with more movement on both placebo trials and when he did not take medication for baseline measurement (see Table 5). This participant’s total area moved was elevated for the second placebo trial with the first placebo trial just within the normal range, with baseline and both medication scores falling within the normal range. Spatial complexity calculations show Participant 1 moved in a more linear manner during baseline and when he was on medication than when he was on placebo.

The M-MAT movement score reflects the average number of position changes. Participant 1 demonstrated fewer position changes than norm-referenced peers during the first medication trial measure (see Table 5). Baseline and all other movement scores were within the normal range; however, as with the number of position changes during the first medication session, his scores were near the low end of the normal range for the second medication trial.

*M-MAT shift analyses.* Data showed Participant 1 averaged 11 shifts in response patterns with marked difference in the number of shifts between medication conditions (V1 = 9, V2 = 2) and placebo (P1 = 13, P2 = 14). Shifts in response style were the highest during baseline (B = 17). M-MAT normative data showed the healthy control group changed their response style around 5.4 times during the 15-minute task. Conversely, the ADHD comparison group shifted response style 12.8 times on average.
Table 5.

*M-MAT Spatial Measures of Motion for Participant 1*

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal Range</th>
<th>Baseline</th>
<th>70 mg</th>
<th>70 mg</th>
<th>Placebo 1</th>
<th>Placebo 2</th>
</tr>
</thead>
<tbody>
<tr>
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<td>.57</td>
<td>1.03</td>
<td>4.00 H</td>
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<tr>
<td>Area</td>
<td>9-48</td>
<td>39</td>
<td>12</td>
<td>10</td>
<td>48</td>
<td>61 H</td>
</tr>
<tr>
<td>Spatial Complexity</td>
<td>1.167-1.381</td>
<td>1.387 H</td>
<td>1.410</td>
<td>1.418</td>
<td>1.238</td>
<td>1.126</td>
</tr>
<tr>
<td>Movements</td>
<td>344-2239</td>
<td>1082</td>
<td>238 L</td>
<td>418</td>
<td>1412</td>
<td>1782</td>
</tr>
</tbody>
</table>

M-MAT spatial measures of motion show Participant 1’s performance was differentially affected by medication for some types of movement, but not for others. Displacement score is the total distance moved by the marker (like an odometer reading). Area scores report the total area covered by the marker (reflective ball on back of head). Spatial Complexity scores the movement path with lower values indicating the marker often moved linearly; high values indicate more convoluted movement. Movement scores are the average number of position changes with below average scores indicating fewer position changes than expected for age. Scores above the normal range are shown in bold with an “H”; below average scores are bold with an “L.”

*M-MAT epoch analysis.* Participant 1 exhibited an attentive response style during 83.3 percent (V1) to 96.7 percent (V2) of the 30-second epochs during the medication condition (see Figure 10). The percent of attentive responding during the placebo trials was discrepant with the first placebo measure (day 3 on placebo) reflecting attentive response patterns for only 43.4 percent of the 30 epochs. Conversely, this child responded attentively during 70 percent of the epochs during the second placebo trial that occurred on the first day of the second placebo phase. Impulsive-pattern responses occurred most often during baseline (B = 11), less frequently during placebo (P1 = 7, P2 = 4), and rarely during medication conditions (V1 = 2, V2 = 1). The only other type of response pattern recorded was distracted responding with significantly higher number of epochs spent distracted during the first placebo condition (P1 = 10) compared to all other conditions (B = 4, V1 = 3, V2 = 0, P2 = 5).
Participant 1 used an attentive-style response during medication conditions. Fewest attentive epochs occurred during the first placebo trial with similar performance at baseline. Scores reflect percent of the 30, 30-second epochs for each response pattern on the M-MAT. Typically developing children were attentive during 82.4% of the 30 epochs and children with ADHD spent only 42.6% of the epochs responding attentively.

Figure 10. M-MAT Epoch Pattern Analysis for Participant 1.

Parent Reports of Inattention and Hyperactivity

On medication days, Participant 1’s parents ranked his attentive behavior within the normal range 65 percent of the time (see Table 6). CPRS-R responses showed only 1 of the 7 data points (T-score > 60) reflected significant (T>70) problems paying attention. In contrast, his parents rated him as having significant problems paying attention on 7 out of 9 (78%) of the daily ratings on placebo days.

Data for parent ratings of hyperactivity was the same as for inattention with most elevated ratings of hyperactivity coinciding with high ratings of inattention (see Table 6).

Teacher Reports of ADHD Symptoms

Participant 1’s scores of inattention at school were in the average range for days he took medication (see Table 7). On days this participant took placebos, his teachers rated him as attentive as typically developing normative control group children for three out of five days. Elevated CTRS ratings of Participant 1’s inattentiveness during two
placebo days ($T$-score = 61 both days) indicated he had moderate problems paying attention. Participant 1’s teachers consistently rated his ADHD symptoms as less severe than did his parents (see Figure 11).

Teacher reports of Participant 1’s activity levels were in the low average range and consistently lower than parent ratings during medication phases (see Table 6). For two out of three placebo days, teacher reports were approximately the same as parent reports.

![Graph of Teacher and Parent ADHD Ratings](image)

Participant 1’s teachers consistently rated his ADHD symptoms as less frequent and/or severe than did his parents. (Conners ADHD Index $T$-scores 61-65 = mildly atypical; 66-70 moderately atypical, >70 markedly atypical).

*Figure 11. Comparison of Parent and Teacher Ratings for Participant 1.*
Table 6.

Daily Parent Ratings of Inattentiveness and Hyperactivity for Participant 1

<table>
<thead>
<tr>
<th>Protocol day</th>
<th>Condition</th>
<th>CPRS Inattention T-score</th>
<th>CPRS Hyperactivity T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>No Pill</td>
<td>77*</td>
<td>74*</td>
</tr>
<tr>
<td>1</td>
<td>70 mg</td>
<td>67*</td>
<td>70*</td>
</tr>
<tr>
<td>2</td>
<td>70 mg</td>
<td>58</td>
<td>64*</td>
</tr>
<tr>
<td>3</td>
<td>70 mg</td>
<td>56</td>
<td>61*</td>
</tr>
<tr>
<td>4</td>
<td>70 mg</td>
<td>52</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>70 mg</td>
<td>73*</td>
<td>61*</td>
</tr>
<tr>
<td>6</td>
<td>70 mg</td>
<td>61*</td>
<td>59</td>
</tr>
<tr>
<td>7</td>
<td>70 mg</td>
<td>54</td>
<td>56</td>
</tr>
<tr>
<td>8</td>
<td>70 mg</td>
<td>50</td>
<td>47</td>
</tr>
<tr>
<td>9</td>
<td>70 mg</td>
<td>67*</td>
<td>59</td>
</tr>
<tr>
<td>10</td>
<td>Placebo</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td>11</td>
<td>Placebo</td>
<td>77*</td>
<td>67*</td>
</tr>
<tr>
<td>12</td>
<td>Placebo</td>
<td>58</td>
<td>47</td>
</tr>
<tr>
<td>13</td>
<td>70 mg</td>
<td>52</td>
<td>59</td>
</tr>
<tr>
<td>14</td>
<td>70 mg</td>
<td>46</td>
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<td>15</td>
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<tr>
<td>16</td>
<td>70 mg</td>
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<td>17</td>
<td>70 mg</td>
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<td>18</td>
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<td>63*</td>
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<td>19</td>
<td>Placebo</td>
<td>75*</td>
<td>67*</td>
</tr>
<tr>
<td>20</td>
<td>Placebo</td>
<td>67*</td>
<td>67*</td>
</tr>
<tr>
<td>21</td>
<td>Placebo</td>
<td>79*</td>
<td>76*</td>
</tr>
<tr>
<td>22</td>
<td>70 mg</td>
<td>58</td>
<td>50</td>
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<tr>
<td>23</td>
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<tr>
<td>26</td>
<td>70 mg</td>
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<td>27</td>
<td>Placebo</td>
<td>75*</td>
<td>76*</td>
</tr>
<tr>
<td>28</td>
<td>Placebo</td>
<td>75*</td>
<td>70*</td>
</tr>
<tr>
<td>29</td>
<td>Placebo</td>
<td>67*</td>
<td>70*</td>
</tr>
</tbody>
</table>

Parent ratings showed Participant 1 was markedly more attentive during medication days compared to days in the placebo condition. *Elevated scores (61-65 mildly atypical; 66-70 moderately atypical, >70 markedly atypical).
School Observations

During school observations when he had taken medication, Participant 1 was more attentive than the comparison child (see Figure 12). Although he was off-task more than the comparison child on days he took placebo, differences in his behavior were subtle and would have been hard for casual observers to detect. Interestingly, Participant 1 was basically as attentive as typically developing children on day 1 of placebo with motor movements clearly increasing during placebo conditions.

Participant 1’s off-task gross motor behaviors consisted largely of chewing inappropriate items (e.g. binder and pencil), foot tapping, and sitting on his feet (including putting feet over the back of his chair), although he appeared to maintain attention. During a math class observation in the first placebo condition, Participant 1 often looked at his paper to doodle.

Teacher report of some impulsive behavior (flipping a light switch on and off), occurred outside protocol observation periods. Post-protocol interviews with this participant, his parents, and teachers, all of whom agreed that his test scores and homework indicate that he is attending and learning despite restless motor movement and doodling.
Table 7.

*Teacher Ratings of Inattentiveness and Hyperactivity for Participant 1*

<table>
<thead>
<tr>
<th>Protocol day</th>
<th>Condition</th>
<th>CTRS Inattention T-score</th>
<th>CTRS Hyperactivity T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70 mg</td>
<td>42</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>70 mg</td>
<td>42</td>
<td>43</td>
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<td>3</td>
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<td>4</td>
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<td>MD</td>
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<tr>
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<td>6</td>
<td>70 mg</td>
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<td>9</td>
<td>70 mg</td>
<td>42</td>
<td>43</td>
</tr>
<tr>
<td>10</td>
<td>Placebo</td>
<td>46</td>
<td>53</td>
</tr>
<tr>
<td>11</td>
<td>Placebo</td>
<td>61*</td>
<td>67*</td>
</tr>
<tr>
<td>12</td>
<td>Placebo</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>13</td>
<td>70 mg</td>
<td>NS</td>
<td>NS</td>
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<td>18</td>
<td>70 mg</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>19</td>
<td>Placebo</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>20</td>
<td>Placebo</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>21</td>
<td>Placebo</td>
<td>56</td>
<td>72*</td>
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<tr>
<td>22</td>
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<td>42</td>
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<tr>
<td>29</td>
<td>Placebo</td>
<td>46</td>
<td>53</td>
</tr>
</tbody>
</table>

Teacher ratings of inattentiveness and hyperactivity for Participant 1 on the CTRS-R indicated he was less attentive and more active during the placebo condition than on days he took medication. *Elevated T-scores (61-65 mildly atypical, 66-70 moderately atypical, and >70 are markedly atypical).*
Participant 1 was off-task less often than the comparison child when he took medication. On days he took a placebo, this student was off-task about the same or just a little more than the comparison child. Lower percentage numbers show reduced ADHD symptomatology.

*Figure 12.* School Observation Interval Data for Participant 1.

**Academic Performance**

**Math**

Participant 1’s speed and accuracy in math did not show marked differences between days on medication and days on placebo (see Figure 13). He scored 20-21 correct problems on 4 out of 5 trials, with his lowest score being a 16. He did not make any errors on any test.

**Reading**

This participant’s oral reading performance was recorded at the same rate during the second placebo trial as for medication trials, which was just within the low-risk range. When he did not take medication and during the first placebo trial (see Figure 14) he read at a level that indicated he was at at-risk for reading problems.
Condition did not appear to differentially affect this child's performance during 1-minute math trials. Participant 1 did not make math computation errors. Total math scores = number attempted – errors.

Figure 13. One-Minute Math Trial Scores for Participant 1.

Reading scores showed Participant 1 exhibited fluency rates within the low-risk range for both medication conditions and the second placebo trial. Total score = Speed – Errors. Scores > 125 are considered to be at low risk for reading problems, with scores between 104 and 125 at some risk, and < 104 at-risk for reading difficulties.

Figure 14. DIBELS 1-Minute Oral Reading Scores for Participant 1.

Compliance

Participant 1’s teachers consistently rated Participant 1’s compliance behavior as being within the average range, regardless of whether he was on medication or placebo (see Figure 15). Their responses did not indicate observation of oppositional behavior.
during all medication days with ratings well within the normal range. While placebo scores were also in the normal range, two of four were slightly higher (T=52, day 21; T=59, day 27).

Conversely, his parents’ responses on the CPRS and ECBI reflected dissimilar trends during each phase with general consistency between instruments. The first medication phase demonstrated an overall increase in compliance behavior with two spikes of oppositional behavior (T=75, day 5; T=67, day 9). The increasing trend in oppositional behavior evident during the second medication phase was counter to predicted effects of medication. Compliance behaviors were stable during the final medication phase with one data point just outside the normal range (T=61, day 2).

Likewise, each placebo reflected different trends: Placebo phase 1 had a 1-day increase in externalizing behaviors (T=69, day 11); Phase 2 demonstrated an increasing trend in non-compliance; and placebo phase 3 showed consistent oppositional ratings in the significant range (T=72, day 27; T=72, day 28; T=69, day 29).

Parent ratings of this child showed different trends of compliance behavior for each phase. Participant 1’s teachers rated this participant’s compliance behavior within the normal range and without differences observed between condition phases. T-scores >60 reflect significant oppositional behavior.

Figure 15. Comparison of Parent and Teacher Compliance Ratings for Participant 1.
**Mood**

Participant 1’s report of feelings of depression, anxiety, and anger were within or below the normal range, regardless of whether he was on medication or placebo (see Table 8).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Depression T-score</th>
<th>Anger T-score</th>
<th>Anxiety T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>70 mg</td>
<td>50</td>
<td>50</td>
<td>NA</td>
</tr>
<tr>
<td>70 mg</td>
<td>50</td>
<td>46</td>
<td>NA</td>
</tr>
<tr>
<td>Placebo 1</td>
<td>42</td>
<td>48</td>
<td>NA</td>
</tr>
<tr>
<td>Placebo 2</td>
<td>44</td>
<td>42</td>
<td>44</td>
</tr>
</tbody>
</table>

Participant 1’s ratings of mood were within the normal range for all conditions and during baseline. T-scores > 60 indicate elevated problems with mood.

**Sleep**

**Sleep Latency**

Participant 1 took an hour and 20 minutes on average to fall asleep on school nights when he took medication, and almost 2 1/2 hours when he was on medication during spring break compared to 1 hour when on placebo (see Figure 16). Missing sleep data resulted when his mother was not available to record time to sleep (e.g. she went to bed prior to participant falling asleep); however, latency records from daily sleep diary data and sleep problems corresponded.
Sleep latency data for Participant 1 showed he took up to 4 hours to fall asleep, with problems falling asleep increasing in the second medication phase, which occurred during spring break.

Figure 16. Daily Measures of Sleep Latency for Participant 1.

Sleep Problems

Insomnia and problems preparing for school were the most severe, commonly occurring sleep problems for this participant, who also had notable problems with morning irritability; however, these difficulties were not differentially affected by condition (see Figure 17). Participant 1’s struggle rising in the morning was less severe on days he took medication compared to days he took a placebo. All other categories of sleep problems did not vary to a great degree between medication and placebo days. Participant 1’s most common sleep problems were: falling asleep, getting up in the morning, irritability, and preparing for school.
Although problems falling asleep and getting ready for school were the most severe, commonly occurring sleep problems for Participant 1, these difficulties were not significantly influenced by condition. Difficulty arising was less of a problem when he took medication compared to placebo. Range of severity scores was 0 (never/no occurrence) to 4 (often/severe).

*Figure 17. Sleep Problems Severity for Participant 1.*

**Side Effects**

There were no significant differences for any potential side effects between days Participant 1 was on Vyvanse and days he took a placebo (see Table 9). There were no reported occurrences of craving sugar, euphoria, dizziness, tinnitus, tics/nervous movements, vomiting, increased cough, skin rash, muscle weakness, or severe itching.

**Discussion of Data for Participant 1**

**Is the child’s ADHD stimulant medication more effective than placebo in reducing core ADHD symptoms?**

Vyvanse 70 mg dose reduced hyperactivity for Participant 1 as demonstrated by reduced scores on M-MAT measures of movement, CPRS parent ratings of hyperactivity, CTRS teacher ratings, and school observations. Most notable results were objective
measures that indicated hypoactivity, as he displayed less activity than typically
developing children in the medication phase. Taken together, results indicate a lower
medication dose may be warranted.

Table 9.
Severity Ratings of Side Effects for Participant 1

<table>
<thead>
<tr>
<th>Possible side effects</th>
<th>x 70 mg</th>
<th>x Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>3.80</td>
<td>4.00</td>
</tr>
<tr>
<td>Stares/daydreams</td>
<td>1.20</td>
<td>.89</td>
</tr>
<tr>
<td>Infrequently talks to peers</td>
<td>.90</td>
<td>.78</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>.80</td>
<td>.56</td>
</tr>
<tr>
<td>Irritable</td>
<td>2.4</td>
<td>2.78</td>
</tr>
<tr>
<td>Stomachaches</td>
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<td>.67</td>
</tr>
<tr>
<td>Nausea</td>
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<td>.11</td>
</tr>
<tr>
<td>Headaches</td>
<td>.85</td>
<td>.78</td>
</tr>
<tr>
<td>Drowsiness/fatigue</td>
<td>.45</td>
<td>.11</td>
</tr>
<tr>
<td>Cries</td>
<td>.15</td>
<td>.22</td>
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<tr>
<td>Worries</td>
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<td>.22</td>
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<tr>
<td>Mood swings</td>
<td>.75</td>
<td>1.11</td>
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<tr>
<td>Runny nose</td>
<td>3.05</td>
<td>2.78</td>
</tr>
<tr>
<td>Sore throat</td>
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<td>0</td>
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<tr>
<td>Fever</td>
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</tr>
<tr>
<td>Infection</td>
<td>.40</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>.05</td>
<td>0</td>
</tr>
</tbody>
</table>

Data shows mean severity of side effects was slightly higher for placebo than for medication conditions for half of the potential side effects. Severity ratings were on a scale of 0 (never) to 4 (severe).

Results on the M-MAT continuous performance task were disparate for Participant 1 with measures of attention falling within the normal range without
differential effect from condition, and activity evaluations ranged from subtle
hyperactivity on placebo to mild hypoactivity on medication. The predominant effect of
70 mg Vyvanse on ratings of activity were high immobility duration scores that resulted from this participant spending more time sitting still than typically developing controls.
Traditional CPT scores (omission) showed attentive performance in the normal range for all conditions; however, shift analysis and time spent attentive were both positively influenced by medication. As with attention, impulsivity did not appear to be differentially influenced by medication according to traditional CPT (commission) scores. Conversely, the percent of epochs with impulsive responding more than doubled when the participant took placebos. Although the stimulant medication did not affect this participant’s response speed (latency), which was in the normal range for all conditions, he displayed a high degree of variance in response speed during baseline and placebo conditions that is characteristic of children with ADHD (Rothenberger, 1995; as cited in Barkley, 1998).

Several factors may account for lower teacher T-scores on ratings of inattention and hyperactivity. Vyvanse has been shown to be clinically effective for up to 10 hours. Participant 1 takes his medication at 6 a.m. on school days and parent ratings of behavior by his teachers are from daytime observations; whereas Participant 1’s parents base their ratings of his behavior on school days from early afternoon to bedtime. Another factor is structured versus unstructured environments: Children with ADHD typically have more problems functioning in less structured settings: Academic periods have a high level of structure; whereas time at home is less structured. Finally, Participant 1 may have worked harder to improve his behavior at school due to awareness of observations.

Although teacher ratings were low for placebo conditions, they commented that they were able to tell when he was on placebo and were looking forward to the end of the study for consistent pharmacological treatment. Both teachers felt Participant 1 was doing well with the new medication. One commented about increased impulsive behavior...
(flipping light switch on and off before class started) that occurred during a placebo phase, which indicates impulsive behavior showed overt condition differences in school.

**Is the child’s ADHD stimulant medication more effective than placebo in reducing oppositional behavior at home?**

CTRS-R Oppositional Index scores showed Participant 1’s teachers viewed him as compliant with scores in the normal range for both conditions. Unlike school ratings, home compliance behavior appeared to be problematic for this participant’s parents for just more than half of the protocol ratings, with twice as many clinically significant ratings during placebo conditions compared to medication. Differing phase trends may be explained by factors uncontrolled by the protocol. The first medication phase showed two spikes of oppositional behavior superimposed with an overall increase in compliance behavior. Phase 1 non-compliance scores corresponded to the time when the child had strep throat. The increasing trend in oppositional behavior evident during the medication Phase 2 showed a reversed trend with increasing oppositional behaviors that can be accounted for by considering uncommon events. In this case the participant’s behavior became more problematic as time at home increased during spring break, just before returning to school. Compliance behaviors were stable during the final medication phase with one data point just outside the normal range (CPRS day 2). Likewise, each placebo reflected different trends: Placebo phase 1 had a 1-day increase in externalizing behaviors; Phase 2 demonstrated an increasing trend in non-compliance consistent with expected effects without medication; and placebo Phase 3 showed consistent oppositional ratings in the significant range. In general, this child was more compliant on medication when uncommon extraneous events were taken into consideration.
Does the participant’s ADHD medication reduce core symptoms at home?

Parent responses on the CPRS-R showed significantly improved core symptoms during the medication condition as compared to placebo.

How does the child’s ADHD stimulant medication affect math and reading fluency in comparison with placebo?

Math scores were not differentially affected by condition. Participant 1’s performance was consistent with no errors and speed/number of problems completed in 1 minute. The outcome for this participant supports previous research that found short-term benefits without long-term gains (e.g. Carlson & Bunner, 1993; Loe & Feldman, 2007; Evans, et al., 2001). Some studies have shown dose-related effects with best cognitive function and academic performance occurring at lower doses (e.g. Evans, et al., 2001; Sprague & Sleator, 1977). Medication affects on reading fluency was equivocal due to incongruent placebo scores (P1 at risk; P2 low risk). A confounding factor with this participant’s placebo measures was plasma levels: Placebo 1 (day 12) measures would have been were taken approximately 74 hours subsequent to his last dose of medication (day 9) after the converted dexamphetamine would have been completely metabolized; Blood plasma levels for Placebo 2 (day 19) occurred only 27 hours post-medication administration, during which around half of the drug would have metabolized. While it is possible reading scores showed more sensitivity to medication than did math scores, one measure is not sufficient to draw said conclusion without further data.
Does the child’s ADHD stimulant medication interfere with sleep?

As noted previously, Participant 1 had significant sleep problems with pre-enrollment information from his parents noting that he takes up to an hour and a half to on average to fall asleep. During the study, he appeared to have problems falling asleep, whether he was on medication or placebo, with problems exacerbated during the second medication phase when he was on break from school. Although this participant’s sleep latency was an average of 80 minutes during the medication condition (excluding spring break), his parents reported this was a tremendous improvement over sleep problems for previous medications (Concerta, Adderall) that increased latency and sleep variability two-fold despite use of sleep medication.

How do the side effects of the child’s ADHD stimulant medication compare to placebo?

Insomnia was the most frequently reported and severe side effect for Participant 1. Although side effects were slightly less severe during medication conditions than placebo, this may be accounted for by marked problems going to sleep during spring break. School vacation appeared to be a more significant factor than medication or placebo for sleep latency. Examination of the data show higher reports of side effects for daydreaming/staring and fatigue, both of which are counter to predicted values since stimulants generally increase alertness and energy. Stimulant doses that are too high can result in staring or “zombie effects” (Barkley, 1998).

With the exception of insomnia and irritability, side effects occurred most frequently and higher ratings of severity during the first medication phase and generally tapered off during the remainder of the study, with increases in severity during placebo
phase for a few side effects (mood swings, stomachache, daydreams). Spikes in fatigue,
anxiety, and runny nose on day 9 of medication Phase 1 corresponded with occurrence of
strep throat.

**Were side effects of the medication tolerable?**

The participant and his parents agreed that side effects were very tolerable,
especially when compared to severity of loss of appetite and increased sleep problems on
previous ADHD medications Concerta and Adderall.

**Individual Protocol Findings for Participant 2**

*Social History and Background*

Participant 2 was an 11-year, 4-month-old white male who lived with his
biological parents, 8-year-old sister, and 6-year-old brother. This 5th grade student was
diagnosed with ADHD (type not specified) by a local psychologist when he was 10 years
old. His parents became concerned when the child was around 3 years old, when he
seemed much more active and prone to mishaps than other children his age. His medical
history was remarkable only for chronic ear infections before age 3. He exhibited mild
stuttering during early speech development that resolved by age 7. Participant 2 was
prescribed a daily 15 mg dose of escitalopram (brand name Lexipro), a selective serotonin
reuptake inhibitor, often prescribed for depression and/or anxiety disorders. In addition to
ADHD symptomatology, parental concerns prior to admission to the study included
bedtime resistance, insomnia, difficulty awakening, morning irritability, some symptoms
associated with restless leg syndrome, grinding teeth, and poor appetite. Participant 2
denied problems with anxiety, depressive mood, suicidal/homicidal ideation, self-
injurious behaviors, aggression, and strange thoughts.
Participant 2’s parents’ scores on the Parent Stress Index indicated significantly high levels of stress that indicated the child’s mood, emotion dysregulation, demandingness, and rigidity contributed to stress in the parent-child relationship. These parents’ profile was similar in pattern to the average profile of parents of children with ADHD and/or ODD. Participant 2’s parents had elevated scores in the parent domain reflecting concerns about their health, experience of depressive mood, and feelings of frustration from parental role restriction. As per protocol, the couple was counseled and given referrals to local mental health service providers. They declined services.

*Referral Source and Reason for Enrollment*

Soon after Participant 2’s pediatrician prescribed Vyvanse 30 mg for this child, he referred him to the study, because he believed he would benefit from titration and monitoring of side effects.

*Protocol Findings for Participant 2*

This child was the only participant who forgot to *not* take his medication on the day of the evaluation. He returned with his mother and took baseline measures mid-morning the following day. For purposes of medication titration, Participant 2 took a post-protocol, unblinded M-MAT test under the supervision of the project pediatrician, to evaluate effects 50 mg Vyvanse with the CPT due to a second dose increase that occurred toward the end of the protocol and after completion of lab sessions. Data from the 50 mg unblinded M-MAT is included for comparative purposes.

Participant 2, like the remaining two participants, was enrolled in the study during school summer break and did not attend summer school; therefore, teacher and school observation data were not available for this child.
During administration of the M-MAT, Participant 2 appeared to attend to the task and put effort into his responses.

*M-MAT attention and impulsivity.* Traditional CPT measures of omission and commission showed Participant 2 was able to attend to this monotonous and demanding test with an age-appropriate level of accuracy in 5 out of 6 M-MAT tests (see Table 10). During the first placebo trial, which occurred on the second consecutive day in the condition, he was the least accurate and most inattentive with scores just outside the normal range. Participant 2’s test results were in the normal range for all conditions for response to non-targets (measure of impulsivity).

### Table 10.

*M-MAT Measures of Attention and Impulsivity for Participant 2*

<table>
<thead>
<tr>
<th>Protocol Day</th>
<th>Condition</th>
<th>Accuracy Normal Range</th>
<th>Omission Normal Range</th>
<th>Commission Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>No Pill</td>
<td>95.1</td>
<td>4.7</td>
<td>5.05</td>
</tr>
<tr>
<td>1</td>
<td>30 mg</td>
<td>96.7</td>
<td>3.8</td>
<td>3.04</td>
</tr>
<tr>
<td>12</td>
<td>40 mg</td>
<td>91.3</td>
<td>11.4</td>
<td>6.25</td>
</tr>
<tr>
<td>24</td>
<td>Placebo</td>
<td><strong>87.3 L</strong></td>
<td><strong>16.8 H</strong></td>
<td>8.59</td>
</tr>
<tr>
<td>28</td>
<td>Placebo</td>
<td>95.8</td>
<td>4.8</td>
<td>3.58</td>
</tr>
<tr>
<td>30</td>
<td>50 mg</td>
<td>97.3</td>
<td>1.3</td>
<td>4.22</td>
</tr>
</tbody>
</table>

Participant 2 exhibited accurate responding with few omission errors for all conditions except the first placebo trial. Commission errors were within the normal range for all conditions. Accuracy scores are percentage of correct responses. Percentage of omission errors (missed target stimuli) are considered to be a measure of inattention. Commission errors are percent of incorrect responses to a non-target stimuli and considered to be an estimate of impulsivity.

*M-MAT latency and variance.* During each condition Participant 2 responded more slowly and inconsistently to targets than expected for a boy his age, which is common for children with ADHD. Participant 2’s latency score (mean time in
milliseconds from stimulus presentation to press of the space bar) was slower than typically developing boys his age regardless of conditions (see Figure 18). His response speed was best for the 50 mg unblinded trial (616 ms) compared to response latency to targets on placebo (P1=913 ms, P2=826 ms) when he did not take a pill for baseline measures (651) and both medication trials (30 mg=680 ms; 40 mg=757 ms).

![Response Latency Scores for Participant 2](image)

Participant 2’s response speed (latency) was slower than normal controls for all conditions with faster responses for baseline and medication conditions than for placebo. Latency scores measure the amount of time between presentation of target stimuli and response to target (press of spacebar) in milliseconds. Lower scores indicate faster response. Normal range is 356-558 and is shown in the grey area.

*Figure 18. M-MAT Response Latency Scores for Participant 2.*

High levels of variance in response speed (variability score, see Figure 19) was evidenced by Participant 2 during baseline ($s_x = 265$), 30 mg ($s_x = 268$), 40 mg ($s_x = 311$), and both placebo conditions ($s_x = 324$; $s_x = 307$). He responded much more consistently in the 50 mg unblinded trial ($s_x = 169$) with a score in the normal range.
Participant 2 evidenced difficulty consistently responding, except during the 50 mg (unblinded) trial. Variability scores (s_x) represent variance in response time (latency) on the M-MAT. Higher scores show greater inconsistency. Normal range is 77-195.

Figure 19. M-MAT Variability Scores for Participant 2.

M-MAT activity. Participant 2’s scores on the MMAT showed he was unable to sit still (immobility duration, see Figure 20; movements, see Table 11) during baseline, placebo, and 40 mg Vyvanse dose conditions, but improved performance with scores within the normal range during the 30 mg and 50 mg Vyvanse conditions. The amount of time being active (Temporal Scaling, see Figure 21) was high for each condition (B=0.94, 30 mg=0.90, 40 mg=0.99, 50 mg=0.64, P1=0.89, P2=0.93) with more time spent sitting still when he took 50 mg for an unblinded trial.

Immobility scores for Participant 2 showed he spent as much time sitting still during the 30 mg (0.12) and 50 mg (0.17) conditions as normal controls (see Figure 20). He had difficulty remaining still during baseline (0.09), placebo trials (P1=0.9, P2=0.067), and the 40 mg (0.05) condition.
Participant 2 spent less time sitting still than typically developing children during baseline, 40 mg condition, and placebo trials. Immobility duration on the M-MAT had a normal range of 0.105–0.290 of the 15-minute task (shown in grey). Low numbers reflect more movement.

*Figure 20.* M-MAT Immobility Duration Scores for Participant 2.

Participant 2’s Displacement scores showed more movement than expected for a typically developing child during all conditions (see *Table 11*). During the follow-up test on unblinded 50mg Vyvanse, his scores showed improvement with displacement and area movements just above the average range. Total area moved was within normal limits for baseline and just within the normal range for day 1 on placebo. Participant 2’s type of movement (spatial complexity) was in the normal to just below normal range, indicating he did not just move side-to-side during testing.
Participant 2 spent more time sitting still during the 50 mg unblinded trial than he did during other conditions. Temporal scaling scores on the M-MAT measure the extent to which the child is active with 0 indicating lack of movement to 1 showing incessant movement. Normal range (shown in grey) is between 0.308 and 0.562.

Figure 21. M-MAT Temporal Scaling Scores for Participant 2.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal Range</th>
<th>Baseline</th>
<th>30 mg</th>
<th>40 mg</th>
<th>Placebo 1</th>
<th>Placebo 2</th>
<th>50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Displacement</td>
<td>0.57-2.72</td>
<td>9.02 H</td>
<td>6.10 H</td>
<td>17.92 H</td>
<td>8.66 H</td>
<td>12.42 H</td>
<td>4.59 H</td>
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<tr>
<td>Area</td>
<td>9-55</td>
<td>111 H</td>
<td>61 H</td>
<td>208 H</td>
<td>89 H</td>
<td>140 H</td>
<td>61 H</td>
</tr>
<tr>
<td>Spatial Complexity</td>
<td>1.167-1.381</td>
<td>1.167 L</td>
<td>1.191</td>
<td>1.01 L</td>
<td>1.167</td>
<td>1.167</td>
<td>1.244</td>
</tr>
<tr>
<td>Movements</td>
<td>344-2239</td>
<td>2859 H</td>
<td>2139</td>
<td>4946 H</td>
<td>2874 H</td>
<td>3354 H</td>
<td>1590</td>
</tr>
</tbody>
</table>

Participant 2’s performance showed high levels of activity for all conditions except spatial complexity. Displacement score is the total distance moved by the marker (like an odometer reading). Area scores report the total area covered by the marker (reflective ball on back of head). Spatial Complexity scores the movement path with lower values indicating the marker often moved linearly; high values indicate more convoluted movement. Movement scores are the average number of position changes with higher scores showing more position changes than expected for age. Scores above the normal range are shown in bold with an “H”; below average scores are bold with an “L.”
Participant 2 showed patterns of hyperactivity with elevated distance scores and increased time spent active. The high movement score (>100 cm²) indicates his hyperactivity would be noticeable by observers.

Subtle hyperactivity was shown for Participant 2 with the 1st protocol day in the 30 mg condition. Although the number of position changes, movement area, and time spent immobile were within the normal range, distance (displacement) and time moving (temporal scaling) were elevated. The modest movement area may mean this pattern of hyperactivity could be missed by observers.

This trial showed a classic and observable pattern of hyperactivity shown by Participant 2 in the 40 mg condition are characterized by increased microevents, displacement, and time active (temporal scaling). He spent little time sitting still, and the spatial scaling exponent is low, suggesting a large number of side-to-side movements.
Participant 2 showed decrease in hyperactivity in the 50 mg condition. Position changes, movement, time active scores were all in the normal range, with total distance moved (displacement) still elevated. This subtle movement may be missed by observers.

First placebo trial (P1) occurred on the 24th protocol day, 2nd consecutive day on placebo.

Modest movement area may lead some to miss this pattern of hyperactivity. Participant 2 had high scores for distance moved and time active (temporal scaling), and number of position changes.

Second placebo trial (P2) on the 28th protocol day was the 2nd day on placebo for that phase.

Observable hyperactivity exhibited by Participant 2 for the second placebo trial. He had high distance, movement, area, and time active (temporal scaling) scores, with a low immobility score.

*Figure 22.* M-MAT Pictorial Representations of Movements in 5-Minute Segments for Participant 2.

*M-MAT shift analysis.* Data showed Participant 2 had almost two-three times as many shifts in response patterns during placebo (P1=14, P2=8) and 40 mg (8) trials than he did during baseline (4) and the 30 mg (4) and 50 mg (5) conditions. M-MAT normative data showed the healthy control group changed their response style an average of 5.4 times during the 15-minute task, as compared to the ADHD group that had a mean response-style shift of 12.8.
M-MAT epoch analysis. Consistent with other M-MAT measures of attention-related behaviors, Participant 2 spent a majority of the epochs in an attentive-response style in all conditions except for the first placebo phase (see Figure 23). His performance was as good during baseline as it was when he took 30 mg of medication, with 93 percent of the epochs showing attentiveness for both trials. He did almost as well during the 50 mg condition with 90 percent of the epochs reflecting attentive responding. He paid more attention during the second placebo test (83%) than he did during the 40 mg dose (73%). His worst performance was in the first placebo phase where he was distracted (50% of epochs) more than he was attentive (40%). Frequent distracted responding also occurred during more than a quarter of the 40 mg sample. Baseline, 30 mg, and 50 mg (unblinded) data consisted of only two epochs of distracted behavior, and the second placebo trial resulted in only three epochs of distracted responding. He showed minimal responding in only one epoch during the entire protocol, which occurred during the first placebo measure. This participant exhibited impulsive responding in two epochs for the 50 mg and both placebo conditions. Random-pattern responses occurred most often during the 20 mg and both placebo conditions. He did not have any predominately random or contrary responses during the protocol.
Participant 2 exhibited an attentive response style during all medication conditions and the second placebo trials. Scores reflect percent of the 30, 30-second epochs for each response pattern on the M-MAT. Typically developing children were attentive during 82.4% of the 30 epochs and children with ADHD spent only 42.6% of the epochs responding attentively. *50 mg scores were taken in an unblinded, post-protocol test.

Figure 23. M-MAT Epoch Pattern Analysis for Participant 2.

Parent Reports of Inattention and Hyperactivity

Participant 2’s mother rated his attentive behavior as being within the normal range for 29 out of 30 days during the data collection phase (see Table 12). His only high inattentive score occurred during day 8, which was a placebo condition. Hyperactivity scores were elevated on the second protocol day during the first 30 mg dose condition.
Table 12.

Parent Ratings of Inattentiveness and Hyperactivity for Participant 2

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Condition</th>
<th>CPRS Inattention</th>
<th>CPRS Hyperactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>No Pill</td>
<td>58</td>
<td>54</td>
</tr>
<tr>
<td>1</td>
<td>30 mg</td>
<td>42</td>
<td>50</td>
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<tr>
<td>2</td>
<td>30 mg</td>
<td>42</td>
<td>67*</td>
</tr>
<tr>
<td>3</td>
<td>30 mg</td>
<td>42</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>30 mg</td>
<td>42</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>30 mg</td>
<td>42</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>Placebo</td>
<td>42</td>
<td>47</td>
</tr>
<tr>
<td>7</td>
<td>Placebo</td>
<td>44</td>
<td>55</td>
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<tr>
<td>8</td>
<td>Placebo</td>
<td>61*</td>
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<tr>
<td>9</td>
<td>40 mg</td>
<td>42</td>
<td>44</td>
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</tr>
<tr>
<td>29</td>
<td>50 mg</td>
<td>42</td>
<td>44</td>
</tr>
</tbody>
</table>

Daily parent ratings of inattentiveness and hyperactivity for Participant 2 on the CPRS showed average attentiveness and activity for all but two data sets. Asterisks indicate elevated scores with 61-65 considered mildly atypical, 66-70 are moderately atypical, and T-scores >70 are markedly atypical and indicate significant problems.
Academic Performance

Math

Participant 2’s speed and accuracy in math did not show significant differences between days on medication, days on placebo, or for the day he did not take medication (see Figure 24). Participant 2 scored 17-21 correct problems during the five trials, with accuracy ranging from 89 percent (baseline) to 100 percent correct (40 mg). Although his speed was consistent throughout the protocol, he produced the greatest number of errors during baseline.

Medication did not differentially affect math calculation fluency for Participant 2. Total score = Speed - Errors.

Figure 24. One-Minute Math Trial Scores for Participant 2.

Reading

Participant 2’s reading scores showed more sensitivity to medication than did math scores (see Figure 25). Participant 2 read at a level that indicated he was at “low-risk” for reading problems when he took Vyvanse (30 mg = 130, 40 mg = 129). His scores were slightly lower during days he took placebo (P1= 110, P2 = 117) falling in the
"at-some-risk" range, and were poorest when he did not take medication ($B = 96$), scoring in the "at-risk" range.

![Graph showing DIBELS 1-Minute Math Trial Scores for Participant 2]

Participant 2's poorest performance was at baseline for reading fluency. Improvement in speed is noted for both medication conditions. Scores > 125 are considered to be at low-risk for reading problems; scores 104 to 125 at some-risk; and < 104 at-risk for reading difficulties.

**Figure 25. DIBELS 1-Minute Math Trial Scores for Participant 2.**

**Compliance**

Parental ratings of oppositional and refusal behavior were consistently lower on the ECBI than on the CPRS for Participant 2, with as much as 38 T-score points difference within same-day ratings (see Figure 26). During the protocol, his baseline score was his only rating in the clinically significant range on the ECBI. Participant 2's mother consistently rated his compliance behavior as being within the average range regardless of whether he was on medication or placebo. Conversely, CPRS Oppositional Index T-scores showed a downward trend (improvement) over the entire protocol period, with poorest behavior ratings not occurring during placebo days, but during the second 40 mg dose phase.
Parental ratings of oppositional and refusal behavior were consistently low on the ECBI compared to CPRS Oppositional Index scores for Participant 2. CPRS ratings showed improved compliance behavior over time that was not sensitive to medication effects. T-scores 61-65 are considered mildly atypical, 66-70 are moderately atypical, and T-scores >70 are markedly atypical indicating significant problems.

Figure 26. Parent Ratings of Oppositional Behavior for Participant 2.

Mood

Participant 2’s report of feelings of depression, anxiety, and anger were within the normal range, regardless of whether he was on medication, placebo, or during baseline (see Table 13). Participant 2 did not appear to experience problems with mood.

Table 13.

Self-Ratings of Mood for Participant 2

<table>
<thead>
<tr>
<th>Condition</th>
<th>Depression T-score</th>
<th>Anger T-score</th>
<th>Anxiety T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>46</td>
<td>46</td>
<td>44</td>
</tr>
<tr>
<td>30 mg</td>
<td>47</td>
<td>47</td>
<td>NA</td>
</tr>
<tr>
<td>40 mg</td>
<td>44</td>
<td>48</td>
<td>NA</td>
</tr>
<tr>
<td>Placebo 1</td>
<td>46</td>
<td>48</td>
<td>NA</td>
</tr>
<tr>
<td>Placebo 2</td>
<td>48</td>
<td>50</td>
<td>44</td>
</tr>
</tbody>
</table>

Participant 2’s scores on the Beck Youth Inventories did not reflect mood problems for any domain. T-scores > 60 indicate elevated problems with mood.
Sleep

Sleep Latency

Participant 2 did not appear to have problems falling asleep, whether he was on medication or placebo (see Figure 27).

Although Participant 2 had problems going to sleep on the 4th protocol day, sleep latency did not appear affected by condition.

Figure 27. Daily Measures of Sleep Latency for Participant 2.

Sleep Problems

Participant 2 appeared to have a few mild sleep problems throughout the protocol (see Figure 28). During the 50 mg condition, no sleep-related problems were reported. Morning irritability was more severe during the 40 mg (\( \bar{x} = 1.45 \)) condition than during the 30 mg phase (\( \bar{x} = 0.80 \)), placebo (\( \bar{x} = 1 \)), or 50 mg (\( \bar{x} = 0 \)). He had significantly fewer problems going to bed when he took 50 mg (\( \bar{x} = 0 \)) and 30 mg Vyvanse (\( \bar{x} = 0.80 \)), compared to placebo (\( \bar{x} = 1.3 \)) and 40 mg (\( \bar{x} = 1.18 \)) conditions. Data indicated he had
no problems falling asleep when he was on 50 mg of the medication compared to when he was on placebo (\( \bar{x} = .80 \)) and the 30 mg dose (\( \bar{x} = .60 \)). Participant 2 had no problems getting up in the morning in the 50 mg condition compared to the 40 mg (\( \bar{x} = 1.09 \)), 30 mg (\( \bar{x} = .60 \)), and placebo (\( \bar{x} = .70 \)) conditions. Daytime napping occurred solely during the 30 mg condition and weakness was reported once each during placebo (\( \bar{x} = .10 \)) and the 50 mg (\( \bar{x} = 1 \)) conditions.

![Graph showing sleep problems severity for Participant 2.](image)

Sleep was differentially affected by dose for Participant 2 who had more problems with irritability and getting up during the 40 mg dose; and increased problems getting ready for bed and falling asleep when he took placebo. Range of severity scores was 0 (never/no occurrence) to 4 (often/severe).

**Figure 28.** Sleep Problems Severity for Participant 2.

**Side Effects**

Participant 2 appeared to tolerate the medication very well (see Table 14). The only notable side effect was decreased appetite with significantly less effect during the 30 mg, early protocol days; otherwise, there was no significant difference between days he was on 40 mg or 50 mg doses and days he took a placebo. Euphoria/unusually good mood was reported once during a placebo day.
Table 14.

Severity Ratings of Side Effects for Participant 2

<table>
<thead>
<tr>
<th>Possible side effects</th>
<th>x 30 mg</th>
<th>x 40 mg</th>
<th>x 50 mg</th>
<th>x Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritability</td>
<td>0.6</td>
<td>0.00</td>
<td>0.00</td>
<td>0.0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0.8</td>
<td>3.82</td>
<td>3.67</td>
<td>2.7</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0.2</td>
<td>0.09</td>
<td>0.00</td>
<td>0.0</td>
</tr>
<tr>
<td>Euphoric/unusually happy</td>
<td>0.0</td>
<td>0.00</td>
<td>0.00</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Participant 2 reported very few side effects. Mean severity for decreased appetite was lowest on 30 mg dose and highest during 40 and 50 mg dose conditions, but not significantly higher than when he took placebos.

Discussion of Data for Participant 2

Is the child’s ADHD stimulant medication more effective than placebo in reducing core ADHD symptoms?

Overall, a 50 mg dose of Vyvanse was the most effective treatment for Participant 2 for nearly all conditions. Undeniably, it would have been beneficial to have the flexibility during the protocol to run an additional lab session during a blinded 50 mg condition.

While 30 mg of the medication was the most effective in reducing commission errors for this child, M-MAT commission data for the 30 mg condition was not significantly better than for placebo. Daily parent ratings did not appear sensitive to medication conditions and were inconsistent with their verbal report. For example, they speculated during one lab session (40 mg, 12th protocol day) that he had been taking placebo; however, their CPRS responses for that period showed low levels of inattention ($T=42$) and hyperactivity ($T=44$).
Inordinate variability in response speed was demonstrated by Participant 2, who may have had vacillating test strategies, fluctuating levels of effort, or lack of persistence. M–MAT database statistics indicate greater variability is not uncommon in older children with ADHD. Additionally, slow response speeds — as shown by this participant — may be indicative of processing speed problems. Excessive latency has most often been observed in some children with learning disorders comorbid with ADHD.

Finally, it was not clear whether Participant 2 displayed inattentiveness that interfered in academic functioning. Should he not demonstrate marked impairment in attention in school, a diagnosis of ADHD–Predominately Hyperactive/Impulsive Type was more consistent with objective measures and parent report and should be considered.

**Is the child’s ADHD stimulant medication more effective than placebo in reducing oppositional behavior at home?**

While the ECBI was not sensitive to behavior changes, ratings on the CPRS Oppositional Index showed an overall trend for improved behavior; however, amelioration cannot be attributed to medication.

**Does the participant’s ADHD medication reduce core symptoms at home?**

Overall, parent ratings on the CPRS-R reflected developmentally appropriate attention and activity levels regardless of condition.

**How does the child’s ADHD stimulant medication affect math and reading fluency in comparison with placebo?**

Clearly, medication did not affect math fluency during the brief samples taken for the protocol. Reading fluency showed more improvement in the 30 mg condition than for
the 40 mg dose. It would have been helpful to have also run the reading test during a blinded 50 mg trial for comparison purposes.

**Does the child’s ADHD stimulant medication interfere with sleep?**

Data did not reflect sleep problems for medication condition in comparison to placebo for this child. Sleep was differentially affected by dose with increase in irritability and difficulty getting up during the 40 mg dose; and increased problems getting ready for bed and falling asleep when he took placebo. No sleep problems were reported after week two of the study indicating habituation to the medication occurred throughout the 4-week protocol despite dosage increase.

**How do the side effects of the child’s ADHD stimulant medication compare to placebo?**

There were no increases in reported side effects when he was on 40 mg and 50 mg of the medication, as compared to placebo. Interestingly, side effects were significantly lower for the 30 mg dose at the very beginning of his protocol; however, medication effects were also not detectible at that dose.

**Were side effects of the medication tolerable?**

Side effects were well tolerated, with decreased appetite being the single notable side effect.

**Individual Protocol Findings for Participant 3**

*Social History and Background*

Participant 3 was a 10-year-old white female who was adopted by her paternal aunt 3 years prior to admission to the study. She and her biological 7-year-old brother, who also was adopted by their aunt, have lived with their aunt for 5 years following
termination of parental rights due to neglect and sexual abuse. This participant’s brother has a diagnosis of ADHD and her biological parents have a history of psychiatric hospitalization, substance abuse, dyslexia, suspected conduct disorder, and incarceration. Participant 3 denied problems with anxiety, depressive mood, suicidal/homicidal ideation, self-injurious behaviors, aggression, or strange thoughts.

Just prior to enrollment in the study, this child received diagnoses of ADHD-PI, adjustment disorder with mixed disturbance of emotions and conduct, and parent-child relational problems subsequent to an evaluation by psychologists at a local behavioral pediatric clinic. The psychologist recommended behavioral interventions and an evaluation for ADHD medication.

Participant 3’s parents’ scores on the Parent Stress Index approximated the mean profile of parents who have children with ADHD comorbid with ODD. Her responses indicated significantly high levels of stress that reflected her daughter’s mood, emotion dysregulation, demandingness, and rigidity contributed to stress in the parent-child relationship. Participant 3’s mother had an elevated score in the parent domain indicating concerns about her ability to accurately understand her daughter’s feelings. As per protocol, this mother was counseled and given referrals to local mental health service providers. She declined services.

**Referral Source and Reason for Enrollment**

This child received a referral to the study subsequent to completion of the psychological assessment by the evaluating psychologist.
Protocol Findings for Participant 3

**M-MAT**

This youngster appeared to put effort into her responses on this 15-minute test that evaluates sustained attention, hyperactivity, and other dimensions of core ADHD symptoms.

*M-MAT attention and impulsivity.* Participant 3 performed within the normal range for all conditions (no pill, Vyvanse, and placebo) for accurate responding to targets and inhibited responses to incorrect targets (commission/measure of impulsivity; see Table 15). Participant 3 had an elevated score for missed targets (omission/measure of inattention), which occurred on the third consecutive day 3 on placebo.

Table 15.

**M-MAT Measures of Attention and Impulsivity for Participant 3**

<table>
<thead>
<tr>
<th>Protocol Day</th>
<th>Condition</th>
<th>Accuracy Normal Range</th>
<th>Omission Normal Range</th>
<th>Commission Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>No Pill</td>
<td>88.7 - 99.0</td>
<td>0.0 - 4.1</td>
<td>0.78 - 18.41</td>
</tr>
<tr>
<td>3</td>
<td>20 mg</td>
<td>93.3</td>
<td>0.4</td>
<td>12.95</td>
</tr>
<tr>
<td>10</td>
<td>Placebo 1</td>
<td>92.2</td>
<td>5.2 H</td>
<td>10.37</td>
</tr>
<tr>
<td>18</td>
<td>Placebo 2</td>
<td>95.3</td>
<td>1.0</td>
<td>8.20</td>
</tr>
<tr>
<td>24</td>
<td>30 mg</td>
<td>98.2</td>
<td>0.8</td>
<td>2.89</td>
</tr>
</tbody>
</table>

Nearly all domains during tests of attention on the M-MAT reflected attentiveness and sustained attention for Participant 3. She missed slightly more target stimuli (omission) than normal controls during the first placebo trial.

*M-MAT latency and variance.* Participant 3’s response speed, which is the latency from presentation of stimuli to response (press of space bar), was within the normal range (368-665 ms) for each condition. Scores in milliseconds were: Baseline = 502, 20 mg = 448, 30 mg = 475, placebo 1 = 518, and placebo 2 = 473 (see Figure 29).
Participant 3's response speed (latency) was within the normal range for all trials. Latency scores are the mean time in milliseconds to correct responses, with normal range between 368–665 ms.

Figure 29. M-MAT Response Latency for Participant 3

No differences between conditions were notable for Participant 3 whose variance ($s_x$) in response time to target stimuli was in the normal range for baseline (132), 30 mg (128), and the second placebo condition (130; see Figure 30). She exhibited more response speed variation than typical controls for the first placebo trial (194). When she took 20 mg Vyvanse, her response speed (74) was more consistent than typically developing girls her age.

Immobility duration scores were high for the 20 mg (1.22), 30 mg (.89), and the second placebo (.37) trials for this participant, indicating she sat still longer than normal controls under the above conditions (see Figure 32). She demonstrated average ability to hold still during baseline and the first placebo trial, both of which yielded immobility scores of .20.
No significant differences between conditions were notable for Participant 3 whose variance in response time to target stimuli (s) was in the normal range for baseline, 30 mg, and the second placebo condition. Normal range is 75–170.

Figure 30. M-MAT Variability Scores for Participant 3.

The average amount of time sitting still for Participant 3 was in the normal range for baseline measures and the first placebo trial; however, she moved significantly less than typical controls during both medication phases and the second placebo trial.

Figure 31. M-MAT Immobility Scores for Participant 3.

*M-MAT activity.* The extent to which Participant 3 was active (temporal scaling, see Figure 32) was within the normal range when she was took placebos (P1 = 0.72,
P2 = 0.50) and 20 mg Vyvanse (0.33). Temporal scaling, which yields scores of 0 (no movement) to 1 (incessant movement), showed widely differential results between baseline (0.81) during which she was remarkably active and the 30 mg condition (0.02), in which she was very inactive.

![Temporal Scaling Scores for Participant 3](image)

Participant 3’s ability to sit still was within the average range for the 20mg dose and both placebo trials. There were significant differences between her baseline and 30 mg condition scores. Normal range is 0.165–0.797.

**Figure 32.** M-MAT Temporal Scaling Scores for Participant 3.

Displacement, one of the M-MAT measures of spatial motion that reflects distance (like an odometer) showed Participant 3 displayed mild, subtle hyperactivity during baseline and the first placebo trial; yet had scores in the normal range for the second placebo test (see Table 16). Medication appeared to dampen movements for this child, with displacement scores showing considerably less movement than normal controls for both the 20 mg and 30 mg phases.
Table 16.  

*M-MAT Measures of Spatial Motion for Participant 3*

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal Range</th>
<th>Baseline</th>
<th>20 mg</th>
<th>30 mg</th>
<th>Placebo 1</th>
<th>Placebo 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Displacement</td>
<td>0.43-2.73</td>
<td>3.82 H</td>
<td>0.53</td>
<td>0.76</td>
<td>3.66 H</td>
<td>2.05</td>
</tr>
<tr>
<td>Area</td>
<td>5-49</td>
<td>37</td>
<td>5</td>
<td>8 L</td>
<td>37</td>
<td>21</td>
</tr>
<tr>
<td>Spatial Complexity</td>
<td>1.209-1.490</td>
<td>1.189 L</td>
<td>1.679</td>
<td>1.52 H</td>
<td>1.250</td>
<td>1.342</td>
</tr>
<tr>
<td>Movements</td>
<td>351-2034</td>
<td>1263</td>
<td>232 L</td>
<td>316 L</td>
<td>1327</td>
<td>792</td>
</tr>
</tbody>
</table>

High displacement scores indicated Participant 3 moved more distance during baseline and the first placebo test session. Area moved was average for all conditions except 30 mg, during which she moved in a smaller space than other girls her age. She exhibited side-to-side movements during baseline and more spatially complex movements during medication phases and also made fewer position changes during 20 mg and 30 mg trials. Displacement score is the total distance moved by the reflective marker on back of head. Area scores report the total area covered by the marker. Spatial Complexity scores the movement path with lower values indicating the marker often moved linearly; high values indicate more convoluted movement. Movement scores are the average number of position changes with low scores showing fewer position changes than expected for age. Scores above the normal range are shown in bold with an “H”; below average scores are bold with an “L.”

Participant 3’s baseline measures showed high ratings for distance moved (displacement) and other activity; however, low movement area during baseline would make this pattern of hyperactivity difficult to detect via observation.

Hypoactivity captured by M-MAT motion-detection camera for the 20 mg trial. She moved within an extremely narrow area with few position changes.
30 mg Vyvanse 4th consecutive day on 30 mg dose; 23rd protocol day

Movement within a narrow area and less position changes than normal again resulted in hypoactivity for the 30 mg condition.

First placebo trial occurred on the 10th protocol day, which was 3rd day on placebo

Movements for the first placebo trial showed the participant's total distance moved (displacement) was elevated; however, all other scores were within the normal range. While the displacement score is the most sensitive measure of hyperactivity, above average score for total area moved in and of itself is not definitive. This type of response may be in the high normal or mild hyperactive range.

Second placebo trial was on the 18th protocol day and the 2nd consecutive day on placebo

Age and gender typical movements were seen during the second placebo trial.

Figure 33. M-MAT Pictorial Representations of Movement in 5-Minute Segments for Participant 3.

M-MAT shift analysis. Data showed Participant 3 shifted response patterns considerably more when she was not on medication (baseline = 13) and when she had taken placebos (P1=9, P2=10) than when she had taken medication (20 mg = 3, 30 mg = 4). M-MAT normative data showed children in the healthy control group changed their response style around 5.4 times during the 15-minute task; however, children with ADHD had a mean response style shift of 12.8.
**M-MAT epoch analysis.** Participant 3 exhibited an attentive response style in 90 percent (20 mg) to 93 percent (30 mg) of the 30-second epochs during the medication conditions (see *Figure 34*). Baseline (73.3%) and placebo scores (P1=77%, P2=83%) were approximate to the percent of attentive epochs for normal controls who had average scores of 82.4 percent. ADHD comparison children were attentive on average for only 42.6 percent of the epochs. Impulsive-style responses for this participant were recorded most often during baseline (26.7%) and the first placebo test (23.3%), with less impulsivity during the 30 mg (3.3%), 20 mg trial (10%), and the second placebo test (16.7%). Her only other type of response pattern occurred during the 30 mg phase, wherein she exhibited a distracted-pattern of responding for 3.3 percent of the epochs.

![Figure 34. M-MAT Epoch Pattern Analysis for Participant 3.](image)

Participant 3 spent the most epochs in an attentive style when she took medication. Overall, the percent of attentive epochs was approximately that of typically developing children (82.4%) for all conditions.
Parent and Daycare Provider Reports of Inattention and Hyperactivity

Participant 3’s mother rated her attentive behavior as being within the normal range for 13 out of 28 days during the data collection phase (see Table 17). She viewed her daughter’s ability to maintain her attention as significantly improved during the second half of study period during 20mg, 30mg doses, as well as during the second and third placebo phases. Although attentiveness approved, parent ratings of hyperactivity were high throughout the protocol regardless of condition. Participant 3’s daycare staff consistently rated the child’s attentiveness, compliance, and activity level as being within the normal range for all conditions (see Table 17).

Academic Performance

Math

Participant 3’s accuracy for simple math problems was as poor when she took 20 mg Vyvanse (17 attempted – 5 errors = 11 total) as it was for the second placebo condition 16 attempted – 3 errors = 13 total; see Figure 35). While her best performance was during the 30 mg condition (22 attempted – 1 error = 21 total), her scores yielded similar results to the first placebo trial (23 attempted – 3 errors = 20 total). She made no errors during baseline, correctly completing 15 problems.
Table 17.

Daily Parent and Teacher Ratings Participant 3

<table>
<thead>
<tr>
<th>Protocol day</th>
<th>Condition</th>
<th>Inattention T-score</th>
<th>Hyperactivity T-score</th>
<th>Inattention T-score</th>
<th>Hyperactivity T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>No Pill</td>
<td>90‡</td>
<td>82‡</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>1</td>
<td>20 mg</td>
<td>79‡</td>
<td>90‡</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>20 mg</td>
<td>85‡</td>
<td>90‡</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>20 mg</td>
<td>90‡</td>
<td>79‡</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>20 mg</td>
<td>88‡</td>
<td>69†</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>20 mg</td>
<td>73‡</td>
<td>64*</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>20 mg</td>
<td>79‡</td>
<td>79‡</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>7</td>
<td>20 mg</td>
<td>MD</td>
<td>MD</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8</td>
<td>Placebo</td>
<td>90‡</td>
<td>89‡</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>9</td>
<td>Placebo</td>
<td>79‡</td>
<td>90‡</td>
<td>68†</td>
<td>58</td>
</tr>
<tr>
<td>10</td>
<td>Placebo</td>
<td>76‡</td>
<td>84‡</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>11</td>
<td>20 mg</td>
<td>70†</td>
<td>79‡</td>
<td>47</td>
<td>46</td>
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<tr>
<td>12</td>
<td>20 mg</td>
<td>73‡</td>
<td>79‡</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td>13</td>
<td>20 mg</td>
<td>79‡</td>
<td>85‡</td>
<td>63*</td>
<td>46</td>
</tr>
<tr>
<td>14</td>
<td>20 mg</td>
<td>64*</td>
<td>84‡</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>15</td>
<td>20 mg</td>
<td>47</td>
<td>50</td>
<td>57</td>
<td>50</td>
</tr>
<tr>
<td>16</td>
<td>20 mg</td>
<td>47</td>
<td>69†</td>
<td>52</td>
<td>46</td>
</tr>
<tr>
<td>17</td>
<td>Placebo</td>
<td>56</td>
<td>79‡</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>18</td>
<td>Placebo</td>
<td>61*</td>
<td>84‡</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>19</td>
<td>Placebo</td>
<td>56</td>
<td>84‡</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td>20</td>
<td>30 mg</td>
<td>67†</td>
<td>90‡</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>21</td>
<td>30 mg</td>
<td>61*</td>
<td>90‡</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>22</td>
<td>30 mg</td>
<td>59</td>
<td>90‡</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>23</td>
<td>30 mg</td>
<td>59</td>
<td>75‡</td>
<td>47</td>
<td>58</td>
</tr>
<tr>
<td>24</td>
<td>30 mg</td>
<td>44</td>
<td>60</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>25</td>
<td>Placebo</td>
<td>50</td>
<td>90‡</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>26</td>
<td>Placebo</td>
<td>50</td>
<td>89‡</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>27</td>
<td>30 mg</td>
<td>47</td>
<td>89‡</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>28</td>
<td>30 mg</td>
<td>90‡</td>
<td>56</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Most parent ratings (76%) were in the clinically significant range, in contrast to few (12.5%) elevated daycare provider daytime ratings. MD = missing data; ND = no data available. Asterisks indicate mildly elevated scores in the 61-65 range; moderately atypical scores 66-70 are shown with †; and the ‡ symbol highlights markedly atypical T-scores >70 that indicated significant problems.
Condition did not differentially affect math scores for Participant 3. Total score = number of problems attempted – errors.

*Figure 35. One-Minute Math Trial Scores for Participant 3.*

**Reading**

Participant 3 demonstrated age-appropriate reading fluency (see *Figure 36*) during medication trials for total scores (20 mg=130; 30 mg 141). Baseline measures were in the at-risk range with fewer errors (speed=106, errors=5) than other conditions. Placebo total scores were in the upper “at-risk” range (P1=113, P2=114).

Although Participant 3’s error rate was not affected by condition, reading fluency increased during medication conditions. Total score = Speed – Errors. Scores > 125 are considered to be at low risk for reading problems, with scores between 104 and 125 at some risk, and < 104 at-risk for reading difficulties.

*Figure 36. DIBELS 1-Minute Oral Reading Scores for Participant 3.*
Compliance

There were insufficient data points to make a comparison between CTRS Oppositional Index ratings of noncompliant behavior by Participant 3’s daycare provider and CPRS Oppositional Index scores by her mother (see Figure 37). In general, T-scores on the CTRS by Participant 3’s daycare staff showed her daytime compliance behavior was most often in the normal range (20 mg $T$-scores: 47–52; 30 mg = 47, $P = 47$), with slightly elevated scores occurring during one placebo condition ($T = 68$) and once during the 20 mg condition ($T = 63$).

This youngster’s mother viewed her oppositional behavior as clinically significant on most days, regardless of condition. T-scores indicated problematic behavior was observed for 85 percent of evenings during all three phases. As with other participants, her mother’s responses on the CPRS Oppositional Index were consistently higher than ratings on the ECBI.

Opposition and noncompliance was predominant for Participant 3 for ratings by her mother for home/evening behavior. Daycare provider $T$-scores were generally in the normal range, with 2 days of elevated scores in placebo and 20 mg conditions. $T$-scores 61–65 are considered mildly atypical, 66–70 are moderately atypical, and $T$-scores >70 are markedly atypical indicating significant problems.

*Figure 37. Parent Ratings of Oppositional Behavior for Participant 3.*
Mood

Participant 3’s report of feelings of depression, anxiety, and anger were within or below the normal range, regardless of condition (see Table 18).

Table 18.

Self-Ratings of Mood for Participant 3

<table>
<thead>
<tr>
<th>Condition</th>
<th>Depression T-score</th>
<th>Anger T-score</th>
<th>Anxiety T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>44</td>
<td>59</td>
<td>37</td>
</tr>
<tr>
<td>20 mg</td>
<td>38</td>
<td>51</td>
<td>NA</td>
</tr>
<tr>
<td>30 mg</td>
<td>37</td>
<td>39</td>
<td>NA</td>
</tr>
<tr>
<td>Placebo 1</td>
<td>40</td>
<td>42</td>
<td>NA</td>
</tr>
<tr>
<td>Placebo 2</td>
<td>36</td>
<td>30</td>
<td>NA</td>
</tr>
</tbody>
</table>

Participant 3 responded to items on the Beck Youth Inventories in a manner that did not indicate problems with mood. T-scores > 60 would indicate elevated problems with mood.

Sleep

Sleep Latency

Participant 3 appeared to have problems falling asleep on some nights with a latency range of 15 minutes to 1.5 hours (see Figure 38). She had significantly variable night-to-night sleep patterns during medication and placebo conditions.

Data showed Participant 3 had substantial night-to-night sleep latency variance independent of condition.

Figure 38. Daily Measures of Sleep Latency for Participant 3.
Sleep Problems

Participant 3 experienced more difficulty falling asleep and getting up in the morning during the 30 mg condition. In addition to problems falling asleep, Severe morning irritability and problems preparing for school occurred for most days of the study and was not differentiated by condition.

Figure 39. Sleep Problems Severity for Participant 3.

Side Effects

There were no significant differences for potential side effects between days Participant 3 was on Vyvanse and days she took a placebo (see Table 19). Parent reports of increase in mood swings corresponded with high ratings of ADHD symptoms and non-compliance. In general, Participant 3 appeared to tolerate the medication very well with irritability and stares/day dreams reported on most days regardless of condition.
Table 19.

Severity Rating of Side Effects for Participant 3

<table>
<thead>
<tr>
<th>Possible side effects</th>
<th>x 20 mg</th>
<th>x 30 mg</th>
<th>x Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritability</td>
<td>3.33</td>
<td>3.86</td>
<td>3.13</td>
</tr>
<tr>
<td>Stares/daydreams</td>
<td>2.75</td>
<td>3.29</td>
<td>3.50</td>
</tr>
<tr>
<td>Cries</td>
<td>2.67</td>
<td>1.71</td>
<td>1.75</td>
</tr>
<tr>
<td>Mood swing</td>
<td>2.83</td>
<td>2.00</td>
<td>1.63</td>
</tr>
<tr>
<td>Talks less</td>
<td>.50</td>
<td>.00</td>
<td>.38</td>
</tr>
<tr>
<td>Headaches</td>
<td>.00</td>
<td>.14</td>
<td>0.00</td>
</tr>
<tr>
<td>Fatigue/drowsy</td>
<td>.00</td>
<td>.29</td>
<td>.00</td>
</tr>
<tr>
<td>Anxious</td>
<td>.17</td>
<td>.00</td>
<td>.00</td>
</tr>
<tr>
<td>Euphoric/unusually happy</td>
<td>.17</td>
<td>.00</td>
<td>.00</td>
</tr>
</tbody>
</table>

Irritability and daydreaming occurred most often for Participant 3, regardless of condition.

Discussion of Data for Participant 3

Is the child’s ADHD stimulant medication more effective than placebo in reducing core ADHD symptoms?

Objective measures of inattention and hyperactivity taken during baseline and placebo conditions did not support parent reports of inattention, hyperactivity, and impulsivity for this child. Participant 3’s mother’s responses on the CPRS Inattentive index showed a downward trend that indicated increasingly attentive behavior; however, the trend continued during the second and third placebo phases (see Figure 40). It is noteworthy that her scores correspond to measures of noncompliance. Taken together, it appears that this participant’s parent ratings of inattention and hyperactivity were influenced by oppositional behavior rather than classic ADHD symptomatology.
Parent ratings of hyperactivity and inattentiveness on the CPRS reflected significant problems for both domains at home during evening hours. Daycare provider ratings were consistently in the average range. T-scores 61-65 are considered mildly atypical, 66-70 are moderately atypical, and T-scores >70 are markedly atypical indicating significant problems.

Figure 40. Comparison of Parent and Daycare Provider Ratings for Participant 3.

One unexplored domain that was not within the scope the study, was the effect of trauma resulting from sexual abuse at a very young age for this child. Research shows the body’s response to trauma is exposure to stress hormones (Putnam, 2006). The body’s limbic system modulates affective states and influences self-control, with the result that chronic exposure to stress hormones — especially at a young age — have been shown to alter neurons in regions of the limbic system that regulate emotion. Even absent gross structural changes, trauma is understood to change brain chemistry, increasing levels of epinephrine, norepinephrine, and dopamine, and inducing hypervigilance, exaggerated startle response, irritability, panic, and intrusive thoughts — behavioral responses symptomatic of PTSD (Debellis et al., 1999). Physiological affects of abuse on this core
system often result in low frustration tolerance and sensory dysregulation thus making it extremely difficult for children to exert self-regulation of affective states and self-control over their behavior. Participant 3’s ADHD symptoms did not appear to be independent of influences of early trauma. Despite her self-report of absence of depressive symptoms, this child appeared to experience significant irritability, sleep problems, frequent tearfulness, anhedonia, difficulty concentrating, and psychomotor agitation, all of which were consistent with depressed mood.

**Is the child’s ADHD stimulant medication more effective than placebo in reducing oppositional behavior at home?**

In general, parent ratings of the participant’s behavior did not show an increase in compliance at home regardless of condition. Four out of 28 protocol days had ECBI and CPRS Oppositional Index scores in the normal range, with two occurring during the 20 mg phase, one during 30 mg condition, and one in the placebo condition.

**Does the participant’s ADHD medication reduce core symptoms at home?**

This child showed improvement in parent ratings of attention during the second half of the protocol that was not differentially affected by condition. Hyperactivity scores generated by her mother’s responses were high throughout the entire protocol and did not reflect differences in condition.

**How does the child’s ADHD stimulant medication affect math and reading fluency in comparison with placebo?**

Reading fluency improved during both medication conditions for Participant 3. Compared to baseline, this child had improved math fluency during the 30 mg condition; however, her scores during the first placebo trial were equally as good. While stimulant
medication may have aided reading, she was able to improve math performance without influence of stimulant medication.

**Does the participant’s ADHD medication reduce core symptoms at home?**

Ratings of oppositional behavior showed periodic improvement during all three conditions; therefore, amelioration cannot be attributed to medication.

**Does the child’s ADHD stimulant medication interfere with sleep?**

According to Participant 3’s sleep data, latency was highly variable and did not appear to be differentially affected by medication; however, on the sleep problem rating scale, her mother’s responses indicated she had more problems falling asleep during the 30 mg condition. Difficulty arising and daytime sleepiness were also more problematic for days she too 30 mg of Vyvanse.

**How do the side effects of the child’s ADHD stimulant medication compare to placebo?**

Mood swings and crying were more severe and frequent during 20 mg condition, which occurred at the beginning of the protocol; however, decrease in labile mood and weeping occurred during the entire protocol, with trends not confined to condition phases. Staring and daydreaming was most frequent during placebo and irritability was roughly equivalent throughout each phase. It is notable that all reported side effects were mood related and/or was symptom that could be readily influenced by emotion (talks less, fatigue).

It did not appear that reported side effects resulted from medication; rather, mood dysregulation appeared to be an overarching problem that tapered off toward the end of the study.
Were side effects of the medication tolerable?

This child experienced more difficulty getting up in the morning and falling asleep when she took 30 mg Vyvanse, which are side effects common to stimulant medication. If severity did not diminish over the next few weeks, these side effects might have become problematic.

For children on polypharmacological therapy, does the ADHD medication under evaluation enhance symptom reduction of the child’s pharmacological regimen?

This child was not on any other prescription medication at the time of the study.

Individual Protocol Findings for Participant 4

Social History and Background

Participant 4 was a 12-year-old white Hispanic American of Puerto Rican birth who was placed with his family at 19 months of age and adopted at age 5. He lives with adoptive parents and two adoptive sisters, ages 15 and 17. Around age 7, he was diagnosed with ADHD, anxiety, and depression. He received pharmacological treatment and psychotherapy for all three conditions. As behavioral problems continued, the child was diagnosed with Reactive Attachment Disorder, Inhibited Type. He was also diagnosed with reading and learning disabilities before age 9. A psychological evaluation in November 2006 showed low average cognitive functioning (FSIQ SS=87), with mild language retrieval and phonological processing problems. He was noted to be academically behind in math and had significant problems with written expression. His adaptive living skills were rated as extremely low (1st percentile). His parents report problems with non-compliant behavior; however, this participant did not meet criteria for oppositional defiance disorder. His mother reported he experiences sleep problems and
had difficulty reading body language and facial expressions, and does not use socially communicative gestures. During the assessment session, Participant 4 denied problems with anxiety, depressive mood, suicidal/homicidal ideation, self-injurious behaviors, aggression, and strange thoughts; however, his baseline responses on the Beck inventories resulted in slightly elevated scores for depression and anger (see Table 23).

As with the other participants, this child’s mother’s responses on the Parent Stress Index indicated significant levels of stress that were incommensurately elevated in relation to stress that resulted from her parenting role. Within the parent domain, her Spouse Index score was also high, which indicated emotional and active support from her spouse was not available. She declined referral services.

Referral Source and Reason for Enrollment

Participant 4 was referred to the study by his pediatrician to investigate whether Vyvanse would be effective in reducing ADHD symptoms and increasing compliance behaviors. This participant had a history of poor response and/or intolerable side effects to first-line ADHD medications methylphenidate (Concerta, Daytrana patch) and amphetamine/dextroamphetamine (Adderall). A trial of non-stimulant ADHD medication atomoxetine (Strattera) also did not produce satisfactory symptom reduction. Current pharmacological treatment of mood problems included 10 mg Lexapro and 300 mg Wellbutrin XL, and sinus allergies were managed with 10 mg Claritin. These medications were taken consistently throughout the study. Seroquel had been prescribed for behavior problems and was discontinued in 2006.
Protocol Findings for Participant 4

Participant 4 was the only participant who reported not taking medication according to protocol. His mother said he did not take any pill on the 15\textsuperscript{th} day of the protocol, instead taking day-15 pill (20 mg Vyvanse) on day 16 (Placebo). Order of actual condition is reflected in this participant’s figures and did not affect lab measures. Lab sessions for placebo conditions were on the 7\textsuperscript{th} and 17\textsuperscript{th} days of the protocol, both of which were the first day of consecutive placebo conditions. Effects of the 20 mg dose was measured during a lab session on the second day of the protocol, with a 30 mg dose lab session occurring on the 23\textsuperscript{rd} day of the protocol and the 5\textsuperscript{th} consecutive day in the 30 mg dose condition.

\textit{M-MAT}

Behavioral observations during the M-MAT were most remarkable for Participant 4, who was observed occasionally holding down the spacebar by the investigator and research assistants during test administration. Except for the baseline session, around midway through the 15-minute task Participant 4’s would eyes droop and close for brief periods of time. The participant denied feeling sleepy and stated that he felt he exerted his best effort during testing.

Results on the M-MAT continuous performance task were equivocal for Participant 4. He performed best or within the normal range during the no-pill/baseline session on measures of attention, impulsivity, accuracy, inconsistency, response speed, and total distance moved. Despite best performance at baseline, the combination of low accuracy, high omission errors, and excessive variance indicated impaired performance consistent with high distractibility that results in pressing the space bar frequently and
randomly. Participant 4 again showed impaired performance during the 20 mg condition with a response pattern of high omission and commission errors, high variability, and slow response rate. This pattern is indicative of poor persistence with random responding that may be from a failure to understand instructions or may be due to neuropsychological deficits. Both placebo conditions yielded similar response patterns to the 20 mg condition. Performance in the 30 mg condition was only slightly better than during the 20 mg condition with slow response time, reduced accuracy, excessive variance, which is also suggestive of poor persistence and distraction.

*M-MAT attention and impulsivity.* Participant 4 missed fewer targets during the baseline session, yielding his lowest omission score (see Table 20); however, his best performance, which was during his baseline, fell just above the normal range. This participant subsequently made more omission errors during both medication and placebo conditions, with no meaningful differences between conditions. Likewise, he made more accurate responses during baseline with similar performance during medication and placebo conditions.

Participant 4 made the fewest commission (impulsivity) errors on the M-MAT during the Vyvanse 30 mg condition; however the percentage of responses to incorrect targets was similar to his performance at baseline (see Table 20). He committed more Commission errors (responses to non-targets) than typically developing children his age during both placebo conditions and the 20 mg condition, with his baseline score falling within the normal range.
Table 20.

*M-MAT Measures of Inattention and Hyperactivity for Participant 4*

<table>
<thead>
<tr>
<th>Protocol Day</th>
<th>Condition</th>
<th>Accuracy Normal Range</th>
<th>Omission Normal Range</th>
<th>Commission Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>No Pill</td>
<td>88.9 – 99.2</td>
<td>0.0 – 12.4</td>
<td>1.1 – 39.2</td>
</tr>
<tr>
<td>2</td>
<td>20 mg</td>
<td>52.4 L</td>
<td>44.3 H</td>
<td>51.17 H</td>
</tr>
<tr>
<td>7</td>
<td>Placebo</td>
<td>51.6 L</td>
<td>40.7 H</td>
<td>56.84 H</td>
</tr>
<tr>
<td>17</td>
<td>Placebo</td>
<td>44.4 L</td>
<td>57.9 H</td>
<td>52.56 H</td>
</tr>
<tr>
<td>23</td>
<td>30 mg</td>
<td>60.7 L</td>
<td>50.1 H</td>
<td>30.25</td>
</tr>
</tbody>
</table>

Participant 4 exhibited inaccurate responding for all conditions on the M-MAT. Commission errors were within the normal range for 30 mg and baseline and omission errors were high for all trials regardless of condition. Accuracy scores are percentage of correct responses. Percentage of omission errors or missed target stimuli are considered to be a measure of inattention. Commission errors are percent of incorrect responses to a non-target stimuli and considered to be an estimate of impulsivity.

*M-MAT latency and variance.* Participant 4’s latency score (417 ms) was within the normal range for baseline (see *Figure 41*). His response speed was just a little slower for both medication conditions (20 mg = 602 ms; 30 mg = 536 ms) with increasingly slower response to targets on placebo (P1 = 721; P2 = 1164).

![M-MAT Response Latency for Participant 4](image)

Participant 4’s baseline latency measure was within the normal range with significantly slower speed during placebo than medication conditions. The 30 mg dose response speed was just outside the normal range. Lower scores indicate faster response to the target. Normal range is 356-531 and is shown in grey.

*Figure 41. M-MAT Response Latency for Participant 4.*
M-MAT measures of variance ($s_x$) indicated Participant 4’s response to targets was highly variable except during baseline with a score (191 ms; see Figure 42) in the normal range. Standard deviation showed this participant displayed slightly more consistent response speed during 30 mg condition (313 ms) than when he took 20 mg of medication (408 ms) and placebo ($P1 = 496$ ms; $P2 = 467$ ms).

![Figure 42. M-MAT Variability Scores for Participant 4.](image)

Participant 4 performed best at baseline, with little difference in speed consistency between placebo condition and 20 mg. Variability scores ($s_x$) represent variance in response time latency on the M-MAT. Higher scores show greater inconsistency. Normal range is 77-195 and is shown in grey.

*M-MAT activity.* This participant’s predominant difficulty was attention and vigilance with mixed patterns of activity that ranged from increasing levels of activity across the 5-minute segments to increasing immobility (see Figure 43). His movements demonstrated behavior indicative of subtle hyperactivity to mild hypoactivity.
Participant 4 began the test sitting very still with increasing movement as time went on. This pattern is often seen in children with ADHD.

Participant 4 spent increasing amount of time immobile, within narrow space. Possible hypoactivity or representative of activity at lowest end of normal range.

Child’s movement more uniform across each 5-minute segment. He had slightly elevated scores time spent sitting still.

Again, Participant 4 spent increasing amount of time immobile, within narrow space. Possible hypoactivity or may be activity at lowest end of normal range.
Subtle pattern of hyperactivity that may be missed by observers is shown by this combination of elevated temporal scaling and displacement.

Figure 43. M-MAT Pictorial Representations of Movement in 5-Minute Segments for Participant 4.

Participant 4 spent very little time sitting still (Temporal Scaling; see Figure 44) on the second placebo lab session (P2=0.825) with movement within the normal range for 20 mg Vyvanse (0.396) and Placebo 1 (P1=0.457) lab conditions. Participant 4’s movements at baseline (0.508) and during the 30 mg (0.57) condition were just slightly higher than the normal range.

Temporal Scaling is the extent to which the child is active (0 = no movement, 1 = incessant movement). Normal range of 0.308–0.491 is shown in grey.

Figure 44. M-MAT Temporal Scaling Scores for Participant 4.
On spatial measures of movement (Movements, Area, Displacement, Spatial Complexity), Participant 4’s scores were in the average range for most conditions. During the second placebo condition, his movements indicated total distance and area moved was greater than expected for his age (see Table 21). Overall, 92 percent of all of his motion analysis scores — including baseline measures — were within the normal range.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal Range</th>
<th>Baseline</th>
<th>20 mg</th>
<th>30 mg</th>
<th>Placebo 1</th>
<th>Placebo 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Movements</td>
<td>344-2239</td>
<td>1016</td>
<td>718</td>
<td>829</td>
<td>896</td>
<td>1845</td>
</tr>
<tr>
<td>Area</td>
<td>9-48</td>
<td>32</td>
<td>23</td>
<td>36</td>
<td>32</td>
<td>H 62</td>
</tr>
<tr>
<td>Displacement</td>
<td>0.57-2.72</td>
<td>2.72</td>
<td>1.91</td>
<td>2.21</td>
<td>2.40</td>
<td>H 5.38</td>
</tr>
<tr>
<td>Spatial Complexity</td>
<td>1.167-1.381</td>
<td>1.39</td>
<td>1.320</td>
<td>1.274</td>
<td>1.252</td>
<td>1.174</td>
</tr>
</tbody>
</table>

Participant 4’s movements were in the normal range for all conditions except Placebo 2 in which he moved in a large area. Movement is the average number of position changes. Area reports the total area covered by the marker (reflective ball on back of head). Displacement is the total distance moved by the marker (like an odometer reading). Spatial Complexity scores the movement path with lower values indicating the marker often moved linearly; high values indicate more convoluted movement.

Participant 4’s Immobility scores showed he sat still longer during the 20 mg Vyvanse dose condition (.393; see Figure 45); however, both medication (20 mg=.393; 30 mg=.320), no-pill (.333), and the first placebo condition (.307), indicated average immobility duration that was longer than expected for children who do not have ADHD. The score for second placebo condition (.140) indicated he spent significantly more time fidgeting during this session; however, the amount of movement was within normal limits.
Participant 4 sat still longer than same-age typically developing children for all conditions except during the second placebo trial, which was in the normal range. Immobility duration measure on the M-MAT reflects the average amount of time spent sitting still. Children in the control group were able to sit still for 0.105–0.290 of the 15-minute task (shown in grey). Low numbers reflect more movement (e.g., fidgeting).

*Figure 45. M-MAT Immobility Scores for Participant 4.*

*Shift analysis.* Data showed Participant 4 averaged 19.6 shifts in response patterns, with little difference between the number of shifts between conditions (baseline = 22, 20 mg = 17, 30 mg = 19, both placebo trials = 20). M-MAT normative data showed the healthy control group changed their response style 5.4 times during the 15-minute task. Conversely, the ADHD group shifted response style 12.8 times on average.

*Epoch analysis.* Attentive responding occurred during 23 percent of the baseline/no-pill 30-second epochs, and none of the epochs during 20 mg medication or second-day placebo conditions (see *Figure 46*). Random-pattern responses occurred most often during the 20 mg and both placebo conditions. Minimal responding occurred most frequently during the 30 mg condition.
Participant 4 exhibited predominantly random responding during both placebo trials and the 20 mg condition. During baseline, he often responded in an impulsive manner. Scores reflect percent of 30-second epochs for each response pattern on the M-MAT. Typically developing children were attentive during 82.4% of the 30 epochs and children with ADHD spent only 42.6% of the epochs responding attentively.

*Figure 46. M-MAT Epoch Analysis for Participant 4.*

**Parent Reports of Inattention and Hyperactivity**

In contrast to objective CPT data, Participant 4’s mother rated his attentive behavior as being within the normal range for 93 percent of protocol data collection (see Table 22). CPRS scores showed slightly elevated concerns related to attention problems on his baseline measure ($T=60$) and the first day of the first placebo condition (protocol day 7; $T=63$). A clinically significant score ($T=70$) on hyperactivity on protocol day 7 corresponded with elevated inattention scores for that day. His mother’s responses ($T=90$) on the CPRS reflected significant concern related to hyperactivity on during the third day of the second 20 mg condition (protocol day 12) with no corresponding increase in observation of inattentiveness. Similarly, hyperactivity rating on the first day of the second 30 mg condition (protocol day 26) was moderately elevated ($T=66$) with an inattention index score within the normal range ($T=53$).
Table 22.

Parent Ratings of Inattentiveness and Hyperactivity for Participant 4

<table>
<thead>
<tr>
<th>Protocol Day</th>
<th>Condition</th>
<th>Inattention T-score</th>
<th>Hyperactivity T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>No Pill</td>
<td>60*</td>
<td>58</td>
</tr>
<tr>
<td>1</td>
<td>20 mg</td>
<td>NS</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>20 mg</td>
<td>42</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>20 mg</td>
<td>53</td>
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</tr>
<tr>
<td>4</td>
<td>20 mg</td>
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<tr>
<td>5</td>
<td>20 mg</td>
<td>48</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>20 mg</td>
<td>Missing data</td>
<td>Missing data</td>
</tr>
<tr>
<td>7</td>
<td>Placebo</td>
<td>63*</td>
<td>70*</td>
</tr>
<tr>
<td>8</td>
<td>Placebo</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>9</td>
<td>Placebo</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>10</td>
<td>20 mg</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>11</td>
<td>20 mg</td>
<td>53</td>
<td>46</td>
</tr>
<tr>
<td>12</td>
<td>20 mg</td>
<td>53</td>
<td>90*</td>
</tr>
<tr>
<td>13</td>
<td>20 mg</td>
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<td>44</td>
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</tr>
<tr>
<td>15</td>
<td>No pill</td>
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</tr>
<tr>
<td>16</td>
<td>20 mg</td>
<td>44</td>
<td>52</td>
</tr>
<tr>
<td>17</td>
<td>Placebo</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td>18</td>
<td>Placebo</td>
<td>49</td>
<td>47</td>
</tr>
<tr>
<td>19</td>
<td>30 mg</td>
<td>48</td>
<td>45</td>
</tr>
<tr>
<td>20</td>
<td>30 mg</td>
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<td>45</td>
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<tr>
<td>24</td>
<td>Placebo</td>
<td>49</td>
<td>45</td>
</tr>
<tr>
<td>25</td>
<td>Placebo</td>
<td>42</td>
<td>50</td>
</tr>
<tr>
<td>26</td>
<td>30 mg</td>
<td>53</td>
<td>66*</td>
</tr>
<tr>
<td>27</td>
<td>30 mg</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td>28</td>
<td>30 mg</td>
<td>48</td>
<td>48</td>
</tr>
</tbody>
</table>

Daily parent ratings of inattentiveness and hyperactivity for Participant 4 on the Conners Parent Rating Scale–Revised showed behavior within normal limits for most protocol days. Asterisks indicate elevated scores with 61-65 considered mildly atypical, 66-70 is moderately atypical, and >70 are markedly atypical scores that indicate significant problems.
Academic Performance

Math

Participant 4’s speed and accuracy in math did not show meaningful differences between experimental conditions or baseline (see Figure 47). Participant 4 made few errors; one during medication condition and once during one of the placebo conditions. He calculated between 6-12 problems correctly during the 5 trials, with his poorest performance (6 problems) during the first day of the first placebo condition. Participant 4 did best during the 30 mg phase with 12 completed and no errors, compared to the 20 mg trial (10 attempted, 1 error). Despite both placebo lab days occurring on the first day of a placebo phase, results varied considerably on the number of correct problems (P1 = 6, P2 = 11) with no differences shown between medication and placebo conditions.

Figure 47. One-Minute Math Trial Scores for Participant 4.
Reading

All of Participant 4’s reading rate scores were in the “some risk” range, with results during the second day of placebo condition showing performance in the at-risk range (Total = 98; errors = 11; see Figure 48). Results during the first placebo trial (Total = 108, speed = 113, errors = 0) was resulted in a much higher score due to making no errors, compared to 11 errors in the second placebo trial. Speed was the same in both medication conditions (123); however, Participant 4 made fewer errors when he took 30 mg of medication (20 mg = 8; 30 mg = 5). There were no differences between baseline and 20 mg medication condition with baseline and yielding total scores of 115, and 30 mg total ending 3 words more at 118 (Baseline errors = 5, speed = 120; 20 mg errors = 8, speed 123; 30 mg errors = 5, 123 speed). Overall there were no meaningful differences in errors made during any of the conditions.

DIBELS oral reading scores from 1-minute trials during lab sessions did not vary greatly for Participant 4; however, the most errors and slowest speed occurred in the second placebo trial. Total score = speed - errors. Scores > 125 are considered to be at low risk for reading problems, with scores between 104 and 125 at some risk, and < 104 at-risk for reading difficulties.

Figure 48. DIBELS 1-Minute Oral Reading Scores for Participant 4.
Compliance

Participant 4’s mother consistently rated his compliance behavior as being more compliant with the Eyberg Child Behavior Inventory (ECBI) than she did on the Oppositional Index of the Conners’ Parent Rating Scale (CPRS; see Figure 49). CPRS T-scores were more than 2 standard deviations ($\bar{x} = 3.8$) higher than ECBI $T$-scores for 60 percent of the protocol period. Her responses on the Conners indicated fewer oppositional behaviors occurred during the 20 mg condition (9 percent $\geq T = 60$) than it did during the 30 mg condition (38 percent $\geq T = 60$), no-pill days (100 percent $\geq T = 60$), or placebo (43 percent $\geq T = 60$). Only two ECBI ratings had a $T$-score of $\geq 60$, which occurred during the baseline measure and the first day of the protocol (20 mg).

Baseline and 30 mg oppositional ratings were higher for Participant 4 as measured by the Oppositional Index of the Conners Parent Rating Scale short version than the Eyberg Child Behavior Inventory. $T$-scores 61-65 are considered mildly atypical, 66-70 are moderately atypical, and $T$-scores $>70$ are markedly atypical indicating significant problems.

Figure 49. Parent Ratings of Oppositional Behavior for Participant 4.
Mood

Participant 4’s report of feelings of depression, anxiety, and anger were within or below the normal range regardless of whether he was on medication or placebo as measured by the Beck Youth Inventories (see Table 23); however, his baseline/no pill measure of depression was mildly elevated \((T = 59)\) and anger was moderately elevated \((T = 61)\). His responses did not exceed normal limits for the remainder of the study.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Depression T-score</th>
<th>Anger T-score</th>
<th>Anxiety T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>59*</td>
<td>61**</td>
<td>49</td>
</tr>
<tr>
<td>20 mg</td>
<td>41</td>
<td>40</td>
<td>NA</td>
</tr>
<tr>
<td>30 mg</td>
<td>41</td>
<td>32</td>
<td>NA</td>
</tr>
<tr>
<td>Placebo 1</td>
<td>40</td>
<td>33</td>
<td>NA</td>
</tr>
<tr>
<td>Placebo 2</td>
<td>41</td>
<td>38</td>
<td>NA</td>
</tr>
</tbody>
</table>

Baseline measures for depression and anger were mildly/moderately elevated for this participant. Beck Youth Inventory T-scores *55-59 are considered mildly elevated, with T-scores between **60-69 seen as moderately elevated.

Sleep

Sleep Latency

Sleep diary records show Participant 4 took longer to fall asleep at the beginning of the study, which tapered off into a typical sleep latency patterns by the end of the first week on medication (see Figure 50). Subsequent to the first week, there were no differences between medication and placebo effects on the time between going to bed and reports of falling asleep. Participant 4 experienced the least variable and shortest latency during the 30 mg condition.
Sleep Problems

Parent reports of problems falling asleep were more frequent for this participant (see Figure 51) and were not consistent with sleep latency data. Infrequent moderate/severe problems were reported for as many medication days as for placebo days. Overall, few sleep problems were reported.

Sleep diary for Participant 4 reflected typical sleep latency patterns following initiation of stimulant medication. Latency/time from getting into bed to reports of falling asleep are shown in minutes.

Figure 50. Daily Measures of Sleep Latency for Participant 4.

Morning irritability was reported to be of moderate severity for three days, all of which were during medication conditions; however, the first of the three moderate ratings for Participant 4 occurred on the first day of the study during initial exposure. The remaining two days occurred during the 30 mg medication phase, for which the dose had been increased.
Reports of difficulty falling asleep were not consistent with sleep diary/latency data for Participant 4. Severe sleep problems were rare, moderate problems occurred infrequently and did not appear to be influenced by protocol condition.

Figure 51. Sleep Problems Severity for Participant 4.

Problems arising were infrequent, with moderate severity reported for only one day of the study, which occurred on the third day of the second placebo condition phase. Moderate problems arising were reported for four days of the total protocol, the first of which occurred on the first day of the study prior to clinically effect blood plasma levels, and during the 30 mg medication phase following a 10 mg dose increase. Data collection did not occur during the school year and the participant was not required to rise early and prepare for school.

Side Effects

On average, potential side effects did not appear to be more severe for either medication dose conditions than for placebo (see Table 24). Irritability, decreased appetite, and mood swings occurred significantly less often during the 30 mg condition than placebo or 20 mg conditions (see Figure 52). Also of note were reports of
drowsiness that occurred during both doses of the stimulant medication, but not when he took placebos.

Table 24.

Severity Ratings of Side Effects for Participant 4

<table>
<thead>
<tr>
<th>Possible side effects</th>
<th>X 20 mg</th>
<th>X 30 mg</th>
<th>X Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>0.92</td>
<td>0.75</td>
<td>0.88</td>
</tr>
<tr>
<td>Stares/daydreams</td>
<td>0.33</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Infrequently talks to peers</td>
<td>0.83</td>
<td>0.88</td>
<td>0.75</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1.42</td>
<td>1.38</td>
<td>1.50</td>
</tr>
<tr>
<td>Irritable</td>
<td>1.50</td>
<td>1.00</td>
<td>1.38</td>
</tr>
<tr>
<td>Stomachaches</td>
<td>0.08</td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td>Headaches</td>
<td>0.17</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Craves sugar</td>
<td>1.58</td>
<td>1.75</td>
<td>1.50</td>
</tr>
<tr>
<td>Drowsiness/fatigue</td>
<td>1.25</td>
<td>0.63</td>
<td>0.88</td>
</tr>
<tr>
<td>Cries</td>
<td>0.58</td>
<td>0.13</td>
<td>0.00</td>
</tr>
<tr>
<td>Anxious</td>
<td>0.42</td>
<td>0.88</td>
<td>1.00</td>
</tr>
<tr>
<td>Mood swings</td>
<td>1.42</td>
<td>1.00</td>
<td>1.38</td>
</tr>
<tr>
<td>Euphoric</td>
<td>0.67</td>
<td>0.13</td>
<td>0.00</td>
</tr>
<tr>
<td>Tintinitus</td>
<td>0.33</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Tics/nervous movement</td>
<td>0.08</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>0.08</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Sore throat</td>
<td>0.08</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.08</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Increased cough</td>
<td>0.25</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Skin rash</td>
<td>0.58</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Fever</td>
<td>0.08</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Severe itching</td>
<td>0.50</td>
<td>0.13</td>
<td>0.00</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.08</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Side effects were generally well tolerated by Participant 4. Table shows mean severity of side effects. Severity ratings were on scale of 0 (never) to 5 (severe).

Discussion of Data for Participant 4

Daily parent ratings of core ADHD symptoms were generally not elevated for this participant. Indeed, parent complaints of behavior more frequently involved mood
regulatory issues, poor social interactions, and other associated characteristics of ADHD (Barkley, 2006), including: deficiencies in adaptive functioning, academic achievement, speech pragmatics, time perception and time management, emotion regulation, empathy, self-awareness, and neurological arousal. Parent report of additional issues not associated with ADHD (Barkley, 2006) involved significant nonverbal working memory, sensory sensitivity, and social perceptual, cognitive, and interaction deficits. It is these functional difficulties that historically have not been shown to respond to medication (Monastra, 2004).

Although results were ambiguous for this participant, he appeared to have more difficulty with arousal during placebo conditions, as evidenced by longer latency to response on the M-MAT and lower reading fluency. His responses were more consistent during the 30 mg dose condition.

During feedback, Participant 4’s mother expressed frustration with behavior that was not reflected in the data for this child. Although this 12-year-old had a diagnosis of Reactive Attachment Disorder, his mother stressed additional concerns not associated with the condition that were identified during a neuropsychological evaluation in 2006. She reported significant problems that may have a neurological component, including slow cognitive processing, language retrieval, phonological deficits, gross motor coordination, comprehension of time, spatial relations, categorization, organization, and tactile sensitivity. She said he had problems generalizing what he learned in one situation to a different context. His mother reported he had difficulty remembering faces and had not been able to comprehend family relationships. Previous tests showed he had excellent auditory memory for simple information, but struggled when required to perform mental
operations. Additionally, Participant 4 was good at rote memorization, but struggled with higher order reasoning. She said he can play chess since he has memorized strategies, but has difficulty with games that require less structured deductive reasoning.

Socially, Participant 4’s mother said he does not respond to social cues (nonverbal language of others), is very literal, does not demonstrate social reciprocity, has difficulty understanding humor, and is unable to achieve perspective taking. Academically, this preteen has significant problems with math calculations and reasoning, and written expression.

Is the child’s ADHD stimulant medication more effective than placebo in reducing core ADHD symptoms?

As discussed above, problems with core symptoms of inattention were not adequately captured with traditional CPT and parent ratings; however, M-MAT pattern shift analysis showed he spent little or no time responding attentively during any of the CPT tests. In fact, this participant’s response patterns were chiefly impulsive and random during baseline, with predominately random, distracted, minimal, and contrary responding styles during medication and placebo trials. Response speed and variance improved with medication. Random responding was the most frequent response pattern during the 20 mg and both placebo trials. These types of severely impaired performances usually stem from poor persistence. The combination of high omission and commission errors, slow response, and high variability during placebo trials suggests either failure to understand the instructions, or is indicative of neuropsychological deficits that seriously interfered with the ability to perform the test.
Hyperactivity data was also convoluted, with classic ADHD responding at baseline, to hypoactivity during the first placebo trial, but exhibited subtle hyperactivity in the second placebo behavior sample. Participant 4 spent more time sitting still than normal controls, but not during the second placebo test, during which he moved in a greater area with the average amount of time (immobility) within the normal range.

In summary, the 30 mg dose increased speed and decreased variance while producing mild hypoactivity. The 30 mg condition also resulted in minimal responding for half of the M-MAT epochs, with distracted responding occurring in around a third of the trial.

Is the child’s ADHD stimulant medication more effective than placebo in reducing oppositional behavior at home?

Data reflects dissimilar results, depending upon which instrument one uses to evaluate Participant 4’s oppositional behavior. The Eyberg (ECBI), which weighs specific refusal behavior more heavily than other aspects of opposition, resulted in elevated scores for only baseline and the first day of the protocol during the 20 mg condition. Despite no significant problems being reflected on the ECBI, scores on the Conner’s Oppositional Index were higher, indicating problem behaviors occurred at home on seven protocol days. Trends on the Conner’s showed decreases in oppositional behavior during the first 20 mg condition, the final 30 mg condition, and on initial placebo days; however, increases in contrary behavior were reflected in an upward trend during the second 20 mg placebo trial and the first 30 mg condition. Taken together, it appears that extraneous environmental events may be as strong an influence on Participant 4’s behavior as is medication or placebo.
Does the participant's ADHD medication reduce core symptoms at home?

In general, parent ratings on the CPRS-R reflected developmentally appropriate attention and activity levels regardless of condition.

How does the child's ADHD stimulant medication affect math and reading fluency in comparison with placebo?

Medication did not differentially improve academic skills sampled during protocol data collection.

Does the child's ADHD stimulant medication interfere with sleep?

Reports of problems arising, morning irritability, and longer sleep latency were greater when medication was started and briefly following dose increase. Data reflected few sleep problems for Participant 4, who did not appear to have increased sleep latency or other stimulant-associated issues regardless of condition. It appeared that neither dose had detrimental effects on sleep.

How do the side effects of the child's ADHD stimulant medication compare to placebo? Were side effects of the medication tolerable?

Overall, side effects were tolerable for Participant 4, who was observed to have less mood lability, irritability, insomnia, anxiety, and drowsiness during the 30 mg or 20 mg conditions. Reports of mild euphoria was the only reported potential side effect that was minimally elevated during the 20 mg condition, but not placebo.

Frequency data showed most side effects occurred during the first half of the protocol during the 20 mg condition (see Figure 52), indicating side effects diminished as he habituated to the medication.
Data for Participant 4 shows frequency of occurrence of side effects showed most effects were experienced during the 20 mg condition, which occurred during the first half of the protocol.

*Figure 52. Side Effects Frequency Data for Participant 4.*

**For children on polypharmacological therapy, does the ADHD medication under evaluation enhance symptom reduction of the child’s pharmacological regimen?**

Although Participant 4’s mood was more stable in the 30 mg dose, there was not sufficient data to determine whether Vyvanse differentially worked to enhance effects of his antidepressant.
Social Acceptability Survey

Results from the post-protocol study were appreciably positive with satisfaction scores ranging from 3 on scale of 1 to 5 for all but one item component of the study, which was scored a 2 (see Figure 53). All participants, mothers, and one father completed the questionnaire.

<table>
<thead>
<tr>
<th>Item</th>
<th>Mean Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 In general, do you feel your participation in this study was worth the time and effort you were required to contribute?</strong></td>
<td><strong>Parents → 4.6</strong></td>
</tr>
<tr>
<td><strong>Very</strong></td>
<td><strong>Very</strong></td>
</tr>
<tr>
<td>Dissatisfied</td>
<td>Satisfied</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Parents</strong></td>
<td>Parents</td>
</tr>
<tr>
<td><strong>2 TEAM MEMBERS</strong></td>
<td><strong>Very</strong></td>
</tr>
<tr>
<td>How satisfied were you with your interactions with our team members?</td>
<td><strong>Parents → SI = 4.2</strong></td>
</tr>
<tr>
<td><strong>Very</strong></td>
<td><strong>Very</strong></td>
</tr>
<tr>
<td>Dissatisfied</td>
<td>Satisfied</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Student Investigator</td>
<td>Students</td>
</tr>
<tr>
<td>Physician</td>
<td>Physician</td>
</tr>
<tr>
<td>Research Assistants</td>
<td>Research Assistants</td>
</tr>
<tr>
<td><strong>3 CONSENT SESSION</strong></td>
<td><strong>Very</strong></td>
</tr>
<tr>
<td>How satisfied were you with your experience during the consent session?</td>
<td><strong>Parents → P = 4.4</strong></td>
</tr>
<tr>
<td><strong>Very</strong></td>
<td><strong>Very</strong></td>
</tr>
<tr>
<td>Dissatisfied</td>
<td>Satisfied</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Procedure explained</td>
<td>Procedure explained</td>
</tr>
<tr>
<td>Risks explained</td>
<td>Risks explained</td>
</tr>
<tr>
<td>Questions answered</td>
<td>Questions answered</td>
</tr>
<tr>
<td>Time spent in session</td>
<td>Time spent in session</td>
</tr>
</tbody>
</table>
### Eligibility Evaluation Session

How satisfied were you with your experience during the eligibility session?

<table>
<thead>
<tr>
<th>Very Satisfied</th>
<th>Very Dissatisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>▼</td>
</tr>
</tbody>
</table>

- Session ran as expected
- Length of tests
- Ease getting to location
- Time spent in session

<table>
<thead>
<tr>
<th>Parents</th>
<th>S = 4.4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L = 4.0</td>
</tr>
<tr>
<td></td>
<td>E = 4.4</td>
</tr>
<tr>
<td></td>
<td>T = 4.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>S = 4.3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L = 4.0</td>
</tr>
<tr>
<td></td>
<td>E = 4.0</td>
</tr>
<tr>
<td></td>
<td>T = 4.3</td>
</tr>
</tbody>
</table>

### Weekly Lab Sessions

How satisfied were you with your experience during the weekly lab sessions?

<table>
<thead>
<tr>
<th>Very Satisfied</th>
<th>Very Dissatisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>▼</td>
</tr>
</tbody>
</table>

- Session ran as expected
- Length of tests
- Ease getting to location
- Time spent in session

<table>
<thead>
<tr>
<th>Parents</th>
<th>S = 4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L = 4.4</td>
</tr>
<tr>
<td></td>
<td>E = 4.4</td>
</tr>
<tr>
<td></td>
<td>T = 4.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>S = 4.3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L = 4.0</td>
</tr>
<tr>
<td></td>
<td>E = 4.0</td>
</tr>
<tr>
<td></td>
<td>T = 4.3</td>
</tr>
</tbody>
</table>

### Medication Delivery/Pick Up

How did you obtain your child’s medication?

- Pick up at pharmacy
- Delivery

Satisfaction with pick-up/delivery:

<table>
<thead>
<tr>
<th>Very Satisfied</th>
<th>Very Dissatisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>▼</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parents</th>
<th>S = 5</th>
</tr>
</thead>
</table>

### Daily School Observations*

Did you receive any complaints from teacher(s) or school staff?

- Yes
- No

*Based on one participant
### DAILY FORMS
How easy or difficult was it for you to complete the forms each evening?

<table>
<thead>
<tr>
<th>Very Difficult</th>
<th>Very Easy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

On average, how much time did you spend filling out forms each evening?

- Less than 5 minutes
- Around 5 minutes
- Around 10 minutes
- More than 10 minutes

### EVENING CONTACT
How convenient was it for you to briefly communicate with the student investigator about the forms, each evening?

<table>
<thead>
<tr>
<th>Very Inconvenient</th>
<th>Very Convenient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Did you complete the forms on a daily basis?

- Yes
- No

If yes, did knowing each evening you were required to answer one question from a random form help you complete the forms on a daily basis?

- Yes
- No

### REPORT
How informative did you find the information from your child’s report?

<table>
<thead>
<tr>
<th>Not at all Informative</th>
<th>Very Informative</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

- Overall report
- Direct child tests
  - MMAT
  - Reading
  - Math
  - Mood
- School observations
- Teacher reports
- Parent reports

Parents ——> 4.2

Parents ——> 4.4

Parents

Parents

<table>
<thead>
<tr>
<th>Overall</th>
<th>MMAT</th>
<th>Reading</th>
<th>Math</th>
<th>Mood</th>
<th>School</th>
<th>Teacher</th>
<th>Parent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall = 4.7</td>
<td>MMAT = 4.7</td>
<td>Reading = 3.8</td>
<td>Math = 3.8</td>
<td>Mood = 3.8</td>
<td>School = 5.0*</td>
<td>Teacher = 5.0*</td>
<td>Parent = 4.7</td>
</tr>
</tbody>
</table>

*Based on one participant.
### Monitoring/Safety

How satisfied were you with the monitoring and emergency procedures?

<table>
<thead>
<tr>
<th>Very Dissatisfied</th>
<th>Very Satisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- Child mood forms
- Physician visit
- Safety procedures
- Emergency flyer
- Access to medication information in emergency (ADHD cell phone)

If you could change one thing about this evaluation procedure what would that be?
- Measuring morning and night on days not in school.
- Would do it during school year.
- Some ratings didn't fit question on forms.

Other comments/feedback:
- Great study
- Lots of info
- Very involved; worth the effort

### Medication

Did you take your medicine around the same time each morning?
- Yes
- No

Did you have problems swallowing the pill?
- Always
- Never

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

### Daily School Observations

How were you comfortable with people watching you and your classmates at school?

<table>
<thead>
<tr>
<th>Very Uncomfortable</th>
<th>Very Comfortable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

Did any of your classmates ask you about being observed?
- Yes
- No

*Based on one participant

### Social Validity Questionnaire

Parents
- Mood = 4.0
- Physician = 5.0
- Flyer = 4.0
- Phone = 4.4

Participants
- Yes = 5
- No = 0

Participants
- 5

Participant
- 3*

---

Figure 53. Social Validity Questionnaire.
CHAPTER IV
DISCUSSION

Single Subject Analyses in Clinical Practice

Medication evaluations within standard medical practice are chiefly based on clinical judgment of the patient’s history, parent report, and observation during brief office visits. And for the 70-80 percent of pediatric patients with ADHD who demonstrate positive response to stimulants, following best practice guidelines is sufficient to manage the child’s symptoms (MTA, 1999; Barkley, 2006). It is the minority presenting with divergent response profiles, showing improvement in some symptom domains, but not others, who would benefit from comprehensive and objective means of response analyses. The purpose of this study was to provide some objective/sign data set that physicians could use to assess whether or not the prescribed stimulant medication showed detectable therapeutic effects for a given child in which positive response to medication was not obvious to parents or teachers via traditional subjective data and/or standardized symptom rating instruments.

In this study, all children were referred for clarification of effects or titration of dosage of Vyvanse. Data sets provided copious and sometimes conflicting information between parent ratings and objective measures. The ability to conceptualize medication effects from both parent responses and direct measures enabled the physician to alter the child’s course of treatment, which could include increasing or decreasing the dose, changing the medication, or terminating stimulant pharmacotherapy if the child was not showing sufficient symptom reduction.
Participants 1, 3, and 4, exhibited typical activity levels during placebo and suppressed movement during medication conditions. Higher scores indicate more time was spent sitting still. Normal Range is shown in grey.

*Figure 544.* Immobility scores for each Participant.

The data show Vyvanse suppressed behavior and mobility for three out of four participants, all of whom had immobility duration scores in the normal range during placebo trials. For those three participants, the main effect of outcomes may be that Vyvanse inhibited activity levels for participants who also responded well to placebos.
Attention and motion data from the M–MAT offered information not otherwise available, allowed a behind-the-scene look at effects of less-obvious processes (e.g. processing speed, patterns of attendant responses, subtle hyperactivity), a process that supports clinical experience and judgment. Daily monitoring of side effects and weekly visits with a physician provided for closer monitoring for potential adverse events. What was reasonably clear for all four participants was that Vyvanse yielded few problems with side effects.

Data plotted over time (parent ratings) or condition (objective measures) painted a different clinical picture for each child. Responses common to all participants included minimal side effects and no discernable effects on sleep. Medication effects were fairly straightforward for two participants, while a more enigmatic picture presented for the final two children. The first participant, who completed the protocol prior to HSIRB/IRB approval to include dose titration, showed medication dosage effects that suppressed hyperactivity more than necessary for learning and successfully participating within the school milieu. While our second participant showed differential effects of medication dose, the adjunct unblinded 50 mg dose appeared to be the most effective treatment; however, confidence could not be as high for unblinded trials as would have been possible with an extended, double-blind placebo trial. Repeating direct measures at the 40 mg dose would also have helped ascertain whether the poor response was an anomaly or an accurate behavior sample.

The third participant's mood emerged as an increasingly relevant piece of her clinical picture, as tracked by the side effects questionnaire and parent ratings of oppositional behavior. Interpretation of the data in the context of her trauma history
clarified her clinical picture and led to a medication change that resulted in remarkable improvement. Our final participant effected the most incongruous data, whose erratic responses on the M-MAT indicated impaired performance with frequently impulsive, random, minimal, or contrary response patterns. Although medication increased his sluggish speed and decreased response variance, simultaneous movement recordings showed suppressed activity levels for this youngster. Further, baseline data reflected better scores than were obtained in subsequent medication trials for most domains for this child. What was missing may have been the most vital component of his clinical picture — variable social/environmental influences (e.g., health status). Time constraints for both travel to the physician’s office and time spent in session precluded feasibility of repeated measures in each condition that would have effected a solid withdrawal design that theoretically would have allowed for confident conclusion, especially when positive response was not evident. Post-protocol interview revealed assessed deficits for Participant 4 in some neurological functions that may respond differentially or not at all to pharmacological treatment (e.g., working memory, goal-directed persistence).

Methodological Limitations

Logistics

Standardized protocols are an inherent necessity in research so that conclusions may be drawn with reasonable confidence about whether an independent variable has actually affected the dependent variable. Within a clinical practice, there is a need to modify standard protocols when a patient responds atypically or does not respond well to treatment. Optimal times to sample potential behavioral effects of a certain dose or placebo can be deduced from published pharmacokinetic data. This research protocol
depended upon availability of the family and physician outside of established clinical
hours. There were divergent expectations for availability for volunteer research, than
there typically is for physician appointments, with much less flexibility in availability for
the study than would be expected for scheduling within clinical practice. For Participant
4, this resulted in behavior sampling during the first day in a placebo day, early in the
day, and may have yielded disparate results.

Other logistical issues included availability of scores from M-MAT. As discussed
earlier (see Methods section), CPT scores were obtained from the server at McLean
Hospital via webpage interface, which generally took just a few minutes to obtain once
connected with the server. A recent move to a new location for the physician’s medical
office did not offer the type of internet connection compatible with the older M-MAT
computer system. The cumbersome equipment was transported and assembled for tests,
then moved and reassembled at another location to access the server via internet. The
revised M-MAT system (now called ADHD Quotient) is technologically compatible with
wireless systems and appears to provide instant, reliable feedback on the child’s CPT
responses.

Blinding Procedure

Making placebo pills and over-encapsulating the medication was an expeditious
and inexpensive procedure. Dated labels were applied to the blister packs and given to
the pharmacist each week to ensure accuracy in filling the blister packs, a procedure that
required around 5 minutes per child per week (excluding delivery to the pharmacy).
Evening Calls

Daily telephone contact was very brief for most of the participants, for a majority of the calls. Advantages included sufficient monitoring to detect serious problems if there had been any. In addition to detection of potential adverse effects, it was likely that dissatisfaction with potentially burdensome procedures (e.g. daily paperwork) would have been discernible. Daily contact allowed for confirmation of schedules or need for rescheduling, as well as, identifying events that might have influenced ratings and/or response to medication.

Objective Measures

One of the strengths of the study was that objective measures – particularly the CPT – provided sign data to incorporate information alongside symptomatic reports by parents and teachers of the clinical picture. Direct measures of ADHD-related behaviors enabled the physician to put subjective reports into perspective. For example, Participant 2’s parents rated their son’s behavior as inattentive or hyperactive once each during the 28-day protocol; yet, he exhibited difficulty holding still, was inconsistent in response speeds, and demonstrated problems sustaining effort during the M-MAT. Parent responses on the CPRS were also incongruent with CPT scores for Participant 3. She showed normal attentiveness and activity levels during baseline and placebo, and scores taken while she was on medication reflected less movement than normal controls.

A clearer picture of medication effects on sleep would have been available with use of actigraph sleep monitoring, had funds been available for that instrument’s inclusion. Sleep diary latency data was inconsistent with parent reports of insomnia on the Daily Sleep Questionnaire and Side Effects rating scale for Participant 4 (e.g. latency
of 10 minutes recorded on sleep diary for the 25th protocol day, with insomnia a maximum problem severity of 4 for the same day). While Participant 1's mother appeared to be a fastidious record keeper, sleep latency times were not available for him for more than one-fourth of the protocol since she went to bed before her son due to health problems.

In summary, objective/sign data confirmed clinical judgment and aided identification of inconspicuous symptomatology for three out four participants. Although incongruent medication effects data did not clear an otherwise cloudy clinical picture for the fourth child, extensive communication with the family led to recommendations for educational and behavioral interventions appeared to have contributed to an improved clinical picture.

Future studies that examine measures of psychopharmacological treatment effects within the clinical milieu could more closely mirror standard clinical practice with a more flexible schedule within the research protocol. Pragmatics dictated daily repeated measures were completed via parent response; whereas, ideally, repeated objective measures with the M-MAT may have clarified some response data, particularly for Participant 4, whose poor response with the 40 mg dose during one lab session was unexpected with apparently better response at baseline, lower and higher doses. The same logic applies to collection of multiple baseline data points that support stable pre-intervention data that facilitates analysis of treatment effects (Poling, et al., 1995). A flexible protocol that allows for extended data collection under blinded conditions would more fully assess titration and medication effects. Scheduling direct measures (e.g. M-MAT) within the clinical practice or with expanded availability with requirements for
data sampling to coincide with optimal blood plasma levels (e.g., placebo measures more than 72 hours into placebo phase) would allow conclusions about the effectiveness of the medication and of the protocol to assess symptomatology to be made with greater confidence. Increasing data would not require the physician to invest more time that was required for the current protocol, since assistants can administer tests. Finally, for children who experience sleep problems, using an actigraph monitor would provide accurate sleep data, since sleep results from this study were not consistent between daily sleep problem questionnaires and sleep diary records.

Discussion and Recommendations for Participants

Discussion of Findings for Participant 1

Objective measures of hypoactivity (M-MAT, school observations), attentiveness (M-MAT, school observations) supported subjective scores of infrequent inattentiveness (CTRS), compliant behavior (CTRS), and few reports of hyperactivity (M-MAT, CTRS, school observations) for Participant 1. His parents were surprised at results of M-MAT and school observations that showed he sat more still than other children. Although evening/parent reports indicated higher levels of core ADHD symptoms and less frequent compliance behavior, externalizing behavior for this child on medication was in the normal to mildly atypical range. Sleep was less disturbed on placebo than on 70 mg Vyvanse.

Parent interview during the eligibility session, indicated that despite occasional struggles with distractibility, Participant 1 was generally able to pay attention, even during periods of increased activity levels. In fact, this participant displayed stable attentive skills throughout the data collection period. The most remarkable were placebo
condition school observations during which Participant 1 exhibited motor restlessness while focusing on an academic task. In another placebo phase observation, he was observed doodling and infrequently glancing at the teacher during a math lecture, yet was able to perform the math problem when called upon. During the exit interview, his parents confirmed similar experiences during which he appeared to not be paying attention, yet could correctly answer questions about earlier instructions or information. Other indicators of minor problems with attention are shown by teacher ratings of inattention were just outside the normal range (CPRS, $T=61$) for 2 out of 5 days when he took placebos. Taken together, results from parent report, continuous performance task, teacher scores, and school observations, Participant 1’s difficulty with attention were mild and did often did not interfere with function, indicating the Predominately Hyperactive-Impulsive Type of ADHD was the best diagnostic fit for this child.

Participant 1 appeared to tolerate the medication very well with noticeable effects of commonly occurring side effects at the beginning of the protocol that tapered off during the second week of the protocol (see Figure 54).

**Recommendations for Participant 1**

Following review of data for Participant 1, it was recommended this participant’s dose of Vyvanse be lowered from 70 mg to 50 mg. To compensate for increased behaviors in the evening, home behavioral interventions were also recommended (e.g. structure for homework, reinforcers, breaks, token system), and it was advised that sleep hygiene be added to the child’s bedtime routine since he was already on a hypnotic.

The family was seen at the WMU Psychology Clinic for three sessions, during which the family reported significant improvement in homework and household task
completion and decrease in oppositional behaviors. Two-month follow-up found the family maintained therapeutic gains with behavioral intervention; however, they were unsatisfied with the results of a month-long trial of 50 mg dose of Vyvanse. The family subsequently requested an increase back to 70 mg. The family reported there was no improvement in sleep problems by adding sleep hygiene.

Some side effects were noticeable for Participant 1 at the beginning of the protocol, but faded by the second medication phase. Elevated reports of somatic complaints increased during the second placebo condition. Higher scores indicate increasing severity.

Figure 55. Daily Side Effects for Participant 1.

Discussion of Findings for Participant 2

Objective measures of core ADHD symptomatology for Participant 2 reflected predominately hyperactive-impulsive responding, conflicting with parent ratings that rarely indicated observation of hyperactive behavior. Response variability indicative of cognitive issues (e.g. slower processing speed, difficulty sustaining effort, and/or fluctuating test strategies) was evident from CPT data sets, but not readily apparent upon observation. As discussed previously, the adjunct unblinded 50 mg dose appeared to be the most effective treatment; however, a blinded trial was needed to confirm optimal titration at 50 mg dose.
Recommendations for Participant 2

Participant 2 performed best in 50 mg dose conditions for most measures, without sleep or side effect problems; thus, was recommended this dose be prescribed for this child. His parents discussed some behavioral recommendations for compliance (e.g. use of Premack Principal computer games after chores done). Also recommended was the book by Vincent Monastra, *Parenting Children with ADHD; 10 Lessons That Medicine Cannot Teach.*

Discussion of Findings for Participant 3

As evidenced by data collected during the protocol, Vyvanse was not effective for this child’s symptoms and the medication was discontinued. Participant 3 was started on an antidepressant (Lexipro 10 mg) to treat depressive symptoms. Follow-up statements by her mother showed marked global improvements in behavior. She said she often mentally ran through CPRS items with the conclusion that scores would have been low. Additional changes included enjoyment playing with her brother, and completion of household chores in a timely manner absent oppositional behavior.

Recommendations for Participant 3

In consultation with this child’s primary care physician, the study’s supervising physician recommended a neuropsychological evaluation to explore effects of trauma on her neurological functioning. Psychotherapy was also recommended and Participant 3’s mother said she would pursue that treatment option.

Discussion of Findings for Participant 4

Participant 4, who has a long history of failed ADHD medications, presented a complex neuropsychological picture that was differentially responsive to medication.
Interestingly, this participant performed best in during no-pill baseline on most objective measures with reports of mood that were slightly elevated for depression and anger, but not for subsequent trials. Particularly confusing were the baseline measures, which may have been an anomaly rather than the norm; however, additional no-pill trials would be needed to clarify the data.

Of principal concern were predominant random, minimal, and contrary response styles on the M-MAT that result from high omission and commission errors, slow responding and high variability may be indicative of significant neuropsychological deficits. The alternative explanation – inadequate cognitive functioning for comprehension of instructions – is very unlikely since his previous intellectual assessments did not indicate he was unable to understand how to take the test. Response speed and consistency were the only performance domains that improved with medication. Without improved attentiveness and accuracy, therapeutic value of the medication appears low.

**Recommendations for Participant 4**

Data collected during the protocol supported findings of cognitive processing problems for this child that did not improve with medication. Recommendations included discontinuation of Vyvanse with implementation of empirically supported behavioral interventions to manage associated deficits (e.g. sleep hygiene for improved sleep habits; social skills training that addresses nonverbal, reciprocity, and perspective-taking deficits; using concrete, step-by-step instructions, in all appropriate contexts; organizational strategies; and use of strengths for learning by pairing auditory information with written instructions).
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APPENDIX A

Eligibility/Screening Worksheet
Eligibility/Screening Worksheets

Was informed consent obtained prior to any study-related procedures being performed?

☐ Yes  ☐ No

Who provided consent?

Father (Initials) __________
Mother (Initials) __________
Guardian (Initials) __________

(If guardian, must provide documentation. Reviewed ☐ Yes ☐ No)

Assessment Scores:

<table>
<thead>
<tr>
<th>M-MAT</th>
<th>Hyperactive</th>
<th>Inattentive</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPRS</td>
<td>ADHD Index ≥ 65</td>
<td>DSM-IV Hyperactive ≥ 65</td>
</tr>
<tr>
<td>☐ Yes</td>
<td>☐ No</td>
<td>☐ Yes</td>
</tr>
</tbody>
</table>

Age of onset of ADHD: __________

Admission to study:

This child is ☐ appropriate ☐ inappropriate for this study.

Signature: ___________________________  Date: ______________________

Physician name, degree

If admitted to the study, weekly sessions will begin on ________________
### VITAL SIGNS

<table>
<thead>
<tr>
<th>Systolic BP (mm/Hg)</th>
<th>Diastolic BP (mm/Hg)</th>
<th>Pulse (beats/min)</th>
<th>CS*</th>
<th>NCS</th>
<th>Will repeat?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

*Clinical significance is based upon the physician's discretion.

Signature of person taking vital signs: ____________________________

### PHYSICAL ASSESSMENTS

Physical Exam:  
Weight: ______ (pounds)  
Height: ______ (inches)

<table>
<thead>
<tr>
<th>BODY SYSTEM</th>
<th>NORMAL</th>
<th>ABNORMAL</th>
<th>NOT DONE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphatic/Hematologic</td>
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<td></td>
</tr>
<tr>
<td>HEENT</td>
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</tr>
<tr>
<td>Respiratory</td>
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<tr>
<td>Cardiovascular</td>
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<tr>
<td>Gastrointestinal</td>
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<td></td>
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<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Allergies</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Neurological</td>
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</tr>
<tr>
<td>Genitourinary</td>
<td></td>
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</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
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</tbody>
</table>

Signature of person performing PE: ____________________________
### MEDICATION HISTORY
List all over-the-counter and prescription medication taken within the previous 14 days. Include the participant's present ADHD medication.

<table>
<thead>
<tr>
<th>Medication</th>
<th>OTC/Rx</th>
<th>Dose</th>
<th>Date last taken</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

### MEDICAL HISTORY AND CURRENT STATUS
List all clinically significant medical history and current status, other than ADHD.

<table>
<thead>
<tr>
<th>Body Category</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Year of onset</th>
<th>Ongoing?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphatics/Hematological</td>
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<td>HEENT</td>
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<tr>
<td>Respiratory</td>
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<tr>
<td>Cardiovascular</td>
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<tr>
<td>Gastrointestinal</td>
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<tr>
<td>Musculoskeletal</td>
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<tr>
<td>Allergies</td>
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<tr>
<td>Neurological</td>
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</tr>
<tr>
<td>Genitourinary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological/Psychiatric;</td>
<td>Absent</td>
<td>Present</td>
<td>Year of onset</td>
<td>Ongoing?</td>
</tr>
<tr>
<td>Obsessive Compulsive Disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
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<tr>
<td>Oppositional Defiance Disorder/Conduct Disorder</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
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</tr>
</tbody>
</table>

Signature of person performing PE: ________________________________
INCLUSION CRITERIA

1. The participant satisfies DSM-IV criteria for a primary diagnosis of ADHD
   - Combined Type
   - Predominantly Hyperactive-Impulsive
   - Predominantly Inattentive
     □ Yes  □ No

2. The participant is in good medical health based on a comprehensive history and physical examination, with no evidence of cardiac, respiration, renal, hepatic, endocrine, glaucoma, tics, agitation, severe anxiety, depression, or other physical condition, which may preclude the use of either methylphenidate or other psychotropic medication that would compromise the participant’s safety during the study.
     □ Yes  □ No

3. The participant’s parent or legally authorized guardian provided a signature of informed consent, and there is documentation of participant’s assent. A “legally authorized” representative is defined in the Code of Federal Regulations as an individual authorized under applicable law to consent on behalf of a prospective participant to the participant’s participation in the procedures involved in the research.
     □ Yes  □ No

4. The participant is 7-12 years of age, inclusive, at the time of the entry into the protocol.
     □ Yes  □ No

5. If female, the participant has not begun menarche.
     □ Yes  □ No

6. The participant has blood pressure and pulse rate measurements within the normal range, as judged by the physician.
     □ Yes  □ No

7. The participant and legal guardian are judged to be reliable with respect to assessments, visit intervals, medication storage and dosing and experimenter directives.
     □ Yes  □ No

8. The participant and legal guardian have a stable address and can be reached by the experimenter via telephone routinely.
     □ Yes  □ No

If any of the above questions are answered “no,” the participant is not eligible to participate in the study.
EXCLUSION CRITERIA

1. The participant has bi-polar disorder, seizure disorder, history of psychosis, or other psychiatric condition that requires psychotropic medication.
   □ Yes □ No

2. The participant has an estimated or documented IQ less than 80.
   □ Yes □ No

3. The participant is a female who has begun menarche.
   □ Yes □ No

4. The participant has an allergy or intolerance to methylphenidate or stimulant-class medications.
   □ Yes □ No

5. The participant has a chronic or acute illness, disability, or other condition that might confound the results of the tests administered in the trial, or that might increase risk to the participant in the opinion of the physician.
   □ Yes □ No

6. The participant has a history of suspected substance abuse or dependence disorder or lives with someone with a current diagnosed substance abuse or dependence disorder (excluding nicotine) according to DSM-IV criteria.
   □ Yes □ No

7. The participant currently or routinely uses steroids of any type.
   □ Yes □ No

If any of the above questions are answered "yes," the participant is not eligible to participate in the study.

This child meets all inclusion and exclusion criteria for protocol approved by the IRB and HSIRB and may be enrolled in the study.

Signature: __________________________  Date: __________________________

Physician's Name, degree
APPENDIX B

Letter to Participant’s Primary Care Physician
Dear Dr. ______:

This letter is a follow-up communication regarding your patient, (child's name), who has been enrolled in our study to evaluate effects of his/her ADHD medication (Brand name) generic name. The protocol will compare the effectiveness and side effects of (Brand name) to placebo during this double-blind study. If for any reason you would determine (child's name) is not an appropriate candidate for this study, please notify us at once.

(child's name) will be prescribed the above medication by Mark Simms, DO between (start date) and (end date). If during that time (child's name) requires a psychotropic medication, please notify our office immediately, as this may disqualify (child) from the study.

Upon completion of the 4-week evaluation, medication effects on attention, hyperactivity, impulsivity, opposition-defiance, academic performance, and sleep for (child's name) a full summary of the evaluation will be forwarded to you.

If you have any questions, please call Dr. Simms at (269) 373-1170 or me at (269) 387-4456.

Sincerely,

(adult's name or student investigator)
ADHD Research Study
Behavioral Pediatrics & Family Studies Lab
APPENDIX C

Informed Consent Handout
ADHD STUDY
Informed Consent Handout for Parents

Purpose of this study is to evaluate medicine effects on
- Attention
- Impulsivity
- Activity
- Compliance (how they follow your directions for things like getting ready for bed)
- Sleep
- Reading
- Math

Benefits to you and science
- You will receive information about whether a new ADHD medicine or placebo is effective in reducing your child’s symptoms.
- Tracking side effects will help determine which medication has fewer side effects for your child.
- You will be contributing to our understanding of the effects of this new medicine.
- Medications are provided free of charge for the duration of the study.
- There is no charge to see Dr. Sloane for office visits or sessions related to this study.

More information about the study
- Comparison of (Brand name of medication) to placebo (capsule without medicine)
- All of the capsules look alike, so neither you nor your child will know whether he/she has taken medicine or placebo for the day.
- Not knowing what medicine your child has taken medicine helps you be an objective observer.
- When the study is over, we will put together all of the information you give us, and you and your child’s physician can decide whether this is the best treatment for your child.

Eligibility session
- Your child must understand the basic idea of the study and agree to participate.
- After you both understand and sign consent form, there is an evaluation process:
  - Your child will take a simple 15-minute computer test
  - A 1-minute reading test
  - You and your child will fill out forms.
- A physician will do a brief physical exam and ask you some questions.
I will let you know if it was determined whether your child is appropriate for this study.
Also, your child’s principal and teacher must agree to allow your child to be observed at his/her school.

**Duration of study**
- 4 consecutive weeks.
- Your participation will not be scheduled over your child’s school break.
- No ADHD medicine **two days** before starting the study if your child is currently on a stimulant.
- No ADHD medicine **three days** before starting the study if your child is currently on atomoxetine (Strattera).
- Your child’s washout period can be scheduled during a school break.
- Once your child has begun the study, you must supervise your child’s medicine very closely
  - Take the pill out of the packaging for the correct day marked on the package
  - Be present when he/she takes it
  - Take it at the same time every morning. Time: ________

**Weekly clinic sessions**
- Your child will take their medication at least one hour before the session
- Bring in the forms you filled out during the week and your child’s pill bubble pack
- Your child will take
  - Simple 15-minute computer test
  - 1-minute reading test
  - 1-minute math test, and
  - Fill out two self-rating forms
- Your child will be weighed, have (his/her) blood pressure taken
- You and your child will meet with the physician
- To insure research assistants are doing their job properly, we video record your child’s sessions
  - Records are reviewed by the investigator and then erased
  - Video records are not retained or used for any other purpose
- Each week (Tuesday — Friday) you will pick up your child’s prescription at the Unified Clinics Pharmacy at 1000 Oakland Dr., in Kalamazoo or be available to sign for delivery.

**School observations**
- Your child will be observed in his/her classroom for about 15 minutes each day.
- One or two trained research assistants will be in your child’s class room and watch your child, as well his/her classmates, periodically writing down codes.

**Daily forms and contact**
- You will fill our four brief forms each evening
Brief evening contact Sunday through Friday to answer one question, via 1-minute phone call or e-mail.

Confidentiality
- A code number will be used on forms and in the database instead of your child’s name.
- No names will be used if the results are published or reported at a professional meeting.
- A master list with the names of the children and the code numbers will be kept locked in the principal investigator’s office and will be destroyed when the study is over.

Risks
- As with any medicine, there may be unanticipated or unforeseeable risks.
- Common side effects your child may or may not experience:
  - Appetite suppression and/or digestive problems
  - Slower weight gain
  - Drowsiness or insomnia
  - Complaints of headache and/or stomachache
  - Some irritability as medicine is wearing off
  - Anxiety (including minor discomfort typically felt when children are being tested)
  - Tics
- Instructions you are to follow if you notice any of these symptoms:
  - Refer to refrigerator flyer
  - Put this flyer with severe symptoms and emergency phone numbers by your telephone, on your refrigerator, or other prominent place where you can find it if you need it.
- As in all research, there may be unforeseen risks to your child:
  - Increase risk of education problems, including:
    - Increased inattention, hyperactivity, impulsivity
    - On-task less
    - More rule-breaking behavior
- In an accidental injury occurs, appropriate emergency measures will be taken; however, no compensation or additional treatment is available.

Alternative treatments
- Research shows that behavioral interventions are an effective way to improve behavior for many children. Some research has shown that the combination of medicine and behavioral intervention may be the most effective treatment for children with ADHD.
- Behavior therapy is basically a system of rewards and consequences for behavior.
- If your child is already on a behavioral treatment plan, such as token economy or reward system, it must be maintained throughout the entire study period.
If your child has not started such a treatment, but you would like that type of treatment for you child and you would like your child to participate in this study, we ask that you begin any behavioral intervention after your child’s participation in this study is completed.

You may choose a behavioral plan instead of a medicine treatment; a referral list of clinics is available.

Right to withdraw

You have the right to withdraw from this study at any time without negative effect on medical, educational, or other services to your child.

If you withdraw before completion of the study, due to lack of information, we will not be able to give you information whether the medicine is effective for your child.

Parent responsibilities

Closely supervise medications, including keeping them in a secure place

Pick up prescriptions from Unified Clinics Pharmacy each week or sign for delivery

Bring your child to clinic for one eligibility/assessment session and 4 weekly sessions

Fill out four forms each evening

Answer one question about the forms each evening

Sign consent forms, including consent to contact school officials and have child observed in classroom

Notify us immediately if symptoms from the emergency flyer are observed
APPENDIX D

Daily Sleep Questionnaire
## Daily Sleep Questionnaire

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Options</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trouble getting up in the morning</td>
<td>a b c d e</td>
<td></td>
</tr>
<tr>
<td>Falls asleep in school</td>
<td>a b c d e</td>
<td></td>
</tr>
<tr>
<td>Irritable in morning</td>
<td>a b c d e</td>
<td></td>
</tr>
<tr>
<td>Naps after school</td>
<td>a b c d e</td>
<td></td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>a b c d e</td>
<td></td>
</tr>
<tr>
<td>Feels week or loses control of muscles with strong emotions</td>
<td>a b c d e</td>
<td></td>
</tr>
<tr>
<td>Reports unable to move when falling asleep or upon waking</td>
<td>a b c d e</td>
<td></td>
</tr>
<tr>
<td>Seeing frightening visual images before falling asleep</td>
<td>a b c d e</td>
<td></td>
</tr>
<tr>
<td>Trouble getting ready and/or going to bed</td>
<td>a b c d e</td>
<td></td>
</tr>
<tr>
<td>Trouble falling asleep or staying asleep</td>
<td>a b c d e</td>
<td></td>
</tr>
</tbody>
</table>

Please rate your child’s sleep behavior for **today**, from getting up this morning, to going to sleep tonight.

Participant No. __________________________________________________ Date _______________
APPENDIX E

Side Effects Questionnaire
**SIDE EFFECTS RATING SCALE**

Participant ID # ___________________ Date ____________________

*Instructions:* Please rate each behavior from 0 (has not occurred today) to (frequently occurred or symptoms were severe today.) Circle only one number beside each item. A zero means that you have not seen this symptom today or the child has not reported this symptom to you today, and a 5 means that you have noticed it at least once during the day and believe the symptom to be severe.

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Frequently</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trouble sleeping (insomnia)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Stares a lot or daydreams</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Talks to friends less frequently</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Irritable</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Stomachaches</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
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<tr>
<td>Headaches</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
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<tr>
<td>Craving sugar</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Drowsiness or fatigue</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Cries</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Anxious or worries</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Mood swings</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Euphonic/unusually happy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Ringing in ears</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Tics or nervous movements</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Runny nose</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Sore throat</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Increased cough</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Skin rash</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Weakness or loss of strength</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Infection</td>
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<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
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<tr>
<td>Severe itching</td>
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<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
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<tr>
<td>Constipation</td>
<td>0</td>
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</tbody>
</table>
APPENDIX F

Assent/Vital Signs
<table>
<thead>
<tr>
<th>Date</th>
<th>Research Assistant</th>
<th>Assent obtained</th>
<th>Systolic BP mm/Hg</th>
<th>Diastolic BP mm/Hg</th>
<th>Pulse Beats/min</th>
<th>Weight</th>
<th>Meds remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>☐ Yes</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>☐ No</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>☐ Yes</td>
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<tr>
<td></td>
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<td>☐ No</td>
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</tr>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td>☐ No</td>
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</tbody>
</table>

Participant No. ________________________________

203
APPENDIX G

Job Aid/Checklist
Weekly Lab Session

Job Checklist

☐ Greet
☐ Collect last week’s instruments from parent(s)
   ☐ Conners’ Parent short version
   ☐ Daily Sleep Questionnaire and Diary
   ☐ Side effets questionnaire
   ☐ Eyberg Child Behavior Inventory

☐ Take vital signs:
   ☐ Weigh child
   ☐ Blood pressure
   ☐ Pulse rate

☐ Confirm medications taken/check chart
☐ Assent confirmed
☐ Random order of administration of academic tests and CPT:
   ☐ M-MAT completed
   ☐ Math test completed
   ☐ Reading test completed
   ☐ Beck Youth Depression Inventory
   ☐ Beck Youth Anger Inventory

☐ Child selected token
☐ Session with Dr. Sloane complete
☐ Parents given packet with instruments to be filled out for following week
☐ Confirm appointment time for next lab session
☐ Paperwork filled out
☐ Prescription faxed to pharmacy
☐ Written prescription delivered to pharmacy

☐ All data reports and paperwork turned in before leaving
APPENDIX H

Recruitment Flyer
Behavioral Pediatrics & Family Studies Lab

is enrolling participants with Attention-Deficit/Hyperactivity Disorder ages 7-12 to evaluate medicine effects on attention, hyperactivity, impulsivity, compliance, reading, math, and sleep. Summary provided to parents reporting effectiveness of ADHD medication for treatment of symptoms at home and at school.

For more information call Tina Head at (269) 387-4456.
APPENDIX I

ADHD Study Brochure
Parents must:
- provide transportation to clinic for 1 assessment and 4 weekly sessions to pediatrician's office at 700 Mall Dr., Suite C, Portage, MI.
- closely supervise medication
- fill out brief forms on child's behavior each evening
- make brief phone or e-mail contact nightly
- consent for child to be observed 15 minutes per day at school

Children must:
- take 15-minute computerized test each week
- take 1-minute math test each week
- take 1-minute reading test each week
- fill out self-rating forms each week
- be observed for 15 minutes each day at school

If child in summer school, teachers and school officials will be asked
- to allow observations
- fill out a brief form each day

The M-MAT is a simple 15-minute computerized task that measures a child's ability to sit still and concentrate.

This study may be particularly helpful for children for whom it is not clear whether their ADHD medication is effective and has tolerable side effects.

WESTERN MICHIGAN UNIVERSITY
Department of Psychology
Behavioral Pediatrics & Family Studies Lab
3700 Wood Hall
Kalamazoo, MI 49008

For more information call
(269) 387-4456

This study has been reviewed and approved by Bronson Methodist Hospital's Institutional Review Board (269) 341-7808 and Western Michigan University's Human Subjects Institutional Review Board (269) 387-8293
The ADHD research study is for children ages 7 to 12 with a diagnosis of Attention Deficit/Hyperactivity Disorder (ADHD), for whom pharmacological treatment has been deemed appropriate by their parents and physician. The purpose of this study is to evaluate the effectiveness of FDA approved ADHD extended release stimulant medication on attention, hyperactivity, impulsivity, compliance, sleep, reading, and math. This study may be especially beneficial for children for whom it is unclear whether their present ADHD medication or a new ADHD medication is effective. The child's ADHD medication will be compared to placebo (sugar pills). Medications that can be evaluated include Vyvanse, Concerta, Ritalin LA, Adderall XR, Metadate ER, Dexedrine spansule, Daytrana, and Focalin XR.

At the conclusion of their child's participation in this 4-week study, parents receive information about whether their child's medicine or a placebo was the most effective in reducing their child's symptoms. Physician services are free of charge for the duration of the study. Some medications may be provided free of charge. Participants' families receive $15 each week to cover transportation, childcare costs, or delivery of medications.

Participation in this study requires parents to bring their child to the clinic each week for 4 weeks. During these weekly sessions children take simple 15-minute computer tests, 1-minute reading tests, 1-minute math tests, and fill out two self-rating forms. To measure how the medicine affects children's ability to sit still and pay attention during school, participants are observed in his/her classroom for 15 minutes each day. Teachers are asked to fill out a brief form each day.

Each child and their parent(s) must participate in a screening or pretreatment session. Eligible children will:
- have physician diagnosis of ADHD (any subtype)
- IQ of 60 or higher
- be able to swallow capsules or use patch
- depression, agitation, or significant anxiety
- history of tics
- glaucoma
- a history of a poor reaction to stimulant medication (e.g. Ritalin®, Concerta®, Adderall®, Metadate®)
- a history of psychosis or seizure disorder
- medications that would cause problems with stimulant medication, such as MAOIs, and
- girls will not have begun menses.
APPENDIX J

Advertisement
Recruitment advertisement

UNSURE ABOUT YOUR CHILD'S ADHD medication? WMU Lab seeks participants, ages 7-12 with ADHD. Objective measures during 4-week study to evaluate effectiveness, side effects of the child's stimulant medication on symptoms, compliance, reading, math, sleep. Report given after completion. Call (269) 873-6191.
APPENDIX K

Letter to Parents with Eligibility/Assessment Session Information
Date

Parent’s name
Address
City, state, zip

Dear (Parents’ Names):

This letter is to confirm your child’s appointment on Saturday, (date), at the Center for Behavioral Pediatrics, 700 Mall Drive, Portage, MI (map enclosed) to determine whether he/she is eligible to participate in the ADHD study.

Please remember to fill out the Sleep Evaluation Questionnaire and Medical History Form you were given during the Consent Session and bring them with you to the upcoming appointment.

As we discussed on the phone, it is important that your child be initially assessed while not taking any medication. **Please do not give your child his/her ADHD medication the morning of this appointment.** In addition to meeting with Dr. Sloane, (he/she) will be taking a 15-minute computer test, 1-minute reading test, and do simple math problems for 1 minute. Additionally, he/she will fill out three forms that tell us how he/she has been feeling recently. While your child is taking these tests, you will fill out two additional forms.

Thank you for your interest in this study. If you have any questions, please call me at (269) 387-4456.

Sincerely,

(Student Investigator or Administrative Assistant’s name)
ADHD Research Study
Behavioral Pediatrics & Family Studies Lab
APPENDIX L

Sleep Questionnaire and Medical History Form
Sleep Evaluation Questionnaire
And Medical History Form

Directions
Please answer each of the following questions by writing in or choosing the best answer. This will help us know more about your family and your child.

<table>
<thead>
<tr>
<th>CHILD'S INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child's name:</td>
</tr>
<tr>
<td>Child's birthdate:</td>
</tr>
<tr>
<td>Child's gender:</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Child's age:</td>
</tr>
<tr>
<td>Child's racial/ethnic background:</td>
</tr>
<tr>
<td>White/Caucasian</td>
</tr>
<tr>
<td>Asian-American</td>
</tr>
<tr>
<td>Hispanic-Latino</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FAMILY'S INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOTHER</td>
</tr>
<tr>
<td>Age:</td>
</tr>
<tr>
<td>Marital Status:</td>
</tr>
<tr>
<td>Single</td>
</tr>
<tr>
<td>Widow</td>
</tr>
<tr>
<td>Education:</td>
</tr>
<tr>
<td>Work:</td>
</tr>
<tr>
<td>Unemployed</td>
</tr>
<tr>
<td>Occupation:</td>
</tr>
<tr>
<td>FATHER</td>
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<tr>
<td>Age:</td>
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<tr>
<td>Marital Status:</td>
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<td>Widow</td>
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<td>Education:</td>
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<tr>
<td>Work:</td>
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<td>Unemployed</td>
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<tr>
<td>Occupation:</td>
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</table>

<table>
<thead>
<tr>
<th>PERSONS LIVING IN HOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
</tr>
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</tr>
<tr>
<td></td>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>ADHD DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset:</td>
</tr>
<tr>
<td>Date of assessment and diagnosis:</td>
</tr>
<tr>
<td>Subtype: ADHD-combined</td>
</tr>
<tr>
<td>Assessed by:</td>
</tr>
<tr>
<td>Physician</td>
</tr>
<tr>
<td>City, State:</td>
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</table>

Participant No.: ___________________________  Date: ______ 9/06 v.1

216
# PAST MEDICAL HISTORY

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>Age of diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent nasal congestion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trouble breathing through his/her nose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic bronchitis or cough</td>
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<td></td>
</tr>
<tr>
<td>Allergies</td>
<td></td>
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<tr>
<td>Allergic to what:</td>
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<tr>
<td>Asthma</td>
<td></td>
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<tr>
<td>Frequent colds or flu</td>
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<td></td>
</tr>
<tr>
<td>Frequent ear infections</td>
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</tr>
<tr>
<td>Frequent strep throat infections</td>
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<td></td>
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<tr>
<td>Difficulty swallowing</td>
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<td></td>
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<tr>
<td>Acid reflux (gastroesophageal reflux)</td>
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<tr>
<td>Poor or delayed growth</td>
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<tr>
<td>Excessive weight</td>
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<tr>
<td>Hearing problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speech problems</td>
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<tr>
<td>Vision problems</td>
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<tr>
<td>Seizures/epilepsy</td>
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<td></td>
</tr>
<tr>
<td>Morning headaches</td>
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</tr>
<tr>
<td>Cerebral palsy</td>
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</tr>
<tr>
<td>Heart disease</td>
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<tr>
<td>High blood pressure</td>
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<td>Sickle cell</td>
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<tr>
<td>Genetic disease</td>
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<tr>
<td>Chromosome problem (e.g. Down Syndrome)</td>
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<tr>
<td>Skeleton problem (e.g. dwarfism)</td>
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<tr>
<td>Craniofacial disorder (e.g. Pierre-Robin)</td>
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</tr>
<tr>
<td>Thyroid problems</td>
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<td></td>
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<tr>
<td>Eczema (itchy skin)</td>
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<tr>
<td>Pain</td>
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Participant No.: ____________________________ Date: __________ 9/06 v.1
### PAST PSYCHIATRIC/PSYCHOLOGICAL HISTORY

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<thead>
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<td>Hyperactivity/ADHD</td>
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<tr>
<td>Anxiety/Panic attacks</td>
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<td></td>
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<tr>
<td>Obsessive Compulsive Disorder</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Suicide</td>
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<tr>
<td>Learning disability</td>
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<td></td>
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<tr>
<td>Drug use/abuse</td>
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<td></td>
</tr>
<tr>
<td>Psychiatric admission to treatment facility/hospital</td>
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</tr>
</tbody>
</table>

Please list any additional psychological, psychiatric, emotional, or behavioral problems diagnosed or suspected by a physician/psychologist.

### CURRENT MEDICAL HISTORY

Please list any medications your child currently takes:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>How often?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### LONG-TERM MEDICAL PROBLEMS

If your child has long-term medical problems, please list the three you think are most important.

1.  
2.  
3.  

Participant No.: ___________________________  Date: _______ 9/06 v.1 _______
### PREGNANCY/DELIVERY

<table>
<thead>
<tr>
<th>Pregnancy</th>
<th>□ Normal</th>
<th>□ Difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery</td>
<td>□ Full-term</td>
<td>□ Pre-term</td>
</tr>
</tbody>
</table>

Child’s birthweight:

### SLEEP HISTORY

#### Weekday Sleep Schedule

Write in the amount of time your child sleeps during a 24-hour period on weekdays (add daytime and nighttime sleep):

- Hours: ___________
- Minutes: ___________

Your child’s usual bedtime on weekday nights:

- Time: __:__

Your child’s usual waketime on weekend mornings:

- Time: __:__

#### Weekend/Vacation Sleep Schedule

Write in the amount of time your child sleeps during a 24-hour period on weekdays (add daytime and nighttime sleep):

- Hours: ___________
- Minutes: ___________

Your child’s usual bedtime on weekday nights:

- Time: __:__

Your child’s usual waketime on weekend mornings:

- Time: __:__

#### Nap Schedule

Number of days each week he/she takes a nap: □ 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7
If your child naps, write in usual nap time(s):

- Nap 1: __:__ a.m. to __:__ p.m.
- Nap 2: __:__ a.m. to __:__ p.m.

#### General Sleep

<table>
<thead>
<tr>
<th>Question</th>
<th>□ Yes</th>
<th>□ No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does your child have a regular bedtime routine?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does your child have his/her own bedroom?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does your child have his/her own bed?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is a parent present when your child falls asleep?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location of Sleep During Nighttime</th>
<th>□ own room in own bed (alone)</th>
<th>□ parent's room in own bed</th>
<th>□ sibling's room in own bed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child sleeps most of the night in...</td>
<td>□ own room in own bed (alone)</td>
<td>□ parent's room in own bed</td>
<td>□ sibling's room in own bed</td>
</tr>
<tr>
<td>Child usually wakes in the morning in...</td>
<td>□ own room in own bed (alone)</td>
<td>□ parent's room in own bed</td>
<td>□ sibling's room in sibling's bed</td>
</tr>
</tbody>
</table>

Your child is usually put to bed by: □ Mother □ Father □ Both parents □ Self □ Others
Write in the amount of time child spends in his/her bedroom before going to sleep: ___________ minutes

<table>
<thead>
<tr>
<th>Question</th>
<th>□ Yes</th>
<th>□ No</th>
</tr>
</thead>
<tbody>
<tr>
<td>After nighttime awakening, child has difficulty falling back to sleep?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is your child difficult to wake in the morning?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is your child difficult to wake in the morning?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is your child a poor sleeper?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Participant No.: ________________________ Date: ___________ 9/06 v.1
### Current Sleep Symptoms

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.</strong> Difficulty breathing when asleep</td>
<td>(a) never (does not happen)</td>
<td>(b) not often (less than 1 day a week)</td>
<td>(c) sometimes (1 to 2 days a week)</td>
<td>(d) often (3 to 5 days a week)</td>
<td>(e) always (6 to 7 days a week)</td>
</tr>
<tr>
<td><strong>2.</strong> Stops breathing during sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3.</strong> Snores</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>4.</strong> Restless sleep</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>5.</strong> Sweating when sleeping</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>6.</strong> Daytime sleepiness</td>
<td></td>
<td></td>
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<tr>
<td><strong>7.</strong> Poor appetite</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>8.</strong> Nightmares</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>9.</strong> Sleepwalking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>10.</strong> Sleeptalking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>11.</strong> Screaming in his/her sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>12.</strong> Kicks legs in sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>13.</strong> Wakes up at night</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>14.</strong> Gets out of bed at night</td>
<td></td>
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<tr>
<td><strong>15.</strong> Trouble staying in his/her bed</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>16.</strong> Resists going to bed at bedtime</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td><strong>17.</strong> Grinds his/her teeth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>18.</strong> Uncomfortable feeling in legs; creepy-crawly feeling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>19.</strong> Wets bed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>20.</strong> Difficulty falling asleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>21.</strong> Sleeps outside of bed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Participant No.: ___________________________  Date: _______ 9/06 v.1

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APPENDIX M

Adverse Reactions/Severe Side Effects Hierarchy Flyer
If these unlikely, but serious side effects occur:
- Uncontrolled movements (motor tics or tremor)
- Verbal tics (grunts, barks, involuntary swearing)
- Fast/pounding/irregular heartbeat
- Chest pain
- Severe headache
- Difficulty urinating

To report serious side effects during non-holiday weekday business hours (8 a.m.-5 p.m.)

Call (269) 353-3070

After business hours Call 9-1-1

If you suspect an overdose (missing medication)
- Severe vomiting
- Persistent tremor, muscle twitching
- Agitation
- Seizures
- Loss of consciousness,
- Confusion, hallucinations
- Sweating, flushing
- Severe headache
- Wide pupils

Call 9-1-1

Or your local emergency room ___________________________ (insert local emergency room phone #)

and/or the national poison hotline at 1-800-222-1222.

Medication information for your child is available at any time. Your physician can access this information from the ADHD Research Study cell phone (269) 873-6191
APPENDIX N

Medication Key Sample
Participant Number: KA08103

**Week 4**

<table>
<thead>
<tr>
<th>Day</th>
<th>Date</th>
<th>Med/Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuesday</td>
<td>8/19/08</td>
<td>Vyvanse</td>
</tr>
<tr>
<td>Wednesday</td>
<td>8/20/08</td>
<td>Vyvanse</td>
</tr>
<tr>
<td>Thursday</td>
<td>8/21/08</td>
<td>Placebo</td>
</tr>
<tr>
<td>Friday</td>
<td>8/22/08</td>
<td>Vyvanse</td>
</tr>
<tr>
<td>Saturday</td>
<td>8/23/08</td>
<td>Vyvanse</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sunday</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
</tr>
</thead>
<tbody>
<tr>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>A</td>
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<tr>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>B</td>
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<tr>
<td>A</td>
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<td>A</td>
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<td>U</td>
<td>B</td>
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<td>A</td>
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<tr>
<td>B</td>
<td>B</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>A</td>
</tr>
</tbody>
</table>

A=medication, B=placebo, U=unblinded (no data collection).
APPENDIX O

Consent Form
You and your child have been invited to be in a research study that is to look at the effectiveness of Vyvanse™ for treatment of symptoms of attention-deficit/hyperactivity disorder in children. The purpose of this study is to compare medication effects of Vyvanse, a new ADHD medication, to placebo, on attention, hyperactivity, impulsivity, compliance, reading, math, and sleep, as well as side effects.

**Child participation**

Permission for your child to be in this study means that each week for 4 weeks your child will be administered simple computerized tasks, 1-minute reading tests, and 1-minute math tests. He/She must also fill out self-rating forms that evaluate symptoms of depression, anxiety, and anger. Your child will be tested individually by research assistants who have been trained to give these tests. These sessions will be recorded to monitor the quality of the research assistants' interaction with your child. These videos will be reviewed by the student investigator and then erased. Also, your child will be observed at school for 15 minutes each school day during a class lesson. Your consent to participate in this study includes consent to contact your child's teacher and school officials. Your child's principal and teacher must agree to participate for your child to be in the study.

Fifty children will be asked to be in the study. All of the children must have a physician diagnosis of attention-deficit/hyperactivity disorder (any subtype). Children who have had a bad reaction to stimulant medications (e.g. Ritalin, Concerta or Adderall) will not be admitted to the study. Children will also not be eligible if they have an IQ less than 80, history of psychosis, seizure disorder, bipolar disorder, or currently use medicine that alters behavior. Other criteria that would keep them from being in the study include: tics, agitation, severe anxiety, depression, heart problems, high blood pressure, hyperthyroidism, glaucoma, or inability to swallow capsules. Due to risk of pregnancy and unknown medicine effects on the fetus, girls who have begun their menstrual period will be excluded from the study.
Parent requirements

All testing will take place at the Center for Behavioral Pediatrics, 700 Mall Drive, Suite C, in Portage. You will not be charged for the medicine or doctor services related to this study. You will receive $15 each week to help pay for transportation, childcare costs, or medication delivery. After your child has finished his/her participation in this study, we will put together all of the information from your child’s participation, and you and your child’s doctor can decide whether Vyvanse or placebo was an effective treatment for your child’s ADHD symptoms. You will also receive information about which medication produced the fewest side effects.

• During the evaluation/screening session, you will be asked to fill out a form that looks at how you interact with your child.
• You will be asked to fill out four brief forms each day and be in brief contact by phone or e-mail each evening.
• Bring your child to the Center for Behavioral Pediatrics for 4 consecutive weeks;
• Pick up the prescription at the Unified Clinics Pharmacy in Kalamazoo, or be available to sign for delivery of medicine;
• Fill out four rating forms each night and communicate briefly with a research assistant by answering one question each night;
• From the time your child goes to bed, until you go to bed, you will be asked to monitor your child’s sleep by marking on a record form when you hear your child make sounds (e.g. rustling sounds from turning over, talking, playing);
• Give your child his/her medicine at the same time each morning;
• Store the medicine in a safe place that cannot be reached by any children; and
• In the event of a severe reaction or emergency, follow the procedures outlined in the Severe Side Effects/Emergency form.
• Your child may be removed from the study if
  o he/she is absent from a lab session without notice and does not make up that session within one week;
  o daily contact from parents is not reasonably maintained;
  o a reasonable attempt to obtain daily instruments from parents are not maintained;
  o safety rules are not followed (e.g. keeping medicine out of reach of children, not taking medication at scheduled time, not following procedures in severe side effects/emergency flyer)

No penalty for withdrawal

Your child will be free at any time – even during test periods – to choose not to participate. If your child refuses or quits, there will be no negative effect on his/her school programming or medical care. Although there may be no immediate benefits to your child for participating, it may be beneficial for you to have an objective evaluation of the effects of his/her medication.
Confidentiality

All test data and information will remain confidential. That means your child’s name will be omitted from all test forms and a code number will be attached. The researchers will keep a separate master list with the names of the children and the code numbers. Once the study is over, the master list will be destroyed. All other forms will be kept for at least 3 years in a locked file in the principal investigator’s office. No names will be used if the results are published or reported at a professional meeting.

Risk of side effects/adverse reactions

Side effects are a risk with any medication. Reports of side effects of these drugs are low, but will be watched closely. Reports of possible side effects, if any, will be sent to, and reviewed by a doctor who has agreed to provide clinical supervision for participants according to standard clinical practice and HSIRB approved protocols. Any new findings that increase the risk of taking these medications will be reported to you. Common side effects your child may or may not have include decreased appetite (35%), problems falling asleep (16%), weight loss (8%), stomachache (6%), irritability (5%) vomiting (5%), dizziness (5%), dry mouth (5%), nausea (3%) and tics (2%). Risks anticipated during testing are minor discomforts typically felt by children when they are being tested (e.g., boredom, mild stress due to the testing situation). Also, during periods when your child may not take medication (prior to the start of the study, and during placebo conditions), your child may experience increases in hyperactive, impulsive, and inattentive behaviors. Participants have an increased risk of being off-task, inattentive, hyperactive and impulsive on days he/she has the placebo patch. A WMU study conducted in the Kalamazoo School District a few years ago, which used the same observation procedures we will be using in this study, found children with ADHD on average were off-task 6% more of the time when they were on placebo than when they had taken medication. Due to the risk of increased impulsivity, participants may also be at greater risk of breaking school or classroom rules when on placebo. It will be up to your child’s principal and teacher whether they will handle disciplinary issues differently for the duration of the study, or allow extra credit or make-up work. I will talk with them, and that will be decided before the start of the study.

One or two trained undergraduate research assistants will observe your child and a comparison child for 15 minutes each day during an academic period, writing down codes on a clipboard. By comparing the amount of time a participant is on-task to a typical student in your classroom at the same time, gives us meaningful data. Research assistants are trained to scan the classroom so that it appears they are watching the entire class. Also, we do not in any way identify the comparison child. The child is only noted as “CC” on our data sheet. We will not schedule your child to be in the study during days the school is administering standardized tests and your child will be prescribed his/her medication for that day.

All of the usual methods used during testing to minimize discomforts will be used in this study. As in all research, there may be unforeseen risks to your child. If an accidental injury occurs, appropriate emergency measures will be taken; however, no compensation or additional treatment will be made available to you or your child except as otherwise stated in this consent form. By signing below, I agree to follow the procedures outlined in the Severe Side Effects/Emergency Events form.
Withdrawal

You may withdraw your child from this study at any time without any negative effect on services to your child. You may contact Dr. Sloane at (269) 373-1170 to answer questions related to this study, including withdrawing from the study. You may also contact either Dr. Alessi at (269) 387-4470, Tina Head at (269) 387-4456. You may also contact the chair of the WMU Human Subjects Institutional Review Board at (269) 387-8293 or WMU’s vice president for research (269) 387-9298 if questions or problems arise during the study. Questions about your rights as a volunteer may be addressed to: James W. Carter, MD, Chairman, Bronson Methodist Hospital Institutional Review Board, 601 John Street (Box 80), Kalamazoo, MI 49007 or you may call (269) 341-7879 between the hours of 8:30 a.m. and 5 p.m.

This form has been reviewed and approved for use for one year by the Western Michigan University Human Subjects Institutional Review Board (HSIRB) and the Bronson Methodist Hospital Institutional Review Board (IRB). The HSIRB and the IRB are groups of scientific and non-scientific people who review and approve or disapprove research involving people by following the Food and Drug Administration (FDA) rules. These groups are also required by the FDA to do periodic review of ongoing research studies. Approval is indicated by the stamped date and signature of the board chairs in the lower margin. Do not permit your child to participate if the stamped dates are more than one year old. This project will fulfill Tina Head’s thesis and dissertation requirements.

Your signature indicates that you, as parent or guardian, agree that your child may be:

- Evaluated by the supervising physician, Dr. Sloane;
- Prescribed medicine and/or a placebo;
- Tested with a computerized attention test;
- Take 1-minute reading tests, 1-minute math tests;
- Observed in his/her classroom;
- Recorded during lab sessions; and
- Asked to fill out self-rating forms.

Signature of Parent/Guardian __________________________ Date __________________

Permission obtained by __________________________ Date __________________

[Stamp: Bronson Methodist Hospital - Institutional Review Board (IRB)]

Approved for use for one year from this date:

WESTERN MICHIGAN UNIVERSITY H. S. I. R. B.
Approved for use for one year from this date:

[Signature: Dr. W. Carter] 1/10/08

[Signature: Chair] 11/7/08
APPENDIX P

Consent for Release of Confidential Information
Consent for Release of Confidential Information

I, ___________________________________________________________ hereby authorize:
(Client’s name or parent/legally authorized guardian)

Teacher ________________________________ Name of School ________________________________

City, State, Zip

To provide the information described below to:

Tina Head, M.A., T.L.L.P. Western Michigan University
Name of School
Department of Psychology
Kalamazoo, MI 49008

Information Provided: Information to evaluate my child’s behavior during the medication study.

From the record of: ________________________________________

To be used ONLY for the following authorized purpose: For communication regarding my child’s participation in the medication study.

Utilization of this form to release information is effective for the following period:

From: ___________ To: ___________ unless revoked by me in writing prior to the termination date.

My signature means that I have read this form and/or have had it read to me and explained in language that I can understand. I know what information is being disclosed. All the blank spaces have been filled in except case number, witness for my signature and the date of signatures.

Signed: ___________________________ Date: ___________________________
(Client/parent/guardian)

Witness: ___________________________ Date: ___________________________
APPENDIX Q

Assent Form
We are doing a research study. A research study is a special way to find out about something. We want to look at whether your ADHD medicine helps you sit still and pay attention. Your ADHD medicine may affect your schoolwork or sleep, and we want to also look at that.

We want to tell you about some things that might happen to you if you are in this study. We want to see if your ADHD medicine helps you sit still and pay attention. Some of the pills (patches) will have medicine in them and some of them may not have medicine in them. You will not know which days you are taking medicine or what we used to call a "sugar pill," which means there is no medicine, but all of the pills ("patches" if using Daytrana) will look alike.

You can be in this study if you want to. If you want to be in this study, you will be asked to
- Come in this office on Saturdays for 4 weeks,
- Take a pill every day that may or may not have medicine on it,
- Take computer tests that are like a video game, which lasts 15 minutes,
- Read sentences out loud for 1 minute,
- Complete addition and subtraction math problems for 1 minute,
- Fill out two forms that tell us how you are feeling, and
- Every school day some people will come to your classroom for about 15 minutes each day and watch you and the other students in your classroom.

Sometimes when people take medicine, it can cause them to not feel good, like having a headache or a stomachache. This can happen if you decide to be in this study and try these medicines. But keep in mind other things can also make us not feel good, like having a cold or a flu. If you decide to be in this study, some good things might happen. The medicines could do a good job helping you pay attention. If you have trouble getting up in the morning, with this medicine you may feel more awake. But we don't
know for sure that these things will happen. We might also find out things that will help other children some day. When we are done with the study, we will write a report about what we found out. We won’t use your name in the report. We will give you and your parent(s) information about how you did with when you took the medicine compared to days when there was no medicine on the patch.

If you don’t want to be in this study, we will tell you and your parent(s) about other things that might help you.

If you have any questions about this study, you may call either Dr. Alessi at (269) 387-4470, Tina Head at (269) 387-4456, or Dr. Sloane at (269) 373-1170.

Please tell me the seven things we talked about earlier that you would be asked to do if you decide to be in this study:

- Come to this clinic on Saturdays for 4 weeks
- Take a pill (wear a patch) every day that might have medicine in it
- Take a computer test that are like a video game for 15 minutes
- Read out loud for 1 minute
- Complete math problems for 1 minute
- Fill out two forms about how I am feeling
- People will watch me at school

The stamped date and signature of the board chair in the lower part of this form means this consent document is approved for use for one year by the Bronson Institutional Review Board and the Western Michigan University Human Subjects Institutional Review Board. Do not participate if the dates stamped are more than one year old.

If you want to be in this study, please sign your name:

I, ________________________________ want to be in this research study.

(write your name here)

__________________________________________ (Date)

Student Investigator’s signature

WESTERN MICHIGAN UNIVERSITY
H. S. I. R. B.
Approved for use for one year from this date:

H. S. I. R. B.
Chair

Bronson Methodist Hospital - Institutional Review Board (IRB)
HHS approved use of this Informed Consent
for 140 days expiring 11-7-08

IRB Chairman
11-20-08

Date
APPENDIX R

Teacher, Principal Agreement Form
(_______), a ___ grade student in your school, and his/her parents have expressed interest in participating in a research study being conducted by the Behavioral Pediatrics and Family Studies Lab at Western Michigan University. The ADHD research study is for children ages 7 to 12 with a diagnosis of Attention Deficit/Hyperactivity Disorder (ADHD), for whom a pharmacological treatment has been deemed appropriate by their parents and physician. The purpose of this study is to compare the effectiveness of his/her ADHD medication to placebo, on inattention, hyperactivity, impulsivity, compliance, sleep, reading, and math. At the conclusion of their child's participation in a double-blind placebo 4-week study, parents receive information about whether this medication is effective for their child.

To measure how their medication affects children's ability to sit still and pay attention during school, participants in this study are observed in his/her classroom for about 15 minutes each day. Some days the child will take medicine, and on a few days the child may take a placebo. Teachers' observations of students' behavior is vital to evaluating treatment effectiveness, so, in addition to daily observations, participating students' teachers fill out the Conners' Teacher Rating Scale short form at the end of each school day. We also are interested in your feedback about the evaluation process. After the data collection phase has concluded, participating teachers will be asked to fill out a 13-item questionnaire.

For (________) to participate in this study:

✓ [child's name] [principal and teacher(s)] give permission to do 15-minute observations each day during an academic period;

✓ [child's name] teacher(s) agree to fill out the Conners' form each day;

✓ [child's name] teacher(s) or their intern(s) agree to identify typical same-gender comparison children for purposes of the observation; and

✓ In the event of severe side effects (or overdose), school staff agree to follow procedures on the emergency flyer, including calling the 24-hour ADHD Study telephone number (269) 567-0111.

During this study, the child's parent(s) are responsible for giving their child his/her medication at prescheduled times. We will not schedule [______________] to be in the study during days the school is administering standardized tests. [child] will be prescribed an unblinded medication for that day. You, his parents, and [______________] will know that he/she has medicine for testing days. Participants have an increased risk of being off-task, inattentive, hyperactive and impulsive on days he/she takes a placebo. Due to the risk of increased impulsivity, participants may also be at greater risk of breaking school or classroom rules when on placebo. It is not our intention to include a child in this study who has a history of severe behavior...
problems or a student whom teacher(s) and/or principals believe would be "out of control" on days he/she was on placebo.

If you have any questions about this study, you may call either Dr. Alessi at (269) 387-4470, Tina Head at (269) 873-6191, or Dr. Sloane at (269) 373-1170.

School name  Address  City, State  Zip

[Principal]: If you agree to allow observations in (______________________)'s classroom, please sign your name.

Principal's Signature  Date signed

[Teacher]: If you agree to allow observations in your classroom, and fill out the Conners' form, please sign.

Teacher's Signature  Date signed

[Teacher]: If you agree to allow observations in your classroom, and fill out the Conners' form, please sign.

Teacher's Signature  Date signed

[Teacher]: If you agree to allow observations in your classroom, and fill out the Conners' form, please sign.

Teacher's Signature  Date signed

[Teacher]: If you agree to allow observations in your classroom, and fill out the Conners' form, please sign.

Teacher's Signature  Date signed

Student Investigator's signature  Date signed

Western Michigan University
H. S. I. R. B.
Approved for use for one year from this date:

HSIRB Chair

Bronson Methodist Hospital - Institutional Review Board (IRB)
Has approved use of this Informed Consent
for 140 days  expiring 11-7-08

IRB Chairman  Date
APPENDIX S

Classroom Observation Form
<table>
<thead>
<tr>
<th></th>
<th>1-1</th>
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</table>

O = On Task  I = Inattentive (neck up)  Q = Off Task Gross Motor (shoulders down)

239
APPENDIX T

Sleep Latency Form
<table>
<thead>
<tr>
<th></th>
<th>8:00</th>
<th>9:00</th>
<th>10:00</th>
<th>11:00</th>
<th>12:00</th>
<th>1:00</th>
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</tbody>
</table>

Participant No. ___________________________ Week of ___________________________
APPENDIX U

Parent and Participant Surveys
ADHD Research Study

Tell us about your experience

1. In general, do you feel your participation in this study was worth the time and effort you were required to contribute? (Mark only one box.)

<table>
<thead>
<tr>
<th>Very Unsatisfied</th>
<th>Very Unsatisfied</th>
<th>Very Unsatisfied</th>
<th>Very Unsatisfied</th>
<th>Very Unsatisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

If you are dissatisfied (a score of 1 or 2), please tell us why.

---

2. Team Members

How satisfied were you with your interactions with our team members? (Please mark one box for each line.)

- Student Investigator
- Physician
- Research Assistants

3. Consent Session

How satisfied were you with your experience during the consent session? (Mark one box for each item.)

- Procedure explained
- Risks explained
- Questions answered
- Time spent in session

---

4. Eligibility Evaluation Session

How satisfied were you with your experience during the eligibility session? (Mark one box for each item.)

<table>
<thead>
<tr>
<th>Very Unsatisfied</th>
<th>Very Unsatisfied</th>
<th>Very Unsatisfied</th>
<th>Very Unsatisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Session ran as expected.
Length of tests.
Ease getting to location.
Time spent in session.

---

5. Weekly Lab Sessions

How satisfied were you with your experience during the weekly lab sessions? (Mark one box for each line.)

<table>
<thead>
<tr>
<th>Very Unsatisfied</th>
<th>Very Unsatisfied</th>
<th>Very Unsatisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Session ran as expected.
Length of tests.
Ease getting to location.
Time spent in session.

---

6. Medication Delivery/Pick Up

How did you obtain your child's medication?

- Check One
- Pick up at pharmacy
- Delivery

Satisfaction with pick-up/delivery

<table>
<thead>
<tr>
<th>Very Unsatisfied</th>
<th>Very Unsatisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

---

7. Daily School Observations

Did you receive any complaints from teacher(s) or school staff?

- Yes
- No

If yes, what problem did they discuss with you?

---

243
8 Daily Forms
How easy or difficult was it for you to complete the forms each evening?

<table>
<thead>
<tr>
<th>Very Easy</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Very Difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
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<td>□</td>
<td>□</td>
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</tbody>
</table>

On average, how much time did you spend filling out forms each evening? (check one)
- Less than 5 minutes □
- Around 5 minutes □
- Around 10 minutes □
- More than 10 minutes □

9 Evening Contact
How convenient was it for you to briefly communicate with the student investigator about the forms, each evening?

<table>
<thead>
<tr>
<th>Very Inconvenient</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Very Convenient</th>
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</thead>
<tbody>
<tr>
<td>□</td>
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</tbody>
</table>

Did you complete the forms on a daily basis?
- Yes □
- No □

If yes, did knowing each evening you were required to answer one question from a random form help you complete the forms on a daily basis?
- Yes □
- No □

10 Report
How informative did you find the information from your child's report? (Please mark one box for each item.)

Direct child tests
- Math □ □ □ □ □
- Reading □ □ □ □ □
- Mood □ □ □ □ □
- School observations □ □ □ □ □
- Teacher reports □ □ □ □ □
- Parent reports □ □ □ □ □

Overall report □ □ □ □ □

11 Monitoring/Safety
How satisfied were you with the monitoring and emergency procedures? (Please mark one box for each item.)

<table>
<thead>
<tr>
<th>Very Dissatisfied</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Very Satisfied</th>
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<tbody>
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</tbody>
</table>

- Child mood forms □ □ □ □ □
- Physician visit □ □ □ □ □
- Safety procedures
  - Emergencyayer □ □ □ □ □
  - Access to medication information in emergency (ADHD cell phone) □ □ □ □ □

12 If you could change one thing about this evaluation procedure, what would that be?

13 Other comments/feedback:

I am child's mother □
I am child's father □
Foster parent/legal guardian □
I am child's grandmother □
I am child's grandfather □
ADHD RESEARCH STUDY

Tell us about your experience

1. In general, do you feel being in this study was worth it? (Please mark one box.)

<table>
<thead>
<tr>
<th>Very Unworthwhile</th>
<th>Very Worthwhile</th>
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<tbody>
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</tbody>
</table>

If you marked a score of 1 or 2, please tell us why.

2. Team Members
How comfortable were you working with our team members? (Please mark one box for each line.)

<table>
<thead>
<tr>
<th>Very Uncomfortable</th>
<th>Very Comfortable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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</table>

- Student Investigator
- Physician
- Research Assistants

3. Consent Session
How well did you understand the information given to you during the consent session? (Mark one box for each item.)

<table>
<thead>
<tr>
<th>Did Not Understand</th>
<th>Understood</th>
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<tbody>
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</table>

- Procedure explained
- Risks explained
- Questions answered
- Time spent in session

4. Eligibility Evaluation Session
How did you think the eligibility session went? (Mark one box for each item.)

<table>
<thead>
<tr>
<th>Very Poor</th>
<th>Excellent</th>
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</thead>
<tbody>
<tr>
<td>1</td>
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</tbody>
</table>

- Session ran as expected
- Length of tests
- Time spent in session

5. Weekly Lab Sessions
How did you feel the weekly lab sessions went? (Mark one box for each line.)

<table>
<thead>
<tr>
<th>Very Poor</th>
<th>Excellent</th>
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<tbody>
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</tbody>
</table>

- Session ran as expected
- Length of tests
- Ease getting to location
- Time spent in session

6. Medication
Did you take your medicine around the same time each morning? (Check one)

- Yes
- No

Did you have problems swallowing the pill?

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<th>Always</th>
<th>Never</th>
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</tbody>
</table>

7. Daily School Observations
How were you comfortable with people watching you and your classmates at school?

<table>
<thead>
<tr>
<th>Very Uncomfortable</th>
<th>Very Comfortable</th>
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Did any of your classmates ask you about being observed? (Check one)

- Yes
- No
APPENDIX V

IRB Approval Certificate
The Bronson Methodist Hospital Institutional Review Board Chair, James W. Carter, MD, FACP, has approved the revisions to the protocol through Expedited Review.

The current IRB approval period is not affected by this change and is valid through November 7, 2008.

Determined Risk: Greater Than Minimal

The primary investigator must comply with the following:

➢ To conduct research in accordance with the approved protocol.
➢ To use only the approved dated Consent Form, signed by the IRB Chair, and as appropriate that each study participant should receive a copy of the consent document.
➢ To obtain pre-approval from the IRB for any changes in the approved research protocol activity, (except when necessary to protect human subjects), and immediately report to the IRB any such emergency changes for the protection of human subjects.
➢ To report any unanticipated problems, serious adverse events, or serious medical events to the IRB within 48 hours of the investigator becoming aware of the event.
➢ To report to the IRB prior to enrolling any vulnerable populations (such as wards of the state, prisoners).
➢ Report any new information that may adversely affect the safety of the subjects or the conduct of the trial.
➢ Provide reports to the IRB concerning the progress of the research, when requested.

APPROVING PHYSICIAN'S COMMENTS:

Assurance: FWA00002688 (IRB00002511)

James W. Carter, MD, FACP
Chairman, Expedited Review Committee
Bronson Methodist Hospital Institutional Review Board

January 10, 2008
APPENDIX W

Sleep Diary
### Sleep Diary

<table>
<thead>
<tr>
<th>Day</th>
<th>Date</th>
<th>Time child got into bed</th>
<th>Time child fell asleep</th>
<th>Time child woke up in morning</th>
<th>Number of wakenings last night</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturday</td>
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<td>Sunday</td>
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</table>

Every night after your child goes to sleep, complete the sleep diary for the current day. Include number of your child’s wakenings from the previous night’s sleep.

Participant No. __________________________ Date __________________________
APPENDIX X

Math Minute Sample
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</tbody>
</table>

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APPENDIX Y

HSIRB Approval Letter
Date: April 30, 2007

To: Galen Alessi, Principal Investigator
Tina Head, Student Investigator for dissertation

From: Amy Naugle, Ph.D., Chair

Re: HSIRB Project Number: 06-10-05

This letter will serve as confirmation that your research project entitled "Evaluation of Methlyphenidate Transdermal Patch on Academic Performance, Sleep and Core ADHD Symptoms in Children" has been approved under the full category of review by the Human Subjects Institutional Review Board. The conditions and duration of this approval are specified in the Policies of Western Michigan University. You may now begin to implement the research as described in the application.

Please note that you may only conduct this research exactly in the form it was approved. You must seek specific board approval for any changes in this project. You must also seek reapproval if the project extends beyond the termination date noted below. In addition if there are any unanticipated adverse reactions or unanticipated events associated with the conduct of this research, you should immediately suspend the project and contact the Chair of the HSIRB for consultation.

The Board wishes you success in the pursuit of your research goals.

Approval Termination: October 18, 2007