STIMULANT ADHERENCE IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A 3-YEAR PROSPECTIVE FOLLOW-UP

By

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A thesis submitted in conformity with the requirements for the degree of
Master of Science
Institute of Medical Science
University of Toronto

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Stimulant Adherence in Children with Attention-Deficit Hyperactivity Disorder: A 3-Year Prospective Follow-up

Master of Science, 1999
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The present study examined reasons for non-adherence, predictors of adherence, and clinical effects of adherence. Sixty-three children with a confirmed diagnosis of Attention-Deficit Hyperactivity Disorder (ADHD) were prospectively followed from their first trial of stimulant for 3 years. Diagnostic, academic, and family evaluations were obtained at baseline. Stimulant adherence (defined as taking stimulant for 3 years) was documented annually through interviews from parent, teacher, and child. Behavioral and academic changes were evaluated at 3-year follow-up. Adherence to stimulant was 52%. Side effects, parents feeling medication was unnecessary or ineffective, and child reluctant to take pills were the reasons for non-adherence. Predictors of adherence included child's younger age, more ADHD symptoms, and absence of comorbid oppositional defiant disorder. Children on stimulant at evaluation improved significantly on ADHD symptoms compared to those off stimulant. Closer monitoring for side effects, educating families, involving children in treatment decisions and behavioral therapy for oppositional problems may enhance adherence.
ACKNOWLEDGEMENTS

I would like to express my sincere appreciation and gratitude to the following people:

To my supervisor, Dr. Russell Schachar who always had the time, interest and patience to help me on this research project. Without his constant encouragement and guidance, this thesis would not have been possible. Thank you very much for all your help.

To my committee members, Drs Howard Barbaree and Gerald Devins for their time, challenging questions and constructive criticisms.

To my loving parents who were supportive, encouraging, and understanding. I thank both of you for instilling in me the importance of education and for giving up so much to complete my thesis.

To my friends and colleagues who were dwelling with me throughout this experience and supported me to get this far.
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Attention-deficit hyperactivity disorder (ADHD) is one of the most prevalent and persistent disorders of childhood and adolescence. Well-controlled short-term studies have found that stimulant medication is effective in ameliorating the core and associative symptoms of ADHD. However, the existing long-term treatment studies show poor outcome of these children even when medicated. Inadequate adherence to the medication may be one of the prime reasons for the limited benefits observed in long-term studies. Information is lacking on adherence among ADHD children over extended periods of treatment. The objectives of the present study were 1) to document adherence to stimulants over a 3-year period; 2) to investigate the reasons for non-adherence; 3) to predict those who adhere to stimulants; and 4) to evaluate whether adherents experience greater improvement on behavior and on academic attainment.

The main purpose of the first three chapters is to provide background information for the problems posed by the present study. Chapter 1 presents a description of ADHD, the impairment associated with the disorder, the assessment of the disorder and the diagnostic process. Chapter 2 provides a critique of short- and long-term studies of the effects of the stimulant treatment. Chapter 3 reviews adherence in general, describes what is known about adherence to stimulants and delineates the requirements of a long-term adherence trial. In addition, this chapter presents the objectives of the present study. Chapter 4 describes how the study was conducted and Chapter 5 presents the findings of the study. The significance of the findings is discussed in Chapter 6 and implications of the findings are reported in Chapter 7.
CHAPTER I
ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN CHILDREN

This chapter provides a brief summary of attention-deficit hyperactivity disorder (ADHD). Although it is a diagnosis applied to adults as well as to children, this review focuses primarily on children because they constitute the majority of individuals receiving stimulant medication (Shukla and Otten, 1999). The impairment associated with ADHD and poor outcome require affected individuals to be diagnosed and treated. The main purpose of this chapter is to inform the reader what these debilitating features of ADHD are and how the disorder is assessed.

FEATURES

ADHD is characterized by developmentally inappropriate levels of restlessness, inattentiveness, and impulsivity. It is one of the most prevalent psychiatric conditions among school-aged children. According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), about 3% to 5% of children in North America are affected by this disorder. ADHD is about four to nine times more prevalent among boys than among girls (American Psychiatric Association, 1994).

In the past, children with one or more of these symptoms were labeled with different terms, such as minimal brain damage (prior to DSM-II, Clements & Peters, 1962), hyperkinetic reaction (DSM-II & American Psychiatric Association, 1968), attention-deficit hyperactivity disorder (DSM-III-R & American Psychiatric Association, 1987), and attention-deficit / hyperactivity disorder (DSM-IV & American Psychiatric Association,
Although all these terms share many of the symptoms and are sometimes used interchangeably, they are not always equivalent.

Core symptoms

At present, ADHD is a diagnosis applied to children and adults who consistently display certain characteristic behaviors over a period of time. The most common behaviors fall into two categories of nine symptoms: inattention and hyperactivity - impulsivity. The current diagnostic criteria (DSM-IV) for ADHD are presented in Table 1. According to DSM-IV, six or more symptoms must be present from at least one of the two categories (inattention, hyperactivity-impulsivity) to make the diagnosis of ADHD. In addition, the behavioral symptoms must persist for six or more months and must begin before age seven. It is also required that the identified symptoms be impairing at home and at school (American Psychiatric Association, 1994).

Associated symptoms and comorbid conditions

Children with ADHD are at higher risk for developing more problems than expected compared to unaffected children of the same age. The association of several disorders is known as comorbidity. The disorders that are commonly comorbid with ADHD include other behavioral, emotional, academic, and social problems. Hyperactive children often have deficits in adaptive functioning which is comprised of social (e.g., relationships with their peers, teachers and parents), communicative (e.g., writing letters), and self-care skills (e.g., taking medication properly) (Roizen, Blondis, Irwin & Stein, 1994; Stein, Szumowski,
Table 1. Diagnostic criteria for Attention-deficit/Hyperactivity Disorder *

A. Either (1) or (2):

(1) six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention
(a) often fails to give close attention to details or makes careless mistakes in school, work, or other activities
(b) often has difficulty sustaining attention in tasks or play activities
(c) often does not seem to listen when spoken to directly
(d) often does not follow through on instructions and fails to finish school work, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
(e) often has difficulty organizing tasks and activities
(f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
(g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
(h) is often easily distracted by extraneous stimuli
(i) is often forgetful in daily activities

(2) six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity
(a) often fidgets with hands or feet or squirms in seat
(b) often leaves seat in classroom or in other situations in which remaining seated is expected
(c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
(d) often has difficulty playing or engaging in leisure activities quietly
(e) is often "on the go" or often acts as if "driven by a motor"
(f) often talks excessively

Impulsivity
(g) often blurts out answers before questions have been completed
(h) often has difficulty awaiting turn
(i) often interrupts or intrudes on others (e.g., butts into conversations or games)

(Continued)
Table 1 cont.

B. Some hyperactive-impulsive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).

D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Code based on type:

314.01 Attention-Deficit/Hyperactivity Disorder, Combined Type: if both Criteria A1 and A2 are met for the past 6 months

314.00 Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type: if Criterion A1 is met but Criterion A2 is not met for the past 6 months

314.01 Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactivity-Impulsivity Type: If Criterion A2 is met but Criterion A1 is not met for the past 6 months

Coding note: For individuals (especially adolescents and adults) who currently have symptoms that no longer meet full criteria, "In Partial Remission" should be specified.

*Adapted from DSM-IV (American Psychiatric Association, 1994)
Blondis, & Roizen, 1995). Oppositional defiant disorder (ODD) consists of problems such as refusing to comply, temper tantrums, stubbornness, and verbal hostility towards adults; it is found in about 35% of the clinically referred ADHD children. About 30% to 50% of children with ADHD may have conduct disorder (CD) with problems such as lying, stealing, truancy, and physical aggression. Likewise, about 25% of children with ADHD are likely to be diagnosed with comorbid anxiety disorder (Biederman, Newcorn, & Sprich, 1991). In addition, these children perform less well in school. Such poor performance could be due to their disruptive behavior in the classroom or could be due to an actual learning disability (LD). LD is a disorder defined as the discrepancy between one’s potential for learning (intelligence) and what one achieves at school. About 20% of ADHD children are likely to be diagnosed with LD (Semrud-Clikeman, Biederman, Sprich-Buckminster, Lehman, Faraone, & Norman, 1992). As a result, children with ADHD are more likely to fail a grade, achieve low marks and to be placed in special classrooms compared to their peers (American Psychiatric Association, 1994).

**Outcome**

About 70% of children diagnosed as ADHD in childhood continue to meet the diagnostic criteria for the disorder in adolescence (Gittelman, Mannuzza, Shenker, & Bonagara, 1985; Barkley, Fischer, Edelbrock, & Smallish, 1990; Klein and Mannuzza, 1991) and about 65% in adulthood (Mannuzza, Klein, Bonagara, Malloy, Giampino, & Addalli, 1991). The associated symptoms of academic underachievement and adaptive dysfunction also continue be significant problems in adolescence (Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1993; Gittelman et al., 1985). As adults, hyperactive children may have obtained
less formal education and achieved lower occupational status compared to their normal controls (Mannuzza et al., 1993).

It is common that some children show symptoms mainly at home, some mainly in school, and others in both settings (American Psychiatric Association, 1994). It has been found that the pervasive type of the disorder (presence of symptoms in more than one setting, such as home and school) is more likely to persist over time than the situational type in which the symptoms are present in only one setting (e.g., home) (Schachar, Rutter, & Smith, 1981). Psychosocial adversity and family dysfunction are also important predictors of persistence of ADHD into adolescence (Biederman et al., 1996a).

In addition to persistence of ADHD symptoms, development of other disorders over the course of the disorder has been documented. Development of psychoactive substance use disorder (PSUD) in adolescence has been associated with comorbid conduct disorder in childhood and persistence of ADHD into adolescence (Biederman et al., 1996b; Biederman et al., 1997). Children who retain ADHD symptoms as adults are also at higher risk for developing antisocial personality disorder than are those whose symptoms remitted (Mannuzza, Klein, Konig, & Giampino, 1989). In summary, pervasiveness of ADHD, psychosocial adversity and the presence of comorbid disorders are significant variables associated with poor outcome. Therefore, evaluations of these factors are needed when evaluating treatment outcome.
ASSESSMENT

The diagnosis of ADHD is usually based on information gathered from an interview of the child's parent(s), the results of rating scales completed by the child's parents and teachers, a direct examination of the child, and a physical examination. Because symptoms displayed by ADHD children usually vary across different settings and because parents and teachers may have different perceptions of the child, input from both the parents and teachers is essential. Since ADHD children are more likely to have an LD, they must be assessed for intellectual ability and academic functioning. In addition, medical history is obtained and overall functioning is assessed to rule out other psychiatric and medical conditions (e.g., middle ear infection and thyroid disease). An assessment for comorbid disorders such as ODD and CD is also conducted. Tourette syndrome for which pharmacological treatment is contraindicated is also evaluated (American Psychiatric Association, 1994; Dulcan, 1997; Goldman, Genel, Bezman, & Slanetz, 1998). Tourette syndrome is a chronic disorder characterized by multiple motor and vocal tics. Some individuals with Tourette syndrome show an increase in their tics when stimulant medication is given to treat comorbid ADHD (Sverd, Gadow, & Paolicelli, 1989). In summary, it is important that children are rigorously assessed as described above to make a confirmed diagnosis of ADHD and to initiate the treatment. The next chapter will discuss the most widely used intervention, stimulant medication for treating ADHD.
CHAPTER II

TREATMENT OF ADHD: STIMULANT MEDICATION

Since a majority of children with ADHD continue to be symptomatic as adults and may develop other psychopathologies such as antisocial personality disorder and psychoactive substance use disorder over time, investigators have studied a wide variety of treatments to manage the symptoms. This chapter provides a brief discussion of available treatments and reviews the most frequently used treatment, stimulant medication, in detail.

TYPES OF TREATMENTS

In the past, both pharmacological and non-pharmacological interventions have been studied in treating ADHD symptoms. The two major pharmacological treatments are stimulant and anti-depressant medication. The two major non-pharmacological treatments are behavior therapy and parent training. Behavior therapy has been used to improve problematic behaviors of the child by modifying the environmental conditions that elicit such problems. Parent training in behavior management skills involves teaching parents to deal with their children's behavior by reinforcing appropriate behaviors and ignoring or punishing inappropriate behaviors. Of all the treatments, stimulant medication has been the most intensively studied. A comprehensive review of available studies indicates that stimulant medication is more effective than anti-depressant or non-pharmacological treatments in treating core and associated symptoms of ADHD. In addition, there is little evidence that combination of stimulant and non-pharmacological treatments is more effective than stimulant alone (Shukla and Otten, 1999, Jadad, 1998).
STIMULANT MEDICATIONS

Stimulant medications are called sympathomimetic compounds because of their structural similarity to certain neurotransmitters. Stimulants are thought to increase the concentration of catecholamines (dopamine and norepinephrine) in the synaptic cleft by inducing their release from presynaptic neuron and blocking their reuptake. Although the mechanism of stimulant action on ADHD brain is not fully understood, it has been suggested that manifestations of ADHD results from decreased dopamine and increased norepinephrine function (Greenhill, 1992; Schachar and Ickowicz, 1999).

The three stimulants that are employed in the treatment include methylphenidate (MPH, brand name: Ritalin), dextroamphetamine (DEX, brand name: Dexedrine), and pemoline (brand name: Cylert). In terms of short-term effectiveness, there is little difference between these different stimulants (Shukla and Otten, 1999). On average, about 70% of children have been found to respond favorably to one of these stimulants (Spencer, Wilens, Harding, O'Donnell, & Griffin, 1996a). MPH has been the most commonly used medication and is used by about 1.5 million US children with ADHD (Safer, Zito and Fine, 1996). It has a plasma half-life of 2 to 3 hours and is metabolized completely within 12 hours. The short acting property of MPH requires that medication be taken two or three times a day to suppress the symptoms throughout the day (Greenhill, 1992). Due to the brief clinical efficacy of standard preparation, sustained release was introduced for both MPH (slow release) and DEX (spansule) so children need not take the midday dose (at school). The sustained release form of the pill contains a wax-matrix vehicle, which allows MPH or DEX to be released slowly. It has been shown to be as effective as standard preparation and
recommended when multiple dosing is problematic (Lawrence, Lawrence & Carson, 1997). Pemoline has a longer duration and therefore it makes once-per-day dosing possible (Greenhill, 1992). However, it is not used currently because of the reports of hepatic failure (Berkovitch, Pope, Phillips, & Koren, 1995; Shukla and Otten, 1999; Dulcan, 1997).

Numerous short-term well-controlled studies have shown that stimulants are effective in treating the symptoms of ADHD (Shukla and Otten, 1999; Jadad, 1998; Jacobvitz, Sroufe, Stewart, & Leffert, 1990). However, there are only a few studies that have examined the effects of stimulants over the long-term (Schachar and Tannock, 1993). The following section reviews the effects of stimulants on core and associated symptoms of ADHD from short- (less than 12 weeks in duration) and long-term studies (12 or more weeks in duration), focusing specifically on behavior and academic functioning.

**Short-term effects**

Stimulant medication has been shown to improve the core behavioral symptoms of ADHD. It increases attention span and decreases restlessness and motor activity. Parents, teachers, and other professionals consistently report the improvements. In addition, associated symptoms such as oppositional and aggressive behaviors and the relationships with family, peers, and teachers are improved. These benefits are apparent very soon after administration of medication and dissipate rapidly when medication is discontinued (Jacobvitz et al., 1990).

Well-controlled studies have shown positive effects of stimulants on academic functioning. These studies consistently show that stimulants increase the number of items attempted, accuracy and efficiency of items completed in mathematical and reading tasks.
These benefits have been documented in both the laboratory setting and the regular classroom. And, these stimulant-induced changes do not appear to be related to comorbid learning disability or conduct disorder (Elia, Welsh, Gullotta, & Rapoport, 1993; Douglas, Barr, O'Neill, & Britton, 1986).

**Long-term effects**

Over the long-term, studies have shown that stimulant medications reduce the severity of the core symptoms of inattention, impulsiveness, and restlessness (Schachar and Tannock, 1993). However, the benefits dissipate once the medication is discontinued even after periods of lengthy treatment (Brown, Borden, Wynne, Schleser, & Clingerman, 1986). Beneficial effects of stimulants on poor social relationships, conduct problems, and low self-esteem are apparent but appear to be limited (Schachar and Tannock, 1993).

Academic performance over the long-term has been usually assessed by measures such as Wide Range Achievement Test (WRAT). Such standardized tests are designed to reflect changes for an entire school year. It was expected that academic performance would be improved over several years based on the increase in academic productivity and on behavioral improvement observed in short-term trials. However, such improvement has not been documented in long-term studies (Schachar and Tannock, 1993; Richters et al., 1995; Jadad, 1998).

**Side effects**

The most prevalent side effects of stimulants include irritability, insomnia, loss of appetite, and headache. Some children experience rebound when the effects of the
medication wear off (4 to 15 hours after taking the last dose). Rebound consists of increased excitability, activity, irritability, and insomnia and may resemble worsening of symptoms. These side effects are usually mild, dose-related, and can be managed by changing the dosage (Ahmann, Waltonen, Olson, Theye, Van Erem, & LaPlant, 1993; Goldman et al., 1998; Jadad, 1998). Many of the reported side effects associated with stimulants such as insomnia, irritability and anxiety are similar to the symptoms of ADHD and therefore the presence of these symptoms must be evaluated before initiating the treatment (Fine and Johnston, 1993; Ahmann et al., 1993). A rare adverse effect of stimulant medication is tics. A recent study has shown no evidence of tics exacerbation in children treated with stimulant medication, whether or not the children have mild tics before the treatment (Law and Schachar, in press). However, it must be used with caution for children who have Tourette syndrome or have a family history of tics (Schachar and Ickowicz, 1999; Gadow et al., 1995; Ahmann et al., 1993; Schachar, Tannock, Cunningham, & Corkum, 1997).

Parents may be concerned that treating ADHD children with stimulants for extended periods of time increases the risk for drug abuse. Prolonged stimulant use does not appear to increase the risk for future drug use or abuse (Shukla and Otten, 1999; Goldman et al., 1998; Hechtman, Weiss, & Perlman, 1984). However, because of the presence of comorbid CD or family history of drug abuse, ADHD children may be at increased risk for drug abuse and therefore need close monitoring (Dulcan, 1997). Stimulant treatment has an immediate impact on appetite and causes weight loss in many children (Schachar et al., 1997). However, there is little evidence that ultimate height and weight are adversely affected by even prolonged treatment (Spencer, Biederman, Harding, O'Donnell, Faraone, & Wilens, 1996b). Nevertheless, periodic evaluation of height and weight has been recommended for
children on stimulant medication for prolonged periods. It is also recommended that these children have drug holidays during which the child stops taking the drug for specified periods of time usually school holidays. Although research does not support this practice, drug holidays have been considered an important aspect of the clinical treatment protocol to prevent growth suppression and to evaluate the need for medication (Shukla and Otten, 1999).

**Methodological problems**

The effects of long-term stimulant use have been far less clear, considering the preponderance of evidence for short-term efficacy on behavioral and academic functioning. Existing long-term studies with a minimum of 3 months in duration have been questioned for many methodological problems including weak study design, low and unspecified attrition, non-adherence and failure to ensure optimal treatment (Schachar and Tannock, 1993; Richters et al., 1995). Specifically, studies with longer duration (more than one year) were usually non-randomized, had a larger percentage of subjects who withdrew from the study (attrition) and limited description of treatment withdrawal (non-adherence). The next chapter will discuss the issues of poor adherence to treatment in detail.
CHAPTER III
ADHERENCE* TO STIMULANT MEDICATION

Adherence or compliance has been defined as "the extent to which a person's behavior (in terms of taking medication, following diets, or executing lifestyle changes) coincides with medical or health advice" (Haynes, 1979, pp1-2). Poor adherence to treatment may be one of the major factors for poor outcome in all disorders, particularly in ADHD (Firestone, 1982; Sleator, Ullmann, & Von Neumann, 1982; Brown, Borden, Wynne, Spunt, & Clingerman, 1987). More than 50% of randomized trials, which were conducted to evaluate the effectiveness of the stimulant treatment, failed to measure or report the degree of adherence to medication (Jadad, 1998). When it has been examined, adherence to stimulant has been examined only for several months and shown to be problematic (i.e. low) among ADHD children (Kauffman, Smith-Wright, Reese, Simpson, & Fowler, 1981; Firestone, 1982; Brown, Borden, & Clingerman, 1985; Johnston and Fine, 1993).

Since non-adherence has been implicated as a potential factor for poor long-term outcome, the goals of the present study are to examine adherence over several years, to investigate the reasons for non-adherence, to identify salient factors influencing adherence and to examine whether subjects who adhere to stimulants receive greater benefits on behavioral and academic functioning compared to those who do not. This chapter supports the need for a study examining long-term adherence to stimulant medication by examining

* The term 'adherence' was initially introduced to overcome the negative connotation of the term 'compliance'. The term 'compliance' was critiqued because it suggested that patients need to follow the orders passively whereas 'adherence' suggested that patients actively seek to cooperate with the treatment decisions. Since compliance is still used widely, in

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the importance of adherence and reviewing the findings from pediatric research in general and from ADHD research.

The chapter is organized into the following sections: 1) the importance of patient adherence; 2) methodological features of an adherence study; 3) literature review pertaining to stimulant adherence; and 4) conceptual framework of the study.

THE IMPORTANCE OF PATIENT ADHERENCE

Poor adherence to medication is a serious concern for patients, health care providers, researchers, and society as a whole. The main concern for patients is poor long-term treatment outcome such as persistence of the disorder into adulthood, development of other serious conditions, and the need for more intensive treatments. For health care providers, it is important to know whether the patient has taken the medication to evaluate its effects. Inappropriate treatment decisions may be made if a physician is unaware of poor adherence to prescribed therapy. Poor adherence also poses a significant problem for researchers who try to evaluate the effectiveness of a medication in clinical trials. If fewer subjects adhere to the treatment, the statistical effect of medication decreases even when the medication is effective. Therefore, to compensate, researchers must increase the sample size in order to detect an effect of the intervention. This increases the cost and time needed to conduct the trial (Hasford, 1999). Finally, the economic cost associated with poor adherence is also clear. Such cost is usually calculated by the lost productivity due to increased severity of the illness and increased hospital admissions, which could have been prevented if patients

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the present study, it is assumed that both terms are equivalent and both terms are used interchangeably throughout the study.
adequately adhered to the treatment (Magometschnigg, 1999). If the treatment is effective, then the burden to society (in terms of service delivery) increases with decreasing adherence.

These serious consequences of poor adherence to treatment demonstrate the need for research to examine factors related to non-adherence so they can be identified and modified to minimize their effects. In this way, patients can be offered the full benefits of the treatment.

**NECESSARY DESIGN FEATURES**

Sackett and Snow (1979) identified a set of methodological standards for two purposes: to help new researchers to design and execute studies that would produce valid results and to help readers to assess the validity of existing studies. The following section describes these issues pertaining to the studies of stimulant adherence.

**Description of the sample and treatment setting**

The way in which the sample is selected and the setting in which the study is conducted are important. Omission of such descriptions can distort conclusions about adherence. Specifically, descriptions of the treatment setting are crucial in interpreting the results because of their relation to adherence. For example, long waiting time, lack of continuing care (e.g., no follow-up appointments), and difficulty in getting the care (e.g., type of clinic) have been negatively related to treatment adherence (Haynes, 1979).

In addition, Sackett (1979) has recommended the use of samples that include newly diagnosed patients who are initially prescribed a treatment for that particular disease. Such a
sample is selected to control for factors such as prior treatment and duration of illness that may influence adherence.

**Definition of adherence**

Studies examining adherence have used many different definitions, ranging from delay in dosing to missing sequential doses to complete cessation of the treatment. Patients may completely adhere, partially adhere, or not adhere at all. Because the term 'adherence' refers to a wide variety of behaviors, it must be explicitly defined for each treatment and for each disorder. Since ADHD is a chronic condition and since medication is effective only when it is taken, children with ADHD are usually prescribed stimulant on a daily basis for several years. However, it is recommended that children with ADHD have drug holidays. Therefore, adherence to stimulant medication must be defined as taking the medication throughout the year with drug holidays scheduled during school holidays.

**Method of measuring adherence**

In general, adherence can be measured by direct or indirect method. Direct methods involve physiological or biochemical measures to test the presence of drug by-product such as blood or urine analysis. Indirect methods involve self-report from patients or other informants or behavioral reports such as pill counting and recording devices. Each method is associated with drawbacks and no single measure is absolutely accurate in capturing all non-compliers. The method must be chosen according to the nature of the treatment and the objectives of the study. It must also be accepted that there will be a degree of error regardless of the method chosen.
The nature of stimulant treatment poses difficulties in employing any direct method of measuring adherence. Because of the short half-life of stimulant medication, the presence of by-products can be determined only if the assay is done shortly after the medication is taken. As it has been shown that patient compliance increases shortly before and after clinic visits, such a test may not indicate whether the patient took the medication between the visits (Cramer, Scheyer, & Mattson, 1990). This effect would result in highly inaccurate assessment of adherence over prolonged therapy. For example, Johnston and Fine (1993) found that urine analysis done at a randomly chosen clinic visit yielded 100% compliance for all the patients whereas parent and teacher reported less compliance. Another concern with the direct method is the biological differences between subjects in absorbing, metabolizing, and excreting the drug.

Indirect methods such as pill counts or electronically monitored containers may also have problems. For example, measuring adherence by unused pill counts is limited by the necessity of returning the pill bottles. For conditions such as ADHD where stimulant medication is prescribed only once a month for several years, families may not always return the bottles. In addition, pill counts or electronic devices cannot prove that the medication has been ingested (Gordis, 1979). Since children often dislike medication and try to avoid taking it (Sleator et al., 1982) and pills are taken at school and at home, using such a method to measure adherence may not be accurate for children.

Verbal reports also have problems such as poor memory for details and self-reporting bias. Although, there are questions regarding the validity of interviews in measuring adherence, it has been suggested that verbal reports identify many non-adherents (Gordis, 1979). One study reported that information obtained from self-reporting, biochemical tests,
and urine analysis produced poorer results than those obtained from interview alone (Haynes, Taylor, Sackett, Gibson, Bernholz, & Murkherjee, 1980). The accuracy of the information obtained from interview can be increased if more than one informant is used. In addition, it is recommended that parents and children be questioned directly about their perspectives of the medication to understand why the medication is discontinued (Morris & Schulz, 1993).

In summary, adherence to long-term stimulant treatment would be best measured with a method that is non-invasive, is less expensive, and can be applied in clinical practice. As described above, there are administrative and technical difficulties in physiological, biochemical, and behavioral methods over the long-term and no single informant seems to be accurate. Therefore, obtaining information from more than one informant to probe the behavior over the long-term seems to be one of the effective, practical methods.

Adequacy of follow-up

Another important feature of adherence research is the inclusion of a sufficiently long and complete follow-up. Since duration of the treatment affects adherence, it is crucial that the length of follow-up closely coincides with the duration of the treatment. Many ADHD children are prescribed with stimulants over extended periods of time (Safer et al., 1996; Safer & Krager, 1994) and therefore studies examining adherence should also be examined over extended periods of time.

In addition, it has been shown that many patients constantly question the need for medications by altering the way they take the medication. Patients who decide to discontinue the medication at one point in time may decide to start the medication again (Morris & Schulz, 1993). In fact, there may be many "patterns" of drug use over the long-
term. Therefore, studies need to follow the subjects over the course of their treatment regardless of their medication status.

However, studies that require long follow-up periods often face the problem of high attrition (unavailability of subjects during the follow-up). Subjects who withdraw from the study may differ from subjects who continue to participate in the study in terms of outcome measures investigated (Cox, Rutter, Yule, & Quinton, 1977; Kazdin, Holland, & Crowley, 1997). Studies must ensure that the rate of attrition is low and a complete description of non-participants is provided so that the validity of the results is not threatened.

**LITERATURE REVIEW**

The following section reviews the few existing studies on adherence to stimulant medication with special attention to the methodological features described above (Table 2).

Kauffman et al (1981) studied adherence to medication in 12 male, hyperactive children between the ages of 6 to 12 years. In a triple-blind crossover design, subjects were randomly assigned to placebo, MPH, or DEX for 6 weeks in each condition. Adherence to medication was measured by weekly urine analysis. On average, about 67% of children adhered to MPH whereas about 61% adhered to DEX. The author concluded that poor compliance to medication might explain the inconsistencies found among stimulant studies of hyperactive children.
Table 2. Studies examining adherence to stimulant medication (MPH) in children with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Method(s) used</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaufmann</td>
<td>12</td>
<td>Urine analysis</td>
<td>percentage of pills taken</td>
</tr>
<tr>
<td>Firestone</td>
<td>56</td>
<td>Verbal report from parents</td>
<td>taking pills for 9 months</td>
</tr>
<tr>
<td>Brown</td>
<td>30</td>
<td>Verbal report from parents &amp; pill counts</td>
<td>no more than 24 pills being returned</td>
</tr>
<tr>
<td>Johnston</td>
<td>24</td>
<td>Verbal reports from parent, teacher &amp; physician, pill counts &amp; urine analysis</td>
<td>no pills missed according to all methods</td>
</tr>
</tbody>
</table>

Table 2. Cont.

<table>
<thead>
<tr>
<th>Author</th>
<th>MPH adherence</th>
<th>Attrition</th>
<th>Duration (months)</th>
<th>Factors associated with adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaufmann</td>
<td>67%</td>
<td>0%</td>
<td>1.5</td>
<td>-</td>
</tr>
<tr>
<td>Firestone</td>
<td>54%</td>
<td>14%</td>
<td>12</td>
<td>Gender, child's IQ, mother's IQ, mother's age</td>
</tr>
<tr>
<td>Brown</td>
<td>47%</td>
<td>50%</td>
<td>3</td>
<td>Severity of impairment, family conflict, child's IQ</td>
</tr>
<tr>
<td>Johnston</td>
<td>67%</td>
<td>0%</td>
<td>3</td>
<td>Mother's IQ</td>
</tr>
</tbody>
</table>
Firestone (1982) examined adherence to MPH in 76 hyperactive children between the ages of 5 and 9 years. Subjects were randomly assigned to MPH only or parent training and MPH for 12 months. About 25% of the families refused to place their children on medication. By the tenth month, about 45% of the children discontinued MPH after being assigned to MPH and the rate of non-adherence did not differ between the MPH only and parent training plus MPH groups. The major reasons given by the parents for non-adherence were that parents were uncomfortable with pills and children were reluctant to take pills.

Families were more likely to discontinue the medication if the child was female or if the child had a lower IQ. In addition, parents of non-adherents were more likely to be younger and have lower IQ than were parents of adherents. Side effects and symptom remission did not appear to be major factors for discontinuance. The author suggested that lack of effectiveness found in long-term studies might partially be due to non-adherence to stimulant medication.

Brown et al (1985, 1987, and 1988) examined the characteristics of families and children, who completely adhered, partially adhered, or dropped out of the study. Thirty ADD children, between the ages of 6 to 12 years were randomly assigned to MPH or placebo for a 3-month period. Medication compliance was measured by pharmacist's monthly pill counts and by parents' report at the end of the treatment. Although parents underestimated the number of pills missed, estimates obtained from pharmacist and parents correlated significantly. Children were defined as partially adherent if they missed two or more doses per week. About 50% of the original sample terminated their participation in the study and about 25% partially adhered. Children who failed to complete the study protocol demonstrated more severe impairments than did those who completed. Interestingly, those
who completed the treatment protocol showed greater family conflict compared to those who
did not. The authors suggested that recognizing and admitting difficulties might be an
important part of treatment adherence. Minority subjects and those with lower IQ missed a
greater number of pills than did those who were white and those with high IQ. The results of
the study suggested that children of lower socioeconomic status might be at a greater risk for
non-adherence (Brown et al., 1987). Furthermore, number of pills missed correlated
positively with difficulties in concentration, attention, and self-control (Brown et al., 1988).
It was concluded that subjects who discontinued medication were in a greater need of
treatment than were those who adhered.

Johnston and Fine (1993) conducted a study to examine whether adherence to MPH
was influenced by parents' acceptance of the MPH treatment, by satisfaction with the
treatment, or by method of treatment evaluation. Twenty-four children with ADHD were
randomly assigned to either the placebo-controlled MPH trial (MT) or the typical clinical
procedure (TCP) condition. In the MT, children were assigned randomly across days to
MPH (high or low dose) or to placebo and behavioral ratings were completed every day. In
the TCP, MPH dose was titrated. Subjects were followed every week for the first 3 weeks, at
6 weeks and at 3 months. Compliance to pills was measured by unused pill counts done at
each visit, by urine analysis done at a randomly chosen follow-up and reports from parents,
teachers, and physicians at the 6-week and 3-month follow-ups. Parents completed a
measure of acceptability at the start of the study and again at the end of the study along with
a measure of satisfaction. At the end of the study, both methods of evaluation (MT and
TCP) resulted in equal acceptance and compliance to MPH. However, parents were more
satisfied with MPH if they were in the MT group than if they were in the TCP group. On
average, 20% of the children failed to comply with the medication over 3 months. However, noncompliance varied from 0% to 30% depending on the measure used and the time assessed. The only factor found to be correlated with compliance was maternal IQ.

Many long-term studies that have been conducted to examine the outcome of children at adolescence and adulthood provided little information regarding the treatment received by these children. Only one study has examined medication use over several years and found that on average, hyperactive children were on stimulant medication for 36 months over an 8-year period (Barkley et al., 1990). Since the purpose of the Barkley et al (1990) study was to report the adolescence outcome of ADHD children, the authors did not report why these children had such incomplete treatment. However, 80% of these hyperactive children retained significant behavioral problems at adolescence.

Summary of findings

The literature review shows that about 45% to 50% of the children terminated the treatment protocol within several months. Subjects who continued to adhere to the medication missed about 25% to 35% of the pills. The magnitude of the problem has prompted researchers to suggest that poor adherence to the treatment may have been one of the major barriers to poor outcome observed in the existing long-term studies. The most salient factors that have been found to correlate with MPH adherence include child’s age, IQ, and severity of the impairment.
Limitations of existing studies

Similar to studies in other diseases and treatments, several methodological pitfalls can be identified from adherence studies in ADHD. The following section briefly explains the issues of these studies.

Selection and description of the sample. Most of these studies had a small sample size, an inadequately described sample, and a lack of information about the recruitment process and the setting in which the study was conducted. Specifically, no study reported the proportion of subjects with comorbid conditions, which could have influenced adherence.

Definition and measure of adherence. All studies have combined those who discontinued the treatment with those who terminated the study when examining the characteristics of non-adherents. Studies have used different definitions of adherence (percentage of pills missed vs. termination of the treatment) and different methods to measure adherence (pill counts vs. verbal reports).

Adequacy of follow-up. Despite the persistence of the disorder and chronic nature of the treatment, the existing studies did not follow the subjects long enough. Only one study proposed to follow subjects for 3 years but failed to report how they fared once they discontinued the medication (Firestone, 1982).

The studies on stimulant adherence of ADHD children offer little conclusive evidence regarding the incidence and factors associated with adherence due to the small
number of such studies, differing definitions and method of measuring adherence, and inadequate follow-up. The review of studies indicated a need for examining stimulant adherence over the long-term. The following section describes the conceptual framework of the present study.

**CONCEPTUAL FRAMEWORK**

In the present study, a sample of newly diagnosed ADHD children was prospectively followed from their first trial of MPH treatment. The sample selected was typical of a child psychiatric clinic where many get assessed and treated with medication. A multi-informant method and a clear and precise definition of adherence were used to document adherence over 3 years. Reasons for non-adherence, factors associated with adherence, and relationships between adherence and outcome were examined. The following section describes the rationale for each hypothesis to be tested in the present study.

**Reasons for non-adherence**

Patients' perspective of non-adherence is one of the important steps toward understanding the issue of non-adherence. Patients may not be ready to suffer the immediate negative effects of the medication (e.g., side effects) in order to prevent the onset of future illness. Alternatively, the treatment regimen may not fit into the patient's life-style. Therefore, parents and children should be asked about the reasons for stopping the medication. This would allow clinicians to recognize and overcome the difficulties patients have in following the treatment regimen and to improve the outcome of patients. How patients and their families view adherence can be explained from a physical, economic,
psychological, or social perspectives (Morris & Schulz, 1993). Morris and Schulz (1993) have argued that noncompliance can be explained partly by patients' experience with treatment. For example, symptomatic improvement or side effects following the treatment may enhance noncompliance. Alternatively, cost of the medication or perceived financial stress (economic) may also cause patients to discontinue the treatment. Psychologically, patients may alter the treatment regime to take control over their condition, to test the need for such treatment, or to avoid the stigma of the disorder. In addition, the patient's relationship with the physician, information obtained from media and social interaction with others such as relatives and friends may also change the way a patient takes his medication.

Only one study, (Firestone, 1982) has examined the reasons for non-adherence and reported that those who discontinued MPH did so because parents felt that medication was not necessary or that children refused to take it. Since we lack adequate information as to how ADHD children and their parents view non-adherence, the present study investigated why children discontinued stimulants.

**Determinants of long-term adherence to stimulants**

Since no other research had examined long-term adherence to stimulants, the present study focused on the relationships between long-term adherence and factors that are specific to ADHD. A comprehensive review by Haynes (1979) identified about 200 variables that are associated with adherence to treatment in general. These can be categorized into one of the following groups: 1) characteristics of the patients; 2) characteristics of the illness; 3) characteristics of the treatment regimen; and 4) characteristics of the health care provider and healthcare setting. Although there are many factors associated with adherence, for the
present study, the author has chosen factors that are related to the child, the family, and the
disorder. The characteristics of treatment (e.g., duration of the treatment), relationship
between patient and physician, and setting were not examined, since subjects in the present
study were treated similarly and followed from their initial treatment. The following section
describes how patient-related, family-related, and illness-related factors may influence
adherence to stimulant medication over the long-term.

Patient / family factors

Child-related. Sleator et al (1982) interviewed hyperactive children, 8 years or older about
how they feel taking stimulant medication. He found that many children disliked the
medication and used various methods to avoid the medication such as refusing to take it,
throwing it away, or not reminding adults when they forget. More than 75% of the children
who avoided taking the pills were older than 12 years. Therefore, older children may exert
more control over the medication and refuse it more successfully than younger children (or
children who refuse and discontinue the medication are likely to be older in age compared to
those who discontinue for other reasons (e.g., side effects)). It has been shown that more
than 20% of mentally retarded children discontinued stimulant medication due to motor tics
and severe social withdrawal (Handen, Feldman, Gosling, Breaux, & McAuliffe, 1991). The
authors have suggested that mentally retarded children with ADHD may experience more
side effects compared to the nonretarded ADHD children. In addition, fewer girls with
ADHD have been taking stimulant medication compared to males (ratio of female to male is
lower for the prevalence of stimulant use than for the prevalence of ADHD) (Safer, 1994;
Safer et al., 1996). Greater tolerance of ADHD symptoms by family members for female
children than for male children may be one of the reasons for gender differences in medication use. Consequently, families may be less likely to adhere to stimulant medication if the child is female than male. Therefore, child's IQ and sex may be important child-related factors and their relations to adherence have been demonstrated in previous studies (Firestone, 1982; Brown et al., 1987). The present study examined whether child's age, IQ, and sex are associated with adherence to stimulants over the long-term.

*Family-related.* Family functioning and psychosocial factors may be important determinants of adherence since children with ADHD are more likely to come from dysfunctional families and to live with high levels of psychosocial adversity (Biederman et al., 1995; Szatmari, Offord, & Boyle, 1989). Having more family problems at home may interfere with parental supervision in giving the medication over the long-term. A review by Cromer (1991) reported that children who had parental support were more likely to adhere to the treatment compared to children who had no support. However, the study by Brown et al. (1985) found that those who adhered and those who partially adhered had more family conflicts than did those who terminated the treatment. The importance of family involvement is clear. However, whether having problems in the family is related to adherence in a negative or positive way is not clear. Therefore, the present study examined whether having family problems interfere with adherence to stimulants as in other conditions. In addition, Brown et al. (1987) suggested that families of lower socioeconomic status might be at a greater risk for discontinuation and therefore the present study also examined the role of psychosocial adversity in adherence to stimulants.
**Disease factors**

Diagnostic factors selected in the present study include severity of symptoms and presence of concurrent conditions.

*Severity of the symptoms.* Children with ADHD often behave differently under different settings (home and school). Consequently, symptoms reported by parents and teachers may be different in severity. Therefore, as reported by Brown et al. (1988), children who have more symptoms according to parents and teachers may be less likely to be adherent compared to children who have fewer symptoms. Since parents may judge the importance of treatment based on the behavior at home, parent-reported symptoms would have the greater impact on adherence compared to teacher-reported symptoms. Therefore, the present study examined the effects of parent-reported and teacher-reported symptoms on adherence (separately).

*Comorbid disorders.* Since 65% of these children will have at least one other condition, the presence of these comorbid disorders may also be significant in determining adherence. For example, Stine (1994) has suggested that children with anxiety may refuse because of fears in taking the medication. Alternatively, children with comorbid ODD or CD may feel that medication controls them and may hesitate to take the pills. Since no study had examined the effects of comorbidity on long-term adherence to stimulants, the present study focused on these factors.
Relationship between adherence and clinical effects

Since it has been suggested that lack of adherence to stimulants may explain the limited long-term benefits of stimulants, it must be known whether adherents experience greater improvements in behavior and academic functioning than do non-adherents. Therefore, the effects of adherence on behavior and academic functioning were also evaluated.

THE STUDY

Objectives

1) To document the incidence of adherence to stimulant over a 3-year period.

2) To investigate reasons for non-adherence.

3) To identify predictors of stimulant adherence.

4) To evaluate whether adherents receive greater benefits on behavior and on academic attainment than do non-adherents.

Hypotheses

1. It is hypothesized that ADHD children are less likely to adhere to the treatment over extended periods of time due to child's older age and with longer duration of the treatment.

2. It is hypothesized that patients and their families discontinue medication because of negative physical experiences with the medication, negative economic aspects of the medication, the psychological meaning of the medication (e.g., viewing medication as an external control), or due to social interaction with others (e.g., peer conformity).
3a. Age, IQ, sex: It is hypothesized that children who are female, older, with lower IQ are less likely than others to be adherents.

3b. Family dysfunction and psychosocial adversity: It is hypothesized dysfunctional families and families with high levels of psychosocial adversity are less likely to adhere compared to others.

3c. Severity of ADHD symptoms at home and school: It is hypothesized that children who have more symptoms at home and school are less likely to be adherents compared to children who have fewer symptoms. The impact would be greater for parent-reported symptoms than for teacher-reported symptoms.

3d. Comorbid disorders (ODD, CD, and anxiety): It is hypothesized that ADHD children who have ODD, CD, or anxiety are less likely to be adherent than ADHD children with no comorbid conditions.

4. It is hypothesized that children who adhere to stimulant medication will show greater improvements in behavioral (ADHD, ODD, CD) and academic functioning (math, spelling, and reading) compared to those who do not adhere.
CHAPTER IV: METHOD

SUMMARY

This is a systematic follow-up of 71 children, who a) had a confirmed diagnosis of ADHD; b) were part of a larger sample of 91 children enrolled in a randomized controlled trial (RCT) for 12 months (described below); and c) had initiated MPH treatment within the first 5 months of the enrollment. Adherence to stimulant medication was documented annually through semi-structured interviews from parent, teacher, and the child for three years. Measures of potential predictors of adherence were obtained at baseline using standardized tests (for IQ and academic functioning), semi-structured interviews (for severity of symptoms and presence of comorbid disorders) and questionnaires (for family characteristics). Clinical effects of adherence were evaluated using behavioral checklists and academic testing done at the 3-year follow-up.

PHASE I: RANDOMIZED CONTROLLED TRIAL

Subjects

The subjects were 91 children, ages 6 to 12 years with a confirmed diagnosis of ADHD. At first, three hundred and two children were referred mainly from medical doctors, school-board psychologists, and mental health agencies for assessment and treatment of ADHD. Children were eligible to participate in the study if they: 1) were between the ages of 6 and 12 years; 2) had six out of 14 symptoms on the ADHD Rating Scale, based on an

* The 3-year follow-up was completed when I joined the lab. I was involved in subsequent follow-ups of the study and coding and analysis of 4- and 5-year data.
informal and general description of the child's behavior at home (DuPaul, 1991); 3) had parent's report of similar complaints at school; 4) had no history of MPH or any other medication; 5) were willing to participate in a randomly assigned treatment group; and 6) had at least one parent able to communicate in English. Children were excluded if they attended a full-time residential or day treatment program or had any neurological problem. Children who met the screening criteria (N=135) were then rigorously evaluated using a parent interview, a child assessment, and a telephone interview of each child's teacher. One hundred and five children met the final inclusion criteria (see 'Diagnostic criteria'). After discussing the complete description of the study procedure, risks and benefits of the treatments, 91 families agreed to participate in the study.

**Procedure**

*Selection procedure.* Upon referral, one of the parents was contacted by telephone to determine whether the child met the screening criteria for the study. If the child met the screening criteria and if the family was interested in the study, then a clinic visit was arranged. During the clinic visit, the parents were interviewed and the child was administered a battery of psychological and educational tests. Also, each child's teacher was interviewed by telephone. Parents and teachers completed behavioral checklists and parents completed a family assessment questionnaire. Diagnostic evaluation was made from parent interview, teacher interview, and child assessment. Those who met the diagnostic criteria were scheduled another visit to the clinic where the results of the assessment and study procedure were discussed. Written consent was obtained from those who chose to participate in the study.
Treatment. Subjects and their parents were randomly assigned to one of four groups: MPH + parent support, MPH + parent training, placebo + parent support, or placebo + parent training. For the present study, the two groups assigned to MPH and the two groups assigned to placebo were combined as there were no observed effects of the non-pharmacological treatments on the symptoms or on adherence to stimulants at 12 months (Schachar, Tannock, Cunningham, & Corkum, 1998). Of the 91 children, 46 children were assigned to MPH group and 45 children were assigned to placebo group. The dosage of the medication was started at 5 mg twice daily (morning and afternoon) and increased by 5-mg until reaching a target dosage of 0.7mg/kg BID while minimizing the side effects.

At the time of enrollment, all participants (families, teachers, and research staff) were blind as to the treatment assignment. Parents were told to give the pills twice daily for 5 days a week. They were also told that they could choose to give the pills on weekends and school holidays. If families requested a switch from the assigned group to the alternative group (for example, from placebo group to MPH group), then a second blind titration was done to reach the target dosage as previously described. If families had concerns regarding the medication, changes were made accordingly. Table 3 shows the problems usually encountered by families and the treatment changes that would be made by the study physician.
### Table 3. Treatment protocol for the RCT phase

<table>
<thead>
<tr>
<th>Concerns made by parents</th>
<th>Changes made by study physician</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Side effects</strong></td>
<td></td>
</tr>
<tr>
<td>Rebound</td>
<td>adding a small dose in the afternoon, sustained release stimulants, or clonidine</td>
</tr>
<tr>
<td>Irritability, headaches, abdominal pain, loss of appetite, or tics</td>
<td>reducing the dose, switching to another stimulant</td>
</tr>
<tr>
<td>Insomnia</td>
<td>adding a small dose before bedtime or clonidine, or reducing the afternoon dose</td>
</tr>
<tr>
<td></td>
<td>adding a third dose or switching to another stimulant</td>
</tr>
<tr>
<td><strong>Lack of effectiveness</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>switching to sustained release stimulant</td>
</tr>
<tr>
<td><strong>Compliance issues</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>adding an antidepressant</td>
</tr>
</tbody>
</table>
Follow-up procedure. After initiating the treatment, clinic visits were arranged at 4, 8, and 12 months. In addition, parents and teachers were contacted at 2, 6, and 10 months through telephone regarding the treatment and an appointment for next visit. Families were encouraged to call at any time regarding medication effects or other problems. If families were unable to come to the clinic, then home visits were arranged. During every contact with the families, the importance of medication compliance was explained and during the first year, compliance was measured by pill counts. Research staff called parents and teachers the week before the clinic visit and inquired about medication adherence and side effects. Parents and teachers completed the behavioral checklists described below. During the clinic visit, the child was assessed for psychological and academic functioning.

Exit procedure. At the end of 12 months, the blind was broken for those who remained on the assigned pills and families were informed of their medication status. If those who never had MPH treatment requested the treatment, MPH titration was done as at baseline.

SAMPLE SELECTED FOR THE PRESENT STUDY

To document adherence, the present study selected a group of subjects (N = 71) from both MPH and placebo groups as follows: 1) subjects from MPH group (N = 46) who initiated the MPH treatment (N = 45); and 2) subjects from the original placebo group (N = 45) who requested MPH within the first 5 months of the enrollment (N = 26)(Table 4).
**Table 4. Selection of subjects**

\[
\begin{align*}
N &= 302 \text{ (referrals)} \\
N &= 135 \text{ (met screening criteria)} \\
N &= 105 \text{ (met diagnostic criteria)} \\
N &= 91 \text{ (chose to participate)} \\
\end{align*}
\]

Random assignment

\[
\begin{align*}
\text{MPH} & \quad \text{Placebo} \\
N &= 46 & N &= 45 \\
\end{align*}
\]

(Time = 0)

\[
\begin{align*}
\text{Never started} & \quad \text{started the trial} & \text{Crossed-over to MPH} & \text{Placebo} & \text{Dropouts} \\
1 & 45 & 26 & 17 & 2 \\
\end{align*}
\]

(Time = 5m)

\[
\begin{align*}
1 & \quad 63 \quad \text{(Time = 3 yr.)} & 12 \\
\end{align*}
\]

documented adherence
PHASE II: FOLLOW-UP

After the completion of RCT, each child's physician was sent a letter and was informed about the continuous annual follow-up. Then, each parent and teacher was contacted by telephone to request permission for the follow-up. If they agreed, an appointment for a clinic visit was made for the families. Adherence to medication, behavioral changes, and academic functioning were assessed at second and third year follow-up in the same manner as was done at the first year follow-up.

After the assessment, the clinical team reviewed, discussed, and made recommendations to the family regarding medication, school, and family. From the assessments, a report was prepared and sent to each child's parent and family physician regarding the overall functioning of the child and any treatment recommendations. After the first year, if a family contacted the clinic regarding starting, changing or discontinuing medication, the study doctor only made recommendations and referred the family to the child's physician.

MEASURES AND INSTRUMENTS

Diagnostic measures

A research staff member experienced in clinical child psychology who was blind to the group assignment conducted a semi-structured interview with the parents of each child. This interview is called the Parent Interview for Child Symptoms (PICS, Schachar & Wachsmuth, unpublished). In the course of this interview, parents are questioned about their child's behavior and emotional difficulties throughout life, focusing particularly on the six months prior to the interview (as per DSM-III-R criteria). The interview is mainly focused on the
symptoms of ADHD, ODD, CD, and anxiety. Each symptom is rated on a scale of 0 (no symptom) to 3 (severe symptom). A particular symptom was considered to be present if a score of 2 or 3 was given on the interview.

Teachers were administered a semi-structured interview called the Teacher Telephone Interview (TTI, Schachar & Tannock, unpublished), a modified version of the parent interview. Presence of symptoms at school was assessed in the same manner, as was presence of symptoms at home. Number of symptoms present was computed for each disorder and for each informant (parent and teacher).

**Psycho-educational measures**

During the clinic visit, children were assessed by means of a test of intellectual ability (obtained at baseline), a measure of anxiety, and a test of academic functioning (obtained at baseline and at each follow-up).

The full-scale intelligence quotient (IQ) was obtained using Weschler Intelligent Scale for Children-Revised (WISC-R, Weschler, 1974) as a measure of the child’s intellectual ability.

The anxiety measure used was the Revised Children's Manifest Anxiety Scale (RCMAS) (Reynolds & Richmond, 1985). This is a questionnaire of anxiety symptoms designed to be completed by children. T score was calculated according to the standardized procedure.

Wide Range Achievement Test, version III-Revised (WRAT-III-R) was used to measure academic attainment. Standard scores for math, spelling, and reading were calculated in accordance with the standardized procedure (Jastak and Wilkinson, 1984).
Family measures

At baseline, the parent interview (PICS) and a self-report questionnaire by parents called Family and Household form assessed non-diagnostic information related to the family and the child. The following operational definitions of the measures were used to examine the relationship between adherence to stimulant medication and family characteristics.

Psychosocial adversity: Each of the following six factors was rated as 0 (absent) or 1 (present): stressful events in the last 12 months, single-parent status, less than complete high school education for the parent with highest level of education, either parent treated for trouble with nerves, subsidized housing, and unemployment. The psychosocial adversity index was calculated by summing scores from these factors so that a higher score represented higher adversity (range 0-6)(Biederman et al., 1995).

Family dysfunction: The Family and Household form, a 12-item scale was used to assess family functioning in six areas: problem solving, communication, roles, affective responsiveness, affective involvement, and behavioral control. Each item on the scale has four response categories: "strongly agree"; "agree"; "disagree"; and "strongly disagree", for which scores of 1, 2, 3, and 4 are assigned respectively. The scale is derived from the McMaster Family Assessment Device (Byles, Byrne, Boyle, & Offord, 1988; Szatmari et al., 1989). A score of family dysfunction was calculated by summing all the items so that higher score represented poor family functioning (range 12-48).
Adherence measures

Adherence to medication was measured annually through inquiries to the parent, teacher, and child. The Treatment monitoring questionnaire used is a semi-structured interview designed for parents and teachers. Research staff experienced in clinical psychology conducted the interviews by telephone.

Parents were first asked the question: "Does your child continue to receive medication?" If parents said yes, then they were asked about the medication(s) taken, dose of the medication, frequency of dosing at the follow-up. If parents said no, then they would be asked the reasons for not taking the medication. Parents were also asked whether the child's teacher knew about the medication.

Teachers were asked the question: "Does your student receive medication at school?" If they said yes, they were further asked about consistency of medication taking, dose of the medication and whether the dispensing was supervised. If the teacher said that the medication was not given consistently, the reason was also recorded.

In addition, at the time of clinic visit, children were questioned about taking pills at home and school through a semi-structured interview, the Child Satisfaction Survey. Children were asked the question: "Do you ever skip taking the pills?" If they said yes, they were asked why they skipped and whether anyone knew about skipping the pills.

When a disagreement was observed between informants, a consensus was obtained among these informants. For example, if the parent and child said that he or she takes the medication and if the teacher said that the child doesn't take the medication, the decision as to whether the child was being considered adhering would be based on other information obtained during the interview. In this case, if the parent said that the child is not being
supervised at the time of medication dispensing and teacher is not aware of the medication, then the information obtained from the teacher would not be used to document adherence.

Pill count was used to validate the interview-based measure of adherence. The measures were found to be significantly correlated ($r = 0.76, \ p < 0.001$).

**Definition of adherence.** Drug holidays were scheduled when the child was not attending school, usually during vacation. A maximum of 14 weeks was allowed for the total length of all drug holidays, which covers all major school holidays (summer vacation, Christmas, and March break). Adherence to stimulants was defined as taking stimulant medication consistently by the child throughout the year with drug holidays totaling no more than 14 weeks per year.

**Adherence groups.** A child was designated as an adherent if there was evidence from parent, child, and teacher that the child adhered to stimulants for 3 years. A child was designated as a non-adherent if there was evidence that the child did not adhere for 3 years. Those who adhered for less than 3 years (non-adherents) were further classified into partial adherents or poor adherents based on number of years adhered. A child was designated as a partial adherent if the child adhered to stimulant for 2 years. A child was designated as a poor adherent if the child adhered to stimulant for one year or less. Since children were expected to adhere for 3 years, adherents were referred as 'good adherents' whenever the three groups were compared (i.e. good adherents, partial adherents, poor adherents).
Reasons for Non-adherence. If the medication status was changed from last evaluation, parents were asked to state their reasons for changing the treatment in an open-ended question in the following manner: "Has there been a break(s) from receiving medication?" If the parent or another informant said yes, then the time, at which the break was taken, the duration of the break, and the main reason for the break were also asked. The most important reason emphasized by the parent was recorded and classified as: 1) side effects; 2) no longer effective; 3) test of effectiveness; 4) child refuses to take pills; 5) drug holiday; or 5) other. Reasons were categorized according to the parent interview only. For example, when parents said that the child refused to take the pills, they were asked why the child refused. Similarly, children would be asked why they refused. However, regardless of child's reasoning for non-adherence, they would be classified under 'child refuses to take pills' category. Specific reasons as to why children discontinued will be discussed. When more than one reason was provided by the parent, a consensus was reached among the research staff and parents for the most important reason.

Measures of treatment effects

Stimulant status at 3-year follow-up. One of the objectives of the present study was to evaluate whether adherents receive greater benefits on behavior and academics than do non-adherents. It has been consistently demonstrated that the effects of stimulant medication dissipate immediately upon discontinuation (e.g., Brown et al., 1986). Therefore, medication status at the time of follow-up was also documented. Adherence groups (as defined previously) were further categorized and analyzed according to the medication status at the follow-up. Comparison between adherents, non-adherents on stimulant, and non-adherents
off stimulants will demonstrate whether there are any cumulative effects of stimulant medication present. Comparison between subjects on stimulants and subjects off stimulants will demonstrate whether the acute, beneficial effects of stimulants are present even 3 years after the treatment initiation.

The child was considered to be on stimulant medication at the end of the 3-year follow-up if the child was taking the medication for the last 6 months of the follow-up. The child was considered to be off stimulants if the child was off medications for the last 6 months of the follow-up. If a child changed the treatment within the last 6 months of the follow-up, that child was excluded from the analysis. Since behavioral ratings obtained at each follow-up covered only a 6-month period (as described below), such exclusion was necessary in order to prevent any difficulties in assessing the behavioral changes.

For example, if a child stopped taking stimulant medication only 3 months prior to the follow-up, it would be difficult to assess whether the overall behavioral change observed was due to the stimulant medication or not. Seven such subjects were excluded from the analysis of the clinical effects of stimulants.

Behavioral changes at the 3-year follow-up. Parents and teachers completed a behavioral checklist called the Survey Diagnostic Instrument-Revised (SDI-R) at baseline and at each follow-up. SDI-R is derived from the Child Behavior Checklist (Achenbach & Edelbrock, 1981) and has additional items necessary to make a diagnosis of ADHD, CD, and ODD in accordance with DSM-III-R. When compared against semi-structured interviews, parent and

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1 In the present study, partial and poor adherents are combined into one group (non-adherents). Due to the small number of subjects in each group, it is not possible to analyze the acute effects of stimulant medication on each group separately.
teacher reports have been shown to be valid measures for assessing childhood psychiatric problems (Boyle, Offord, Racine, Szatmari, Sanford, & Fleming, 1997; Boyle, Offord, Racine, Szatmari, Fleming, & Sanford, 1996). It inquires about the child's symptoms of ADHD and other co-existing conditions during the last 6 months of completing the checklist. The items on the checklist have 3 possible responses for each symptom: "never or not true"; "sometimes or somewhat true"; and "often or very true", for which scores of 0, 1, and 2 are assigned respectively. For each disorder, a total score is given based on the frequency and severity of the symptoms.

Symptomatic improvement was a continuous measure referring to improvement in the magnitude of symptoms. Symptomatic improvement was calculated for ADHD, ODD, and CD and for each rater (parent and teacher) by subtracting the total score obtained at 3-year follow-up from the total score obtained at the baseline so that higher score represented greater improvement.

*Academic changes at the 3-year follow-up.* Academic improvement was a continuous measure referring to improvement in the magnitude of standard scores obtained from WRAT-III-R (described in 'psycho-educational assessment'). Academic improvement was calculated for math, spelling, and reading by subtracting the baseline scores (standard scores) from the 3-year follow-up scores so that higher scores represented greater improvement.
DIAGNOSTIC CRITERIA

Diagnosis of pervasive ADHD was made as follows: children had to have 8 or more of the symptoms listed in DSM-III-R criteria in either at home (PICS) or at school (TTI) and 5 criteria or more in the other setting; and presence of these symptoms before the age of 7 for at least 6 months. Based on the parent or teacher interview, categorical diagnoses (presence or absence of the disorder) were also made for ODD and CD in accordance with DSM-III-R. Diagnosis of anxiety was made as follows: DSM-III-R criteria for overanxious or separation anxiety based on parent interview (PICS); or a T score of 60 or above, based on child-reported symptoms obtained on the RCMAS. The child was given a diagnosis of learning disability (LD) if the child received a standard score below 78 on math, spelling, or reading (WRAT-R). Inter-rater reliability was assessed and found to be very good for all diagnoses (Schachar et al., 1997).

Children were excluded from the study if they did not receive a diagnosis of pervasive ADHD, received a primary diagnosis for one of the other disorders such as anxiety, Tourette syndrome or affective disorder, or had an IQ of less than 80.

DATA ANALYSIS PROCEDURE

Data analysis was done in accordance with the objectives of the present study and are described in five parts: 1) characteristics of the sample, 2) rate of adherence to stimulant, 3) reasons for non-adherence, 4) predictors of adherents, and 5) effects of stimulant adherence on behavior and academics.
Data were analyzed using the Statistical Package for the Social Sciences (SPSS-8.0). Both descriptive statistics of the study sample and bivariate analysis were used. To compare categorical data, the Mantel-Haenszel chi square test was used; when the expected value of a cell was less than 5, Fisher's Exact two-tailed test was chosen. Normality of continuous data was examined by the Kolmogorov-Smirnov test. To compare continuous data with 2 groups, the Student t-test was used; when the data were not normally distributed, the Mann-Whitney U two-sample test was chosen. To compare continuous data with more than 2 groups, the one-way ANOVA was used; when the data were not normally distributed, the Kruskal-Wallis test was used. If significant effects were seen (p < 0.05), comparisons between multiple groups were made by Turkey's b test. This procedure was chosen because it takes number of groups being compared, lack of independence of the comparisons, and the post hoc (unplanned) nature of the comparisons into consideration. Table 5 presents the types of variables and analyses used in the present study. The following section provides the analytic plan for each of the questions addressed.

1. **Characteristics of the sample**

   This section examined the characteristics of the study sample. The characteristics that were examined include child's characteristics such as age, sex, and IQ, family characteristics such as psychosocial adversity and family dysfunction and diagnostic characteristics such as number of symptoms of ADHD (at home and school), presence of ODD, CD, anxiety, and LD. For categorical variables, percentage was used and for continuous variables, mean (with standard deviation) was used as a measure of central tendency to describe the study sample.
### Table 5. Types of variables and analyses used

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Source of information</th>
<th>Type of Variable</th>
<th>Type of analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>PICS</td>
<td>Continuous</td>
<td>Student t-test or Mann-Whitney test</td>
</tr>
<tr>
<td>Sex</td>
<td>PICS</td>
<td>Nominal</td>
<td>Chi-square or Fisher's Exact Test</td>
</tr>
<tr>
<td>IQ</td>
<td>WISC-R</td>
<td>Continuous</td>
<td>Student t-test or Mann-Whitney test</td>
</tr>
<tr>
<td>Number of symptoms on ADHD at home</td>
<td>PICS or TTI</td>
<td>Continuous</td>
<td>Student t-test or Mann-Whitney test</td>
</tr>
<tr>
<td>Number of symptoms on ADHD at school</td>
<td>TTI</td>
<td>Continuous</td>
<td>Student t-test or Mann-Whitney test</td>
</tr>
<tr>
<td>Presence or absence of ODD (at home or school)</td>
<td>PICS and TTI</td>
<td>Nominal</td>
<td>Chi-square or Fisher's Exact Test</td>
</tr>
<tr>
<td>Presence or absence of CD (at home or school)</td>
<td>PICS and TTI</td>
<td>Nominal</td>
<td>Chi-square or Fisher's Exact Test</td>
</tr>
<tr>
<td>Presence or absence of anxiety (parent or child identified)</td>
<td>PICS and RCMAS</td>
<td>Nominal</td>
<td>Chi-square or Fisher's Exact Test</td>
</tr>
<tr>
<td>Presence or absence of LD (math, spelling, or reading)</td>
<td>WRAT-III-R</td>
<td>Nominal</td>
<td>Chi-square or Fisher's Exact Test</td>
</tr>
<tr>
<td>Family dysfunctioning</td>
<td>Family and Household Form</td>
<td>Continuous</td>
<td>Student t-test or Mann-Whitney test</td>
</tr>
<tr>
<td>Psychosocial adversity</td>
<td>Family and Household Form</td>
<td>Continuous</td>
<td>Student t-test or Mann-Whitney test</td>
</tr>
</tbody>
</table>

### Predicting adherence to medication

<table>
<thead>
<tr>
<th>Measures</th>
<th>Source of information</th>
<th>Type of Variable</th>
<th>Type of analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence groups</td>
<td>Treatment Monitoring Questionnaire</td>
<td>Nominal</td>
<td>Logistic Regression</td>
</tr>
</tbody>
</table>

### Cumulative effects of stimulant adherence

<table>
<thead>
<tr>
<th>Measures</th>
<th>Source of information</th>
<th>Type of Variable</th>
<th>Type of analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent-rated improvement on ADHD</td>
<td>SDI-R (Baseline-outcome)</td>
<td>Continuous</td>
<td>One-way ANOVA or Kruskal-Wallis test</td>
</tr>
<tr>
<td>Teacher-rated improvement on ADHD</td>
<td>SDI-R</td>
<td>Continuous</td>
<td>One-way ANOVA or Kruskal-Wallis test</td>
</tr>
<tr>
<td>Parent-rated improvement on ODD</td>
<td>SDI-R</td>
<td>Continuous</td>
<td>One-way ANOVA or Kruskal-Wallis test</td>
</tr>
<tr>
<td>Teacher-rated improvement on ODD</td>
<td>SDI-R</td>
<td>Continuous</td>
<td>One-way ANOVA or Kruskal-Wallis test</td>
</tr>
<tr>
<td>Parent-rated improvement on CD</td>
<td>SDI-R</td>
<td>Continuous</td>
<td>One-way ANOVA or Kruskal-Wallis test</td>
</tr>
<tr>
<td>Teacher-rated improvement on CD</td>
<td>SDI-R</td>
<td>Continuous</td>
<td>One-way ANOVA or Kruskal-Wallis test</td>
</tr>
<tr>
<td>Improvement on math</td>
<td>WRAT-III-R (Outcome-baseline)</td>
<td>Continuous</td>
<td>One-way ANOVA or Kruskal-Wallis test</td>
</tr>
<tr>
<td>Improvement on spelling</td>
<td>WRAT-III-R</td>
<td>Continuous</td>
<td>One-way ANOVA or Kruskal-Wallis test</td>
</tr>
<tr>
<td>Improvement on reading</td>
<td>WRAT-III-R</td>
<td>Continuous</td>
<td>One-way ANOVA or Kruskal-Wallis test</td>
</tr>
</tbody>
</table>
2. Adherence to stimulants

Objective 1 of the present study was to examine the rate of adherence over the 3-year follow-up. Frequency distribution (and percentage) was used to describe the three adherence groups (good adherents, partial adherents, and poor adherents).

3. Reasons for non-adherence

The second objective was to investigate the reasons for non-adherence obtained from parents. Descriptive statistics were used to display the frequency (and percentage) of each response category. In addition, the mean age of children who refused and consequently discontinued the medication was compared with the mean age of children who discontinued for other reasons (e.g., side effects). Age at discontinuance was calculated to compare the two groups. For example, if a child were 8 years when he entered the study and discontinued the stimulant medication during the third year follow-up, age at discontinuation for this child would be 11 years.

4. Factors predicting adherence to stimulant medication

For logistic regression analysis, the number of predictors (independent variables) should not exceed 10% of the total number of events. Therefore, group comparisons were first made by an appropriate statistical test (e.g., t-test or chi-square) for variables that were considered as potential risk factors. The following factors were examined as potential risk factors for non-adherence: age, IQ, sex, number of symptoms of ADHD (at home and school separately), presence or absence of ODD, CD (at home or school), anxiety (parent or child identified), and any LD (math, spelling, or reading), psychosocial adversity, and family
dysfunction. In the next step, the factors that were related to adherence were entered into a multivariate logistic regression using a liberal entry criterion for the variables ($p < 0.25$).

Factors associated with adherence were examined in 2 separate steps. First, the factors that are associated with partial adherents and poor adherents were examined. Since there were no differences between the two groups on potential risk factors (Appendix C1), these two groups were combined into one group (non-adherents) for further analysis. Secondly, the factors that are associated with adherents (also referred to as 'good adherents' previously) and non-adherents were examined.

5. **Clinical effects of stimulant adherence**

Adherents, non-adherents on stimulants and non-adherents off stimulants were compared on behavioral (ADHD, ODD, and CD) and on academic improvements (math, spelling, and reading). In addition, subjects on stimulants and subjects off stimulants were compared on all of the measures to examine the acute effects of stimulants.

There have been problems (e.g., reliability) raised with the use of change score in quantifying change over time (Francis, Fletcher, Stuebing, Davidson, & Thompson, 1991). Therefore, clinical effects of stimulant were re-analyzed using mixed-model ANOVA with repeated measures. Since there were no differences between the two types of analyses (one-way ANOVA with change scores and ANOVA with repeated measures), results from only one analysis was used (one-way ANOVA).

The use of one-way ANOVA to examine the impact of adherence on behavior and academics may affect by the presence of factors that are confounded with adherence. The relationship of baseline characteristics with adherence and clinical effects was assessed
because factors such as age and family dysfunction may be related to adherence and to the outcome of ADHD children in general. There were no baseline characteristics that significantly correlated with both clinical effects and adherence groups. Therefore, differences on clinical effects observed among adherence groups were not likely to be due to any differences between adherence groups on baseline characteristics.
CHAPTER V: RESULTS

CHARACTERISTICS OF THE SAMPLE

This section examined whether the results from the present study can be generalized to the initial sample selected. Of the 71 children selected to examine adherence, 63 completed the 3-year follow-up. The time of dropout and the primary reason for terminating participation in the study were examined and are presented in Table 6. The major reasons for refusing to participate include parents being uncooperative (37.5%, 3/8), moving away (25%, 2/8), and no longer being interested in continuing the study (37.5%, 3/8).

To determine whether the sample completed the 3-year follow-up was representative of the sample selected, baseline characteristics of those who completed the 3 year follow-up (N = 63) and those who did not complete (N = 8) were compared (Table 7). There were no significant differences observed in the age, sex, IQ, number of symptoms of ADHD, presence of ODD, CD, anxiety or LD. However, subjects who dropped out of the study before completing the 3-year follow-up had higher scores on psychosocial adversity than those who completed the follow-up (t = 2.176, p = 0.03). Below, it was considered whether psychosocial risk was associated with adherence.

The distributions of continuous measures were examined and ranges of age, number of ADHD symptoms, family dysfunction, and psychosocial adversity were 6-12, 6-14, 12-34, and 1-5 respectively (Appendix A). To make group comparison, a non-parametric test (e.g., Mann-Whitney test) was chosen for age, number of symptoms (home and school), and psychosocial adversity index.
Table 6. Reasons for terminating the study (N = 8)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncooperative parent</td>
<td>3</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Moved out</td>
<td></td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Not interested anymore</td>
<td>2</td>
<td>1</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8</td>
</tr>
</tbody>
</table>
Table 7. Characteristics of subjects who completed the study (participants) and subjects who did not complete (non-participants) (N = 71)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Participants (n = 63)</th>
<th>Non-participants (n = 8)</th>
<th>P-value (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>8.12 (1.57)</td>
<td>8.40 (1.28)</td>
<td>0.45</td>
</tr>
<tr>
<td>Sex: % of females</td>
<td>21</td>
<td>13</td>
<td>1.00</td>
</tr>
<tr>
<td>IQ (WISC-R)</td>
<td>109.32 (14.51)</td>
<td>111.00 (21.92)</td>
<td>0.77</td>
</tr>
<tr>
<td>Number of ADHD symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At home (PICS)</td>
<td>10.97 (2.78)</td>
<td>11.50 (2.27)</td>
<td>0.71</td>
</tr>
<tr>
<td>At school (TTI)</td>
<td>10.65 (2.61)</td>
<td>9.63 (3.20)</td>
<td>0.39</td>
</tr>
<tr>
<td>Comorbidity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ODD (home or school)</td>
<td>67</td>
<td>50</td>
<td>0.44</td>
</tr>
<tr>
<td>ODD (home)</td>
<td>52</td>
<td>38</td>
<td>0.48</td>
</tr>
<tr>
<td>ODD (school)</td>
<td>32</td>
<td>25</td>
<td>1.00</td>
</tr>
<tr>
<td>CD (home or school)</td>
<td>10</td>
<td>13</td>
<td>0.58</td>
</tr>
<tr>
<td>CD (home)</td>
<td>6</td>
<td>13</td>
<td>0.46</td>
</tr>
<tr>
<td>CD (school)</td>
<td>5</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Anxiety (parent or child)</td>
<td>40</td>
<td>20</td>
<td>0.71</td>
</tr>
<tr>
<td>Anxiety (parent)</td>
<td>21</td>
<td>25</td>
<td>0.67</td>
</tr>
<tr>
<td>Anxiety (child)</td>
<td>21</td>
<td>25</td>
<td>0.67</td>
</tr>
<tr>
<td>LD (WRAT test)</td>
<td>37</td>
<td>50</td>
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</tr>
<tr>
<td>Family characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosocial adversity</td>
<td>1.48 (1.08)</td>
<td>2.38 (1.30)</td>
<td>0.03</td>
</tr>
<tr>
<td>Family dysfunctioning</td>
<td>22.33 (6.12)</td>
<td>22.67 (2.50)</td>
<td>0.80</td>
</tr>
</tbody>
</table>
ADHERENCE TO STIMULANTS

Eighty-one percent of subjects were adhering over the first year, 67% were adhering over the first and second year, and 52% were adhering over 3 years. There were 33 adherents (52%, adhering for 3 years), 18 partial adherents (29%, adhering for 2 years) and 12 poor adherents (19%, adhering for 1 year or less)(Appendix B1).

REASONS FOR NON-ADHERENCE

Reasons for discontinuing stimulant medication

The reasons for stopping stimulant medication and the time of stopping are presented in Table 8.

Of the 63 children, 30 children discontinued stimulant medication during a 3-year period. The reasons given by parents include side effects (43%, 13/30), concerns with effectiveness (16.5%, 5/30), parents feeling that medication was not necessary (16.5%, 5/30), not comfortable in giving stimulants (3%, 1/30) and child refusing to take the medication (20%, 6/30). During the first two years, side effects were the major concern whereas during the third year, child's reluctance to take the medication was the major reason.

Side effects reported by parents include social withdrawal, rebound, irritability, and tics. Parents who had concerns about effectiveness discontinued stimulant medication: to see if medication was needed (2/5) or for lack of effectiveness (3/5). Parents said that stimulant medication was not necessary for one of the following reasons: parents believed that their child was not ADHD and no need for the treatment (i.e. no symptoms, 3/5); parent (1/5) or teacher (1/5) felt that the child could be managed without medications (i.e. symptoms improved).
Table 8. Reasons given by parents for discontinuing stimulant medication (N = 30)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Side effects</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>13 (43.0)</td>
</tr>
<tr>
<td>Concerns with effectiveness</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>5 (16.5)</td>
</tr>
<tr>
<td>Not necessary</td>
<td>3</td>
<td>2</td>
<td></td>
<td>5 (16.5)</td>
</tr>
<tr>
<td>Not comfortable</td>
<td>1</td>
<td></td>
<td></td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Child refusal</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>8</td>
<td>9</td>
<td>30</td>
</tr>
</tbody>
</table>
Children refused treatment for one of the following reasons: did not like pills, felt that medication was accomplishing all the tasks, felt no benefit, interfered with sports, or side effects. To determine whether children who refused taking the pills and succeeded in discontinuing the medication were older, the effect of age on child refusal and subsequent discontinuance was examined. Children who discontinued because they did not want to take the pills were significantly older at discontinuation than were children who discontinued for other reasons ($t = -2.478$, df = 28, $p = 0.02$).

Another interesting finding was that many subjects were using sustained release to avoid missing a dose at school (65%, 13/20). These children generally disliked taking the pills at school. Others (35%, 7/20) started taking sustained release mainly because of rebound effects in the early evenings (Appendix B2).

**PREDICTORS OF ADHERENCE TO STIMULANTS**

Five variables were selected as independent variables from group comparisons (e.g., t-test with $p < 0.25$) to be entered into logistic regression (Appendix C2). These included age, ADHD symptoms at school, presence of ODD at school, presence of anxiety, and family functioning. Psychosocial risk index was forced into logistic regression since psychosocial adversity was higher among subjects who dropped out of the study compared to those who completed. As shown in Table 9, adherence was predicted by younger age (odds ratio [OR] 1.8, 95% confidence interval [CI] 1.1 to 2.8), greater number of teacher-rated symptoms (OR 1.6, CI 1.1 to 2.1), and absence of comorbid ODD at school (OR 9.9, CI 1.7 to 56.7).
Table 9. Predictors of Adherence (N = 63)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sig</th>
<th>Odds ratio</th>
<th>95% CI for odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (younger)</td>
<td>0.02</td>
<td>1.75</td>
<td>1.08</td>
</tr>
<tr>
<td>Severity of ADHD at school (greater)</td>
<td>0.01</td>
<td>1.55</td>
<td>1.12</td>
</tr>
<tr>
<td>Comorbid ODD at school (absence)</td>
<td>0.01</td>
<td>9.95</td>
<td>1.75</td>
</tr>
<tr>
<td>Comorbid anxiety (absence)</td>
<td>0.08</td>
<td>3.48</td>
<td>0.85</td>
</tr>
<tr>
<td>Family problems (greater)</td>
<td>0.06</td>
<td>1.12</td>
<td>0.99</td>
</tr>
<tr>
<td>Psychosocial adversity (less)</td>
<td>0.56</td>
<td>1.21</td>
<td>0.64</td>
</tr>
</tbody>
</table>
There was a trend showing an increased rate of adherence among children with no anxiety (OR 3.5, \( p = 0.08 \)) and with dysfunctional families (OR 1.1, \( p = 0.06 \)). The logistic regression model correctly predicted adherence in 78% of subjects compared to 50% predicted by chance alone (\( p = 0.0009 \)).

**CLINICAL EFFECTS OF STIMULANT ADHERENCE**

This section describes whether those who adhered to the stimulant for 3 years improved in behavior and academic attainment compared to those who did not adhere. Effects on total scores on ADHD, ODD, and CD were analyzed as rated by parents and teachers. Effects on academic functioning were analyzed using changes in standard scores for math, spelling, and reading.

**Behavioral changes**

A one-way ANOVA revealed no significant differences between adherents, non-adherents on stimulants, and non-adherents off stimulants on ADHD, ODD or CD (both parent-rated and teacher-rated)(Table 10). However, student's t-test revealed the beneficial effect of stimulant status at the time of evaluation: subjects who were taking stimulant medication at the 3-year follow-up improved more on ADHD symptoms as rated by teachers than did subjects not taking any medications (\( t = -2.169, \text{ df} = 49, p = 0.03 \)) (Appendix D).
<table>
<thead>
<tr>
<th>Clinical effects (Mean, SD)</th>
<th>BEHAVIORAL changes</th>
<th>ACADEMIC changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-adherents OFF stimulant Non-adherents ON stimulant Adherents ON stimulant P-value</td>
<td>(n = 14)</td>
<td>(n = 9)</td>
</tr>
<tr>
<td>ADHD (parent)</td>
<td>6.8 (5.7)</td>
<td>3.8 (5.8)</td>
</tr>
<tr>
<td>ADHD (teacher)</td>
<td>2.7 (6.3)</td>
<td>7.2 (4.2)</td>
</tr>
<tr>
<td>ODD (parent)</td>
<td>2.9 (3.8)</td>
<td>0.6 (4.7)</td>
</tr>
<tr>
<td>ODD (teacher)</td>
<td>2.8 (5.9)</td>
<td>0.2 (4.2)</td>
</tr>
<tr>
<td>CD (parent)</td>
<td>1.2 (2.3)</td>
<td>0.9 (1.9)</td>
</tr>
<tr>
<td>CD (teacher)</td>
<td>1.2 (1.7)</td>
<td>2.0 (3.9)</td>
</tr>
</tbody>
</table>

* Seven subjects were not included based on the stimulant status at year 3

(Used in this analysis varied between 48 and 56 as data were not available for number of subjects)
Academic performance

The magnitudes of improvement in the subtests of academic attainment (math, spelling, and reading) were not significantly different among adherents, non-adherents on stimulants and non-adherents off stimulants (Table 10). The magnitudes of improvement in the subtests of academic attainment were not significantly different among subjects who were taking stimulants and subjects who were not taking stimulants at the follow-up (Appendix D).
CHAPTER VI: DISCUSSION

The present study is the first continuous follow-up that has examined adherence to stimulants over several years. Sixty-three children with a confirmed diagnosis of ADHD were followed annually from their first trial of MPH for 3 years. The objectives of the current study were (1) to estimate the rate of adherence to stimulants over the study period; (2) to investigate the reasons for non-adherence; (3) to predict adherence to stimulant medications; and (4) to evaluate whether adherents experience greater improvement in behavior and academic achievement than non-adherents.

The results indicated that (1) adherence to stimulants over the 3-year period was 52%; (2) reasons for non-adherence included side effects, parental feeling that medication was not effective or not necessary, and children beginning to refuse to take the medication; 40% of the children who discontinued stimulant were back on medication mainly due to poor school performance; (3) adherence was predicted by younger age, more ADHD symptoms and absence of comorbid ODD at school; and (4) according to teachers, subjects who were taking stimulants at the follow-up showed significant improvement in ADHD symptoms compared to subjects who were not taking stimulants; there was no difference between the groups in academic improvement.

Characteristics of the sample

Of the 71 children selected for the present study, 63 (89%) completed the 3-year follow-up. The rate of attrition in the present study was lower than the rates of 20% to 55% found in many non-randomized long-term treatment studies (Schachar and Tannock, 1993) and
adherence studies (Brown et al., 1985; Firestone, 1982). Attrition prevention strategies undertaken in the present study (e.g., encouraging families to stay in the study regardless of medication status, arranging home visits, and frequent telephone contacts) might have produced such a small attrition.

The majority of families that were lost to follow-up were uncooperative or said that they dropped out because they were not interested in continuing the follow-up. Those who dropped out of the study had a higher score on the psychosocial adversity index at the time of entry into the study compared to those who completed the study. This finding is consistent with other research which found that families who dropped out of child and adolescent therapy were likely to have lower socioeconomic status, more stress, and more adverse living conditions compared to those who completed the study (Kazdin et al., 1997).

A total of 63 subjects ranging in age from 6 to 12 years participated in the study. The mean age of the sample was 8.12 years with a standard deviation of 1.57. Male to female ratio in the present sample was 4:1. This ratio is comparable to the lower limit of nationwide ratio of 4 to 9:1 (American Psychiatric Association, 1994).

ODD (home or school) was found in about 67% of the present sample whereas it was found in only 35% of the clinically referred ADHD children in general population (Biederman et al., 1991). Similarly, diagnoses of anxiety and LD were much higher among the subjects in the present study compared to those found in other clinically referred sample (40% and 37% vs. 25% and 20% respectively) (Biederman et al., 1991; Semrud-Clikeman et al., 1992). However, CD was found in only 10% of the present sample, a much lower rate than 30% to 50% reported in other studies (Biederman et al., 1991). In general, the subjects in the present study appear to have more comorbid disorders (except for CD) than do ADHD
children in the general population. It has been suggested that much of the morbidity may be accounted for by the associated symptoms of ADHD (Shukla and Otten, 1999). Therefore, subjects of the present study might have been referred to the clinic mainly because of high comorbidity (referral bias, see 'limitation'). Because comorbidity is one of the significant variables associated with poor outcome, this bias may in part explain the low attrition in the present study.

Since those who dropped out of the present study and those who remained were equally impaired in the symptoms of ADHD and comorbid disorders, the results from this study are generalizable to the sample selected for the present study. The low attrition enhances the ability to generalize the findings from the present study to other clinically referred sample.

**Adherence to stimulant medication**

In the present study, 79% of the participants adhered to MPH over the first 12 months. While many short-term studies examined adherence on a day to day basis for several months, only one study has examined the discontinuation of the treatment over a year (Firestone, 1982). However, the study by Firestone reported a much lower rate of adherence over a 1-year period (55%). The discrepancy between the two studies might have resulted from differences in the selected samples. Patients in the Firestone study were referred to a psychology department where they were assessed and treated. Families who get referred to a psychology clinic may have very different needs and expectations compared to those who are referred to a psychiatric clinic (as in the present study). For example, patients who are
directed to a psychology clinic may prefer non-pharmacological intervention whereas patients who are directed to a psychiatric clinic may prefer pharmacological intervention.

At the first year follow-up, 81% of the subjects adhered to stimulants (MPH, DEX, and pemoline combined). As was predicted, adherence declined with increasing duration of treatment and at the second year, 67% and at the third year, 52% were adhering to stimulants without interruptions. The rate of 52% is low and comparable to the rate of approximately 50% in other long-term medication regimens (Sackett and Snow, 1979). This low rate, at face value, appears to be serious and clinically important (from public health and practical perspective).

However, another important finding was that 40% of the subjects who discontinued once before the 3-year follow-up were back on stimulant by the third year (Appendix B1). This finding has never been reported. This suggests that not only more and more children will discontinue the medication over time, but also they will restart the treatment once it is deemed necessary. Here, parents stated poor school performance as the main reason to put their children back on the pills. The continuity of care provided by the present study might have also influenced families to resume the treatment.

**Reasons for non-adherence**

There were 30 subjects who discontinued stimulant medication at least once over the 3-year period. The major reason given by parents for discontinuing stimulants was side effects (13/30). This has not been reported in previous studies examining stimulant adherence. However, all previous studies have examined adherence for several months only and might not have had the chance to detect long-term side effects or worsening of short-
term side effects. In the present study, frequently reported side effects included withdrawal, irritability, insomnia and rebound. Rebound refers to the worsening of behavioral symptoms compared to baseline. This occurs during late afternoons or early evenings when the effects of the typical twice-a-day regimen wear off. Side effects resulted in discontinuation in these cases despite the structured and rigorous response to emerging side effects. The responses included ready availability of staff for telephone consult concerning side effects or other problems, availability of medical or psychiatric consultation, possibility of adjustment in dose, time, frequency of dosing and type of stimulant (standard vs. sustained release or MPH vs. DEX).

Another major reason for non-adherence is associated with effectiveness of the medication (5/30). While some parents reported that the medication was not effective others stated that they discontinued to see whether the medication was working (test of effectiveness). Morris and Schulz (1993) referred to this process as the rational-empirical method. Here, patients would resume the medication if they felt worse without it. The majority of subjects in the present study took stimulants twice a day (morning and afternoon) and therefore the effects of the medication might have dissipated when children returned home in the early evening. In fact, the analysis of behavioral effects in the present study (discussed below) showed that parents don’t see any behavioral or academic improvements when their children were taking stimulants. However, Schachar et al., (1997) showed that side effects were evident at home. Therefore, its apparent ineffectiveness along with side effects might have influenced parents to discontinue the medication (see Chapter VII for clinical implications).
It must be noted that when families complained about side effects or ineffectiveness of stimulant medication, every effort was made to ensure that patients had minimal side effects and maximum effectiveness. Appropriate decision regarding treatment changes was made in accordance with specific need of the child (Table 3). Since most of the subjects with severe side effects to one stimulant would not have them with the other (Elia, Borcherdng, Rapoport, Keysor, 1991), if discontinuation of MPH were required, the child would be prescribed another stimulant medication (DEX or pemoline). In the present study, adverse effects or lack of effectiveness rarely resulted in recommending subjects to discontinue stimulant medication. Therefore, discontinuing the treatment was not considered as an appropriate response for any of the subjects.

The third reason for terminating stimulant medication was the question of perceived need for stimulant treatment (6/30). Perceived need of parents for the treatment may be different from that of the physician. Consequently, changes in parental perceived need could have an impact on adherence to the treatment (Jay et al., 1984). Examples for such change were evident in this sample. Despite the effectiveness and lack of side effects, five parents refused the medication because they did not feel it was necessary. Three of these 5 families who discontinued the medication during the first year were unconvinced about the diagnosis (e.g., believing that their child had learning rather than behavioral problems). The remaining 2 families who discontinued during the second year of treatment stated that their children improved. Another factor affecting perceived need for the treatment may be changes in the symptoms of ADHD over time. For example, when children move into adolescence, inattention and impulsivity remain as significant problems whereas hyperactivity decreases. Such developmental change of ADHD symptoms might have led families and others to
decide that their child had improved (Firestone, 1982) and to discontinue the medication. Parental perceived need could also be affected by the pressure parents experienced to put their child on medication. Specifically, some of these families might have felt compelled to get an assessment and treatment because of behavioral problems at school. For example, one of the parents discontinued the medication because he was not comfortable in giving medications to deal with his son's behavior although all families initially accepted the treatment when they entered into the study. In summary, for the majority of families, the perceived need for the treatment and consequently its adherence declined during the early part of treatment.

Non-adherence also appeared when children started to refuse taking medications during the later part of the follow-up (6/30). In spite of the fact that medication seems to help children, psychological meaning of the medication may change over time and lead to non-adherence (Stine, 1994). As children get older, they may start to view the medication as a form of external control and dislike taking it, especially at school. For example, one child reported that he did not like taking the medication because he felt that medication was accomplishing all the tasks and that his efforts were not responsible for improvement. In addition, the stigma attached to having the disorder might be worse when the medication was taken in front of peers therefore he or she might have discontinued to avoid that outcome.

Morris and Schulz (1993) indicated how patients' views of non-adherence could be explained by physical, psychological, economic, or social aspects of the medication. In the present study, the reasons given by parents illustrate that ADHD children discontinued stimulants due to the physical experiences (side effects and lack of effectiveness) and psychological aspects of the medication (lack of need for the treatment and child refusal).
Psychological impact of the medication may become a bigger barrier to adherence as children reach adolescence (i.e. child refusal).

Predictors of adherents and non-adherents

*Child factors.* As was expected, non-adherents were more likely to be older than were adherents. An odds ratio of 1.75 suggests that adherence decreases by 75% when child’s age is increased by one year. Since subjects in the present study were between the ages of 6 to 12 years at enrollment, this finding can only be generalizable to this age group. The effect may not be similar when children reach adolescence. Among non-adherents, older children were more likely to refuse and discontinue the medication than were younger children. These findings support the findings of Sleator et al. (1982) that older children were more likely to refuse taking the medication and to succeed in discontinued compared to younger children.

It was hypothesized that children with lower IQ may be less likely to be adherents compared to children with higher IQ. In the present study, IQ was not associated with adherence. However, the present study excluded subjects with an IQ of less than 80. We might be able to identify a relationship between IQ and non-adherence for IQ less than 80. Firestone (1982) noted that female children were more likely to discontinue the treatment than males. However, gender was not associated with adherence in the present study.

*Family factors.* Contrary to what was expected, adherents tended to have more family conflicts than non-adherents. However, the finding from the present study was not significant (p=0.06). Adherence increases by 12% when family dysfunction increased by 1
unit in the 12 to 48 scale (OR = 1.12). Brown et al (1987) also found a similar relationship between adherence and family conflicts. They suggested that acknowledging the family problems might be an important step toward long-term adherence. Alternatively, family problems might have emanated from the child’s behavioral disturbances and therefore, these families might have kept their children on medication to deal with their conflicts and child’s behavior. A lack of evidence for the involvement of psychosocial adversity in adherence might have been due to the low scores available from the present study (range of 0-5 with a mean of 1.5).

*Disease factors.*

Severity of disease: It was hypothesized that children who were more inattentive, hyperactive, and impulsive would be less likely to adhere compared to their counterparts. However, in the present study, results indicated that a child was more likely to be adherent if he or she had more ADHD symptoms.

Presence of behavioral symptoms specifically at school seemed to predict adherence to stimulants. Parents might have adhered to stimulants so that the symptoms wouldn't interfere with the child's learning. Alternatively, parents might not have judged the need for the treatment based on the symptoms at home since the beneficial effects of stimulants were not evident at home (discussed below).

Comorbid disorders: It was hypothesized that presence of comorbid disorders would significantly affect how children adhere to stimulants. As predicted, presence of ODD was associated with adherence. The odds ratio indicated that non-adherence was 10 times as
prevalent among children with comorbid ODD as it was among children with no comorbid ODD. The adjusted odds ratio of 10 (results from logistic regression, Table 9) is much higher than the unadjusted odds ratio of 1.67 (results from descriptive characteristics, Appendix C2). ADHD symptoms at school is positively correlated with comorbid ODD at school \( (r = 0.43, p<0.001) \). However, these two factors are interacting with adherence in opposite directions. This means, for a child who has higher ADHD symptoms and a comorbid ODD, the probability of adhering to stimulants is greater than for a child who has fewer ADHD symptoms and the presence of comorbid ODD. Therefore, having comorbid ODD may not decrease the probability of adherence by 10 times as the odds ratio shows. Although it was not significant, there was a trend \( (P = 0.08) \) suggesting that having anxiety was associated with 3.5 times increase in the probability of discontinuing at least once. Lack of relationship between comorbid CD and non-adherence might have been due to the small proportion of ADHD children with CD in the present study.

**Behavioral and academic effects of stimulant adherence**

There were no significant cumulative effects seen among adherence groups on any of the measures examined. As indicated by Brown et al (1986), lack of cumulative effects shows that the effects of stimulant are temporary and experienced only when it is taken.

As expected, acute effect of stimulant was noted on teacher-rated ADHD symptoms. However, medicated and unmedicated children were found to be equally improved on parent-rated ADHD symptoms. Although this was not anticipated, this finding has been reported in many other studies (Firestone, 1982; Schachar et al., 1997). Because the majority of the children in the present study were taking the medication twice a day (as is
done in typical clinical practice) and because stimulants are short-acting, many parents of adherents might not have observed the benefits of the medication at home.

In contrast to the behavioral improvement documented at school, there were no significant differences found between adherents and non-adherents in academic performance. Although this finding has been consistently reported by other studies (Jadad, 1998; Schachar & Tannock, 1993), it was expected that documenting adherence would allow us to find a relationship between academic attainment and adherence to stimulant. Stimulant medication may help only the behavioral aspect of the disorder and the difficulties in learning should be addressed by other means (e.g., educational intervention).

Although adherents and non-adherents on stimulant at year 3 improved equally in behavior at home and academics, we don't know whether there are other consequences of intermittent drug use over the long-term.

Summary

About 50% of the children discontinued the stimulant medication at least once over the 3-year period. Forty percent of those who discontinued resumed the medication at year 3. Physical and psychological aspects of the medication appeared to influence adherence to stimulants. The most salient factors that predicted adherence to stimulants include child's age, severity of ADHD symptoms, and comorbid ODD at school. Subjects who were on stimulant at year 3 improved more on symptoms at school than did subjects who were off medications. However, there were no differences observed on symptom improvement at home or on academic improvement.
Limitations

The results must be interpreted in the context of the methodological limitations of the present study. First of all, the use of the convenience sampling method, the small sample consisting of 63 subjects and subjects with high comorbidity limit our ability to generalize the findings to treated ADHD in the general population. Results that were not significant for predicting adherence (e.g. family dysfunction and anxiety) and for evaluating the clinical effects were found to have power less than 80% to detect the presence of an effect suggesting small sample size. A sample of 91 children would be necessary to predict non-adherence using 5 variables (age, severity of ADHD symptoms, comorbid ODD, comorbid anxiety, and family dysfunction) (Power = 0.80, \( \alpha = 0.05 \), assuming an event rate of 50%, OR of 1.75 for age and correlation of 10% between age and other 4 predictors as in the present study). A sample size of 35 per group would be required to detect a difference on ADHD symptoms between the 3 adherence groups (Power = 0.80, \( \alpha = 0.05 \), assuming an effect size of 0.72 as in the present study).

In terms of level of supervision, there was only one follow-up per year after the first year and the study period was only 3 years. Semi-structured interviews were used to document adherence. Therefore, assessment of adherence was dependent on the memories of the informants and their willingness to truthfully report their behavior and perspectives.

Another major limitation of this study is that adherence was measured in the context of a research study. Subjects in the present study acknowledged their need for the treatment and willingly participated in a randomly assigned treatment group. In addition, medication dosage was carefully titrated and subjects were cautiously monitored for side effects. Therefore, research subjects who are part of clinical trials are likely to have fewer side
effects and to adhere better than are patients in the community. However, the present sample had a higher comorbidity than what is normally found among patients in the community. Because absence of comorbid ODD predicted adherence in the present study, patients in the community may adhere better compared to clinical samples. Potential lack of generalizability of the present findings to the patients in the community is therefore, a major limitation of the study.

It is also important to note that individual factors determining non-adherence may interact with each other in various ways. For example, when families notice some side effects and little beneficial effects, they may be more inclined to discontinue the medication (reaching the “threshold” for non-adherence) compared to families who notice clear improvements with similar side effects. Alternatively, presence of side effects may actually diminish perceived behavioral benefits. Therefore, asking families about non-adherence may be the best way to understand the process of discontinuation. However, it may not be possible to quantify the effect of each factor (given by parents) on non-adherence (e.g., number of side effects one must reach to discontinue the treatment).

Furthermore, other factors that were not explored in the study could have influenced adherence. For example, there is a growing preference in the present sample for sustained release preparation over standard preparation. The majority of subjects started taking sustained release mainly due to the difficulty in getting the midday dosing at school (Appendix B2). This suggests that number of doses per day may be important in predicting adherence to stimulants. The review by Haynes (1979) showed that in general, frequency of dosing is important only when it exceeds more than 3 times a day. Nevertheless, whether the child takes a dose at school (i.e. standard vs. sustained release) may be crucial (rather than
frequency of dosing) in determining stimulant adherence over the long-term. First, children who attend school may hesitate to take the pills at school because they don’t want to be different from their peers or because they don’t want to be seen taking pills (stigmatization). Second, it is a problem to make inattentive children responsible for taking their own pills. Therefore, the type of preparation (standard vs. sustained release) might be an important factor and the present study did not examine this factor.

Despite these limitations, the present research has been the first known study to examine adherence to stimulants over an extended period of time, to investigate why many children discontinue stimulants and to report the involvement of relevant predictors of non-adherence. The findings from the present study should be confirmed and extended by further research. The next chapter will discuss the implications of the present findings for clinicians and for researchers.
CHAPTER VII: IMPLICATION OF THE FINDINGS

Recommendations for clinical practice

Implications for medical practice arise mainly from the findings relating to 3 main areas (1) reasons for non-adherence; (2) predictors of non-adherence; and (3) behavioral and academic effects of stimulant adherence.

Reasons for non-adherence. Reasons for non-adherence given by parents would help to develop strategies for improving adherence. During the first year, the foremost factor that appeared to be influencing adherence was side effects. Therefore, closer monitoring of children for side effects is crucial during the first year of the treatment. Furthermore, parents must be educated about the adverse effects of stimulants and about the availability of alternative stimulants so they will not discontinue therapy prematurely once they notice side effects.

In addition, there were some families who complained that the medication was not effective although its effectiveness was established at treatment initiation. These families may have seen the side effects from stimulant and the adverse effects with absence of beneficial effects at home may have influenced them to discontinue. Physicians should assess the parental perception of effectiveness by prescribing an extra dose so that beneficial effects last throughout the day. An extra dose at the evening would also help alleviating rebound effects many children experienced in the present study. Clinicians try to avoid three-times-a-day (tid) administration because of possible increase in side effects. Compared with placebo, the severity of side effects has been shown to be greater in the tid but not in the
bid dosing. However, when directly compared, the severity of side effects has not been shown to differ between bid and tid dosing (Stein et al., 1996; Kent, Blader, Koplewicz, Abikoff, Foley, 1995). Therefore, medication trials should be conducted for each child, who exhibits the symptoms at home to evaluate the relative costs versus benefits of bid and tid dosing.

Children who reach adolescence may have difficulties adhering to the treatment due to the challenges posed by development. Some of the psychological issues surrounding adolescent development include striving for independence, the need for peer conformity, and increased experimentation. Therefore, physicians must include children in the discussion of treatment decisions and must assess their responsibility for handling health-related behaviors (taking medication). Strategies to improve adherence must be tailored to individual patients focusing on the specific demands they are facing. This might include shifting focus from educating parents about the disorder and treatment during the early part of the treatment to understanding the child's difficulties during adolescent development. However, educating parents should not be a one-time event. When children are first diagnosed with the disorder, the anxiety associated with the diagnosis may make it hard for parents to listen to and to remember details. Therefore, verbal and written instructions about the disorder and the treatment must be provided in an on-going manner in order to improve and maintain adherence (Cromer, 1991).

*Predictors of non-adherence.* Child's age, severity of symptoms, and comorbid disorders must be considered as potential risk factors for non-adherence. As was discussed above, children must take part in treatment decisions made by the physicians; and interventions to
enhance adherence must address the issues posed by adolescent development. Those who have comorbid ODD may not only be non-compliant with treatment but also with all parental requests in general. Therefore, behavioral therapy consisting of shaping and reinforcing good behaviors and punishing non-compliant behaviors such as time-out may help control general oppositional problems and consequently treatment compliance problems (Cromer, 1991).

Although the evidence is not conclusive, the findings from this study suggested that long-term regular follow-up, education for the family, discussion of potential concerns with adolescents about medications, and behavioral therapy for comorbidity may lead to improved adherence to the treatment.

Behavioral and academic changes. Lack of evidence for effectiveness of stimulant at home might have been due to twice daily dosing. Therefore, adding a third dose or combining sustained release with standard preparation may improve behavior at home. Stimulant medication may not be enough to address academic difficulties. Therefore, other interventions such as tutoring must be an integral part of the treatment for these children.
Recommendations for future clinical research

1) Follow a larger cohort of children from various socioeconomic backgrounds and from families with different degrees of family conflicts. Larger sample would permit investigation of effect of broader range of factors on adherence (and their interactions).

2) Since side effects were the major reason given by parents for non-adherence, severity of side effects must be examined to see if it predicts adherence to stimulants.

3) Longer follow-up with closer monitoring (i.e., frequent contacts and multiple assessments). Longer duration of follow-up would allow us to examine how children adhere when they reach adolescence (critical period in the long-term treatment). From the present study, it appears that many children will take the medication over many years (of those who discontinued at least once over the 3-year period, 40% had resumed the treatment at the follow-up).

4) Conduct a long-term study
   a) To examine the effects of standard vs. sustained release preparation of stimulants on behavior, academics, and adherence.
   b) To examine the effects of frequency of dosing (two times a day vs. three times a day) on behavior, on parents' perceptions about the medication, and on adherence.

4) Similar study conducted in a different setting (e.g., in a general practitioner's clinic).
REFERENCES


Boyle, M.H., Offord, D.R., Racine, Y., Szatmari, P., Fleming, J.E., & Sanford, M.


Brown, R.T., Borden, K.A., Wynne, M.E., Schleser, R., & Clingerman, S.R.


Appendix A: Distribution of scores

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1</td>
<td>Age of subjects by frequency</td>
<td>94</td>
</tr>
<tr>
<td>Figure 2</td>
<td>IQ of subjects by frequency</td>
<td>95</td>
</tr>
<tr>
<td>Figure 3</td>
<td>Number of ADHD symptoms present in subjects (at home) by frequency</td>
<td>96</td>
</tr>
<tr>
<td>Figure 4</td>
<td>Number of ADHD symptoms present in subjects (at school) by frequency</td>
<td>97</td>
</tr>
<tr>
<td>Figure 5</td>
<td>Family dysfunction index of subjects by frequency</td>
<td>98</td>
</tr>
<tr>
<td>Figure 6</td>
<td>Psychosocial adversity index of subjects by frequency</td>
<td>99</td>
</tr>
</tbody>
</table>
Figure 1. Age of subjects by frequency

Std. Dev = 1.57
Mean = 8.1
N = 63.00
Figure 2. IQ of subjects by frequency

Std. Dev = 14.51
Mean = 109.3
N = 63.00
Figure 3. Number of ADHD symptoms present in subjects (at home) by frequency

Number of ADHD symptoms at home

Std. Dev = 2.78
Mean = 11.0
N = 63.00
Figure 4. Number of ADHD symptoms present in subjects (at school) by frequency

Number of ADHD symptoms at school

Std. Dev = 2.61
Mean = 10.7
N = 63.00
Figure 5. Family dysfunction index of subjects by frequency

- Std. Dev = 6.12
- Mean = 22.3
- N = 58.00

Family dysfunction index
Figure 6. Psychosocial adversity index of subjects by frequency

Std. Dev = 1.08  
Mean = 1.5  
N = 63.00

Psychosocial adversity index
Appendix B1. Patterns of adherence over 3 years, adherence groups, and number of subjects

Patterns of adherence over 3 years

<table>
<thead>
<tr>
<th>Adherence groups</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th># of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor adherents (N=12)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Partial adherents (N=18)</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Good adherents (N=33)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>33</td>
</tr>
</tbody>
</table>

* Non-adherents who had resumed stimulant treatment (mainly due to poor school performance)

Legend

0 not adhered (according to the definition)
1 adhered
### Appendix B2. Number of subjects to which each of the treatment changes apply

<table>
<thead>
<tr>
<th>Concerns made by parents</th>
<th>Changes made by study physician</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Side effects or lack of effectiveness</td>
<td>adding or switching to sustained release stimulant</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>switching to another stimulant</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>adding clonidine</td>
<td>6</td>
</tr>
<tr>
<td>Compliance issues</td>
<td>switching to sustained release stimulant</td>
<td>13</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>adding an antidepressant</td>
<td>1</td>
</tr>
</tbody>
</table>

Total: 33
### Appendix C1. Characteristics of partial adherents and poor adherents (N = 30)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Partial (n = 18)</th>
<th>Poor adherents (n = 12)</th>
<th>P-value (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>8.45 (1.88)</td>
<td>8.88 (1.70)</td>
<td>0.53</td>
</tr>
<tr>
<td>Sex: % of females</td>
<td>22%</td>
<td>33%</td>
<td>0.68</td>
</tr>
<tr>
<td>IQ (WISC-R)</td>
<td>112.50 (15.96)</td>
<td>107.67 (16.17)</td>
<td>0.43</td>
</tr>
<tr>
<td>Number of ADHD symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At home (PICS)</td>
<td>11.06 (2.71)</td>
<td>10.42 (2.94)</td>
<td>0.55</td>
</tr>
<tr>
<td>At school (TTI)</td>
<td>10.11 (2.56)</td>
<td>10.25 (3.11)</td>
<td>0.90</td>
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<tr>
<td>Comorbidity (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ODD (home or school)</td>
<td>72%</td>
<td>75%</td>
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<tr>
<td>ODD (home)</td>
<td>61%</td>
<td>42%</td>
<td>0.30</td>
</tr>
<tr>
<td>ODD (school)</td>
<td>39%</td>
<td>50%</td>
<td>0.55</td>
</tr>
<tr>
<td>CD (home or school)</td>
<td>17%</td>
<td>0%</td>
<td>0.26</td>
</tr>
<tr>
<td>CD (home)</td>
<td>11%</td>
<td>0%</td>
<td>0.50</td>
</tr>
<tr>
<td>CD (school)</td>
<td>11%</td>
<td>0%</td>
<td>0.50</td>
</tr>
<tr>
<td>Anxiety (parent or child)</td>
<td>50%</td>
<td>50%</td>
<td>1.00</td>
</tr>
<tr>
<td>Anxiety (parent)</td>
<td>50%</td>
<td>17%</td>
<td>0.42</td>
</tr>
<tr>
<td>Anxiety (child)</td>
<td>17%</td>
<td>33%</td>
<td>0.39</td>
</tr>
<tr>
<td>LD (WRAT test)</td>
<td>33%</td>
<td>50%</td>
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<tr>
<td>Family characteristics</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Psychosocial adversity</td>
<td>1.72 (1.41)</td>
<td>1.33 (1.37)</td>
<td>0.46</td>
</tr>
<tr>
<td>Family dysfunction</td>
<td>21.04 (5.77)</td>
<td>21.54 (4.86)</td>
<td>0.81</td>
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</table>
Appendix C2. Characteristics of subjects who continued on stimulants (adherents) and subjects who stopped taking stimulants (non-adherents) (N = 63)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Adherents (n = 33)</th>
<th>Non-adherents (n = 30)</th>
<th>P-value (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>7.65 (1.17)</td>
<td>8.63 (1.79)</td>
<td>0.05 *</td>
</tr>
<tr>
<td>Sex: % of females</td>
<td>15</td>
<td>27</td>
<td>0.26</td>
</tr>
<tr>
<td>IQ (WISC-R)</td>
<td>108.18 (13.22)</td>
<td>110.57 (15.95)</td>
<td>0.52</td>
</tr>
<tr>
<td>Number of ADHD symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At home (PICS)</td>
<td>11.12 (2.83)</td>
<td>10.80 (2.77)</td>
<td>0.60</td>
</tr>
<tr>
<td>At school (TTI)</td>
<td>11.09 (2.44)</td>
<td>10.17 (2.74)</td>
<td>0.20 *</td>
</tr>
<tr>
<td>Comorbidity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ODD (home or school)</td>
<td>61</td>
<td>73</td>
<td>0.29</td>
</tr>
<tr>
<td>ODD (home)</td>
<td>52</td>
<td>53</td>
<td>0.89</td>
</tr>
<tr>
<td>ODD (school)</td>
<td>21</td>
<td>43</td>
<td>0.06 *</td>
</tr>
<tr>
<td>CD (home or school)</td>
<td>9</td>
<td>10</td>
<td>1.00</td>
</tr>
<tr>
<td>CD (home)</td>
<td>6</td>
<td>7</td>
<td>1.00</td>
</tr>
<tr>
<td>CD (school)</td>
<td>3</td>
<td>7</td>
<td>0.60</td>
</tr>
<tr>
<td>Anxiety (parent or child)</td>
<td>30</td>
<td>50</td>
<td>0.11 *</td>
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<tr>
<td>Anxiety (parent)</td>
<td>15</td>
<td>27</td>
<td>0.26</td>
</tr>
<tr>
<td>Anxiety (child)</td>
<td>18</td>
<td>23</td>
<td>0.61</td>
</tr>
<tr>
<td>LD (WRAT test)</td>
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<td>40</td>
<td>0.58</td>
</tr>
<tr>
<td>Family characteristics</td>
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</tr>
<tr>
<td>Psychosocial adversity</td>
<td>1.39 (0.70)</td>
<td>1.57 (1.38)</td>
<td>0.93</td>
</tr>
<tr>
<td>Family dysfunctioning</td>
<td>23.25 (6.71)</td>
<td>21.26 (5.29)</td>
<td>0.22 *</td>
</tr>
</tbody>
</table>

* Variables used to predict non-adherence
Appendix D. Acute effects of stimulant medication (N = 56*)

<table>
<thead>
<tr>
<th>Clinical effects</th>
<th>OFF stimulants (n = 14)</th>
<th>ON stimulant (n = 42)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>BEHAVIORAL changes</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ADHD (parent)</td>
<td>6.7 (5.7)</td>
<td>5.6 (5.9)</td>
<td>0.61</td>
</tr>
<tr>
<td>ADHD (teacher)</td>
<td>2.7 (6.3)</td>
<td>7.7 (7.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>ODD (parent)</td>
<td>2.9 (3.8)</td>
<td>1.4 (4.6)</td>
<td>0.32</td>
</tr>
<tr>
<td>ODD (teacher)</td>
<td>2.8 (5.9)</td>
<td>0.7 (5.7)</td>
<td>0.29</td>
</tr>
<tr>
<td>CD (parent)</td>
<td>1.2 (2.3)</td>
<td>1.2 (2.3)</td>
<td>0.63</td>
</tr>
<tr>
<td>CD (teacher)</td>
<td>1.2 (1.7)</td>
<td>0.6 (3.0)</td>
<td>0.27</td>
</tr>
<tr>
<td>ACADEMIC changes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Math</td>
<td>-1.9 (10.2)</td>
<td>2.0 (14.9)</td>
<td>0.44</td>
</tr>
<tr>
<td>Reading</td>
<td>11.0 (12.4)</td>
<td>7.3 (12.2)</td>
<td>0.40</td>
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<tr>
<td>Spelling</td>
<td>16.6 (12.6)</td>
<td>13.3 (13.4)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

* Seven subjects were not included based on the stimulant status at year 3
(N used in this analysis varied between 48 and 56 as data were not available for number of subjects)