

COMPLIANCE AND PERSISTENCE WITH STIMULANTS AMONG
ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY
DISORDER IN THE GEORGIA MEDICAID POPULATION

by

YAN DIANE DONG

(Under the direction of Dr. Jeffrey Kotzan)

ABSTRACT

Objectives: First, to assess the compliance and persistence with stimulants among adolescents with ADHD. Second, to examine the relationship between compliance and persistence with stimulants and the dosage form of the medication. **Method:** Adolescents with ADHD in the Georgia Medicaid program were followed retrospectively for 12 months in 1995 and their prescription claims data were examined to evaluate for compliance and persistence with stimulant treatment. **Results:** Of the 1,081 study cohort, 66% consumed only immediate-release stimulants, and 83.6% took the same stimulant during the course of study. The median compliance and persistence was 120 days and 65 days respectively. Logistic regression demonstrated that younger age, being non-blacks, incorporating sustained-release stimulants in the treatment regimen, and making changes in the stimulant predicted compliance and persistence. **Conclusions:** Compliance and persistence were poor among adolescents with ADHD. Sustained-release stimulants were associated with better persistence with stimulants.

INDEX WORDS: Attention-deficit/ hyperactivity disorder, Stimulant medication, Adolescents, Compliance, Persistence, Dosage form, Georgia Medicaid, Claims data

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YAN DIANE DONG

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YAN DIANE DONG

Approved:

Major Professor: Jeffrey Kotzan

Committee: William Spruill
William McCormick

Electronic Version Approved:

Gordhan L. Patel
Dean of the Graduate School
The University of Georgia
May 2002

DEDICATION

To my husband, Eric, who has been my faithful cheerleader every step of the way; my sweet girl, Tiffany, who is the brightest sunshine when my sky is gray.

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TABLE OF CONTENTS

	Page
ACKNOWLEDGMENTS	v
CHAPTER	
1 INTRODUCTION	1
1.1 Purpose of the Study	1
1.2 Objective and hypotheses	3
2 LITERATURE REVIEW	4
2.1 Clinical definition and diagnosis of ADHD.....	4
2.2 Etiology of ADHD	5
2.3 Prognosis and Comorbidity of ADHD.....	6
2.4 Epidemiology of ADHD.....	7
2.5 Impact of ADHD.....	8
2.6 Treatment of ADHD	10
2.7 Compliance issues.....	17
3 METHODOLOGY	23
3.1 Data source.....	23
3.2 Design of the study	24
3.3 Data extraction	24
3.4 Statistical analysis.....	27

4	STUDY RESULTS	29
4.1	Summary of the study population	29
4.2	Univariate statistics of compliance and persistence.....	31
4.3	Chi-square test for independence of outcomes and study variables	32
4.4	Logistic regression analysis	34
5	DISCUSSION	38
5.1	Statistical inference	39
5.2	Strength of the study	45
5.3	Limitations of the study	46
5.4	Conclusions	47
	REFERENCES	49
	APPENDIX.....	55
	DSM-IV Criteria for ADHD	55

CHAPTER 1

INTRODUCTION

1.1 Purpose of the Study

Attention -deficit /hyperactivity disorder (ADHD) is one of the most commonly diagnosed behavioral disorders of childhood, with profound impact on affected individuals, their families and society as a whole. Over 70 percent of children diagnosed with ADHD will have persistent symptoms in adolescence and adulthood.¹ It is not surprising, therefore that, there has been considerable interest in the development of effective treatment programs.

Clinical management of ADHD includes an effort to alleviate the core symptoms and complications of ADHD with pharmacotherapy. Stimulants, including amphetamine, methylphenidate and pemoline, are the most widely studied and commonly prescribed treatments for ADHD. In adolescents, however, problems of medication monitoring, compliance with frequent dosing, and abuse potential are challenging issues in the management of ADHD.² The beneficial short-term effects of stimulant medications on the classroom and social behavior of ADHD children have been well documented.^{1,3,4} However, there is little evidence to support the long-term positive impact of stimulants on outcome for children with ADHD. Lack of compliance has been suggested as one of the possible explanations for suboptimal long-term treatment outcome in ADHD.⁴

Compliance with therapeutic regimens has been a neglected issue in the treatment of adolescents with ADHD. Only 8 peer-reviewed articles were published between 1970 and 2001, which addressed stimulant compliance among children with ADHD. Nevertheless, converging evidence indicates that poor compliance or adherence to prescribed dosage among ADHD patients is pervasive. According to recent estimates, 50 to 75 percent of teenagers with ADHD discontinue their medications.⁵ A study conducted by Firestone found that about 20 percent of patients had discontinued medication by the 4th month of the study and that only 55 percent of the children were still taking the prescribed medication by the end of 10th month.⁶ A recent study by Thirmchelvam (2001) reported that 81% of children continued to use stimulant medication for 12 months, 67% for 2 years, and 52% adhered to stimulant treatment for 3 years.⁷ Many adolescents resist taking medications because they fear losing control as well as being stigmatized by peers, particularly if they have to take a mid-day dose in the school. It has been shown that complexity of the drug regimen including its form and schedule is negatively correlated with patient compliance.^{8,9} Because of their half-lives, frequent dosing of most of the stimulant medications increases the risk of noncompliance. As Litt suggested, poor compliance accounts for variability in outcome data and creates problems in evaluating efficacy of medications.⁸

Previous studies examining stimulant compliance have limitations in scope and design. Most of studies examined discontinuation of stimulant from 18 weeks to 12 months. The sample sizes were consistently small, ranging from 12 to 56 subjects after attrition. Most of studies measured compliance by pill counts, and, or patient/parent's self-report. These methods can be unreliable and overestimate compliance.^{6,10,11,12,13} The

study by Thiruchelvam (2001) was the first continuous follow-up of children with confirmed diagnosis of ADHD over a period of 3 years.⁷ There is no compliance study specifically for adolescents with ADHD and the relationship between compliance and dosage form of the medication is yet to be explored. This project will assess compliance and persistence with stimulants in the Georgia Medicaid population. The target group is adolescents with ADHD. This study will provide valuable information to health care professionals and help them identify potentially noncompliant patients.

1.2 Objective and hypotheses

The main purpose of the study is to investigate the relationship between stimulant compliance and persistence and age, race, gender, as well as dosage form of the medication and patient's behavior of changing stimulants. Based on the objective of the study, the following hypotheses are proposed:

H₀₁: Compliance and persistence with stimulants are not related to age

H₀₂: Compliance and persistence with stimulants are not related to gender

H₀₃: Compliance and persistence with stimulants are not related to race

H₀₄: Compliance and persistence with stimulants are not related to dosage form of the medication

H₀₅: Compliance and persistence with stimulants are not related to patients' behavior of changing stimulants

CHAPTER 2

LITERATURE REVIEW

The following sections of this chapter will review ADHD in the aspects of its clinical definition, prognosis and outcome, epidemiology and pharmacological treatment. Issues related to compliance with the therapeutic regimen for ADHD will also be discussed in this chapter.

2.1 Clinical definition and diagnosis of ADHD

Attention –deficit/ hyperactivity disorder (ADHD) is characterized by developmentally inappropriate activity levels, impulsivity, distractibility and inability to sustain attention and concentration.⁴ Since it was first described clinically as a defect in moral control by George Still in 1902, the definitional boundaries and labels assigned to this complex of problematic behaviors have undergone more than 25 name changes to arrive at its current definition in the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)*.¹⁴ Roughly synonymous terms include hyperactive child syndrome and minimal brain dysfunction or damage (1940-1960, pre-DSM-II), attention deficit disorder (ADD) and hyperkinetic reaction with attention and impulse control as the core deficits (1970s-1980s, DSM-II), attention deficit disorder with and without hyperactivity (ADD/H, 1987, DSM-III-R), and attention deficit/hyperactivity disorder (ADHD, 1994, DSM-IV).^{4,15,16} The criteria in DSM-IV distinguish three subtypes of

ADHD (see appendix 1): predominantly inattentive type (meeting at least 6 of 9 inattention behaviors), predominantly hyperactive-impulsive type (meeting at least 6 of 9 hyperactive-impulsive behavior), or combined type (meeting at least 6 of 9 behaviors in both the inattention and hyperactive-impulsive lists).^{17,18} Despite the limitations presented in DSM-IV criteria, the diagnostic criteria in DSM-IV have demonstrated high interrater reliability of individual items and of overall diagnosis when used appropriately by examiners.^{15,19}

The overall approach to appropriate diagnosis of ADHD should involve a comprehensive interview with the parents, use of ADHD-focused parent and teacher rating scales, a mental status examination of the child, a medical evaluation of the child for general health, including hearing, vision and neurologic status, a cognitive assessment of the child's intellectual ability, and use of a school report.^{1,3,17}

2.2 Etiology of ADHD

Numerous attempts have been made to clarify the pathophysiology of ADHD. At present time, heredity appears to represent the most common identifiable cause of ADHD.^{1,15,16} Although a specific genetic pattern of inheritance has not been identified for ADHD, it has long been recognized that ADHD runs in families. Genetic studies have revealed that hyperactivity was noted in the parents of hyperactive children four times as commonly as in those of controls. Adopted children with ADHD symptoms have biologic, rather than adoptive parents with similar symptoms and concordance rates for ADHD are much higher in full siblings than half-siblings, and in monozygotic than dizygotic twins.^{15,16,20}

Despite the high rate of heritability for ADHD, it is been suggested that environmental factors such as lead, alcohol, and cigarette smoking, appear to be capable of making a contribution to ADHD. Suboptimal parenting skills and particular parenting characteristics have not been demonstrated to be causative for ADHD. In fact, in a study by Barkley, negative maternal behaviors were found to be the result rather than the cause of the child's difficult behavior.¹⁵

In addition, abnormalities have been noted in the brains of those with ADHD in magnetic resonance imaging studies, single photon emission computed tomography and neurophysiological studies.^{1,16} Although the results from those studies need to be validated by future research with larger cohorts using more specific diagnostic criteria, the findings provide increasing support for the concept of ADHD as a neuropsychiatric condition or set of conditions. Taken as a whole, ADHD, to date, remains a purely behaviorally defined disorder without a specific biologic marker or clear unitary etiology.

2.3 Prognosis and Comorbidity of ADHD

ADHD begins in childhood. The observable symptoms change in quantity and quality across development. On average, symptoms of ADHD diminish by about 50 percent every 5 years between the ages of 10 and 25 years. Hyperactivity declines faster than impulsivity or inattentiveness.¹

Despite the methodological variability in diagnostic criteria, sample characteristics, assessment instruments, and the timing of follow-up assessments, studies have consistently documented the persistence of ADHD into adolescence and young adulthood. Weiss *et al.* (1985) reported in their 15-year follow-up study that 66 percent

of children with ADHD had persistence of a full or partial DSM-III attention deficit disorder syndrome into young adulthood.²¹ In a study by Barkley *et al.* (1990), 72 percent of boys with ADHD were found to meet the DSM-III-R criteria for this disorder 8 years later.²² Biederman *et al.* (1995) also reported in their 4-year follow-up study that 85 percent of children with ADHD continued to experience the disorder and 15 percent remitted. Of those who remitted, half did so in childhood and the other half in adolescence. It was also found in this study that familiarity of ADHD, psychosocial adversity, and comorbidity with conduct, mood, and anxiety disorder could predict the persistence of ADHD into adolescence.²³

A variety of other psychiatric and developmental disorders frequently occur with ADHD. It was estimated that as many as one third of children with ADHD have one or more coexisting conditions.¹⁷ The available data suggest that comorbidity between ADHD and conduct disorder/oppositional defiant disorder is between 43% and 93%. Relatively lower rates of comorbidity are found between ADHD and the internalizing disorders such as depressive disorder and anxiety disorder (13% to 50.8%).^{17,24}

2.4 Epidemiology of ADHD

ADHD is the most common neuropsychiatric disorder of childhood. It is also one of the most prevalent chronic health conditions affecting school-aged children.^{17,25} Prevalence estimates for ADHD vary substantially because of changing diagnostic criteria over time, variations in ascertainment in different settings, difference in population sampled and variations in measures used.^{1,3,17} The American Academy of Pediatrics estimated the prevalence in school-aged children to be 4% to 12%.²⁵ In a

community study in New York, Cohen (1993), using DSM-III-R criteria, reported that ADHD existed in 8.5% of girls and 17.1% of boys aged 10 to 13 years, 6.5% of girls and 11.4% of boys aged 14 to 16 years, and 6.2% of girls and 5.8% of boys aged 17 to 20 years.²⁶ In the Ontario Child Health Study, Szatmari (1989) found ADDH (DSM-III) in 3.3% of girls and 10.1% of boys between 4 to 11 years of age and in 3.4% of girls and 7.3% of boys between 12 to 16 years of age.²⁷ In general, ADHD appears more frequently in males than in females. With DSM-IV criteria, male-to-female ratio range from 4:1 for the predominantly hyperactive –impulsive type to 2:1 for the predominantly inattentive Type.^{18,28} As Gaub (1997) found in their study, ADHD boys and girls have somewhat different expressions of ADHD symptoms. Compared with boys, ADHD girls displayed lower levels of hyperactivity, lower rates of other externalizing behavior, but greater intellectual impairment.²⁹ Search of medical literature reveals limited prevalence data for adolescents and adults.

2.5 Impact of ADHD

Children with ADHD often suffer from various combinations of impairments in functioning at school and at home. They have difficulty in sitting still and concentrating in class. As a result, they experience the negative consequences of such behavior, such as lower-than-expected grades, achievement test scores, failure to complete or turn in homework assignments, as well as poor organizational and study skills.^{3,18,30} The behavioral difficulties related to ADHD also result in constant friction between the student and peers, the teacher, and the parents. Children with ADHD are often rejected by peers due to their aggression, impulsivity and non-compliance with rules.³ The study by

Barkley *et al.* (1990) confirmed that hyperactive children are at substantially higher risk for negative outcome in the domains of psychiatric, social, legal, academic, and family functioning.²²

ADHD has also taken a heavy toll in adolescents with regard to academic, emotional, and family functioning, psychiatric status, as well as high-risk behavior. In terms of psychiatric status, over 60% of adolescents with ADHD also have oppositional defiant disorder, 22% to 43% manifest conduct disorder, 29% also have major depressive disorder and 27% manifest anxiety disorders.^{22,31} Adolescents with ADHD are at least 3 times more likely than non-ADHD peers to have failed a grade, been suspended or expelled, failed to graduate high school, or failed to attend college.²² ADHD adolescents are at higher risk for more sexually transmitted disease and teen pregnancies due to having more sexual partners and using birth control less frequently than non-ADHD teens.³¹ Adolescents with ADHD are at risk for initiating cigarette smoking 2 years earlier than their peers without ADHD. The cohort with ADHD and conduct disorder is 2 to 5 times more likely to initiate substance abuse than pure hyperactives or non-ADHD children.^{22,31} Individuals with ADHD consume a disproportionate share of resources and attention from the health care system, criminal justice system, education systems, and other social service agencies.³⁰ Leibson (2001) compared medical care use and costs among persons with and without ADHD and found persons with ADHD exhibited substantially greater use of medical care in multiple care delivery settings. The study reported that the 9-year median costs for persons with ADHD, compared with those without ADHD, were more than double (\$4306 vs. \$1944).³² Additionally, the indirect cost of ADHD to the society is also large. For example, in 1995, additional national

public school expenditures on behalf of students with ADHD may have exceeded \$3 billion.³¹

2.6 Treatment of ADHD

2.6.1 Epidemiologic findings associated with stimulants

ADHD is strongly associated with comorbid disorders and wide-range effects of behavioral problems. Multimodal treatments, including pharmacotherapy, psychosocial therapy and school-based approaches are highly recommended.^{1,3}

Medication is the primary therapy for children and adolescents with ADHD and in most cases, central nervous system (CNS) stimulants, including immediate-, and sustained-release dextroamphetamine (Dexedrine®), and immediate-, and sustained-release methylphenidate (Ritalin®), and pemoline (Cylert®) are the three most common drug treatments for ADHD.^{33,34} Representing over 90% of the stimulant medication market, Ritalin® is by far the most widely prescribed stimulant in the treatment of ADHD.^{15,35,36}

Stimulant prescriptions (primarily Ritalin®) have been on a steady increase over the last two decades, rising from 1.1% of public elementary students receiving medication for ADHD in 1971 to 5.96% of students in 1987.³⁷ Stimulant prescriptions temporarily decreased to 2.2% in 1989 after a two-year media blitz and well-publicized threatened lawsuit against methylphenidate.³⁸ Subsequent studies documented its resumed upward climb in the 1990s. Zito *et al.*, using Maryland Medicaid data, reported that percentage of enrollees aged 5 to 14 being treated with methylphenidate between 1990 and 1994 increased from 1.9% in 1990 to 4.7% in 1994.³⁹ Similarly, a more recent

study by Rushton and colleagues, using North Carolina Medicaid data, also reported stimulant prescription prevalence in school-aged children 6 to 14 years rose from 4.4% in 1992 to 9.5% in 1998.⁴⁰ Other studies of methylphenidate prevalence based on Michigan triplicate prescription data and Baltimore County public school nurses' headcount of students medically treated for ADHD yielded similar results.^{36,41} Overall, the findings from regional and national databases indicate that there was a fairly consistent pattern of a sizable rate of increase in the prevalence of methylphenidate treatment for ADHD in the 1990s. In mid-1995, approximately 2.8%(or 1.5 million) of youths aged 5 to 18 in the United States were receiving this medication.³⁹

There are several explanations to the increased stimulant treatment for ADHD in the United States. These include increased diagnosis resulted from heightened public and physician awareness of the condition. Several studies reported that from 1990 to 1994, number of patients diagnosed as having ADHD increased from 900,000 to 2 million, and the number of outpatient visits for ADHD rose from 1.7 million to 4.2 million.^{42,43} Whether the numbers cited above represents the actual increase in the true prevalence of ADHD awaits more research. There is also evidence to suggest that stimulants in ADHD populations are being used for longer periods with fewer interruptions in treatment. For instance, the percentage of middle school students taking stimulants for ADHD rose from 0.59% in 1975 to 2.98% in 1993, and the percentage of high school students more than tripled from 0.22% in 1983 to 0.70% in 1993.⁴⁴ Studies also indicate that the proportion of adolescents in public schools who receive medication for ADHD continue to double about every 5 years.³⁹ This increase may be explained by the greater knowledge of the illness course as well as the safety and efficacy of stimulants.

2.6.2 Pharmacology and Pharmacokinetics

Information on dosage, action, and half-life on the 4 major stimulants (i.e., Dexedrine®, Ritalin®, Ritalin-SR®, Cylert®) is presented in the table 1 below.^{15,34,45,46} Although the pharmacological effects of the stimulants have been studied extensively, the exact mechanism of action involved in the treatment of ADHD has not been determined. In general, stimulants increase the release of the catecholamines (both dopamine and norepinephrine) and inhibit their reuptake into the presynaptic neurons.^{15,34,47} Contrary to the previous assumption that children with ADHD have a paradoxical “calming” response to the stimulants, “response to stimulants is not diagnostic, as hyperactive and normal children have qualitatively similar cognitive and behavioral responses.”^{1,3} Thus, a positive response to stimulants does not confirm a diagnosis of ADHD.³

Dosages for stimulants are usually not weight dependent. Although most studies have found a linear dose-response relationship in group data, individual dose-response curves are highly variable. For a particular child, a dose that produces maximal effects on attention, task completion and behavior change may have no effect or even lead to impairment in learning abilities.^{3,4,15} Clinicians should start with a low dose of medication and titrate upward to find the best dose that leads to optimal effects with minimal side effects. The first dose that the child responds to may not be the best one to improve function.²⁵

Table 1. Common Stimulants in Children and Adolescents

GENERIC (BRAND)	DEXTRO-AMPHETAMINE (DEXEDRINE®)	METHYL-PHENIDATE (RITALIN®)	METHYL-PHENIDATE (RITALIN-SR®)	PEMOLIN (CYLERT®)
Age	>=3 yrs. od	>=6	>= 6	>= 6
How supplied(mg)	5; spansule(SR) 5,10,15	5,10,20	20	18.75,37.5,75
Daily dose range (mg/d)	5-40	10-40	20-40	18.75-112.5
Daily dosage schedule	BID – TID (immediate release) QD – BID (SR)	BID - TID	QD - BID	QD - BID
Plasma half life (in children)	6-8 hr	1-2 hr	2-4 hr	7-8 hr
Onset of action	30-60 minutes 1-2 hr for spansule	30-60 minutes	1-2 hr	Variable Higher dose (2mg/kg): 2 hr Lower dose: up to 3 wks
Duration	<4 hr; 6-8 hr (SR)	3-5 hr	About 8 hr	About 8 hr

2.6.3 Short Term Clinical Effects

Hundreds of randomized controlled trials have consistently demonstrated the short-term efficacy of stimulants in controlling the core symptoms of ADHD: inattention, impulsivity, and overactivity.^{1,15,25,45} In short term trials, stimulants are more effective in alleviating the target symptoms than placebo and nonpharmacological therapies.^{34,48} Stimulant medications as a group led to an average improvement rate of over 70%, compared to 39% for placebos.^{15,34} In a study by Elia, using a wide range of doses of methylphenidate and dextroamphetamine, the efficacy rate increased to 96% when a second stimulant was tried in children who did not respond to the first drug.^{33,47} Current evidence suggests that in younger, more inattentive and hyperactive children with poorer motor coordination and less anxiety symptoms, the response to stimulant treatment is better.¹⁵

Stimulants improve attention span, and decrease distractibility. Stimulants also reduce the task-irrelevant restless and motor activity level of the child with ADHD, especially in structured, task-oriented situations.^{15,48} In terms of impulsivity and overactivity, the behavior of children with ADHD who were treated with stimulants became indistinguishable from those of their non-ADHD peers.⁴⁵

Observational studies have also demonstrated that treatment with stimulant medications significantly improved the quality of social interactions between children with ADHD and their teachers, peers and parents. Barkley reported improved maternal-child and sibling interactions and increased compliance with parental commands.^{15,48} Studies also found that those treated with stimulants have improved peer relations, primarily through reductions in aggression.^{45,47}

Although some studies have documented immediate improvement in performance on spelling and arithmetic, such changes occur too quickly to reflect a real increase in reading and math achievement. It is probably more appropriate to interpret such changes as improved ability to function in the test setting. To date, there is no conclusive evidence that stimulants improve academic performance.^{4,45}

2.6.4 Long Term Clinical Effects

Most studies of stimulants have demonstrated the efficacy over several days or weeks. The multimodal treatment study extends the demonstrated efficacy to 14 months.²⁵ Although highly effective in short-term symptomatic improvement, the evidence of enduring positive effects following stimulant treatment is inconclusive.^{1,25} Those who have examined the long-term effects have generally found minimal or

negative results of stimulant drugs on scholastic achievement, peer relationships, or behavior problems in adolescence.^{15,48} Hechtman (1985) reported no difference in any important domain of functioning between children with ADHD who had been on stimulant medications but were off their medications at the time of follow-up and those who had never received pharmacotherapy.⁴⁹ The poor long-term treatment outcome may have several possible explanations: 1) for ethical reasons, it is difficult to conduct a sufficiently long term study with random assignment of children to medication or placebo, and 2) the validity of studies even as short as 5-months in length, is also undermined by the wide-spread poor compliance with medication.^{3,4,10} Despite limited information about the long-term efficacy of stimulants, Barkley suggested that stimulant treatment “is not a short-term solution to ADHD but rather an intervention that must often be employed on a chronic basis to maintain positive effects.”¹⁵

2.6.5 Side Effects

Side effects for all stimulants are generally mild, transient, dose-related and subject to individual differences. Many of the side effects diminish within 1 to 2 weeks of initiating medication and disappear upon stopping pharmacotherapy.^{1,3} The most common side effects are insomnia, decreased appetite, weight loss, headache and abdominal pain. Negative mood changes such as sadness, proneness to crying, and irritability have also been reported, especially by ADHD children who take stimulants. On the contrary, adults are more likely to report euphoria, not dysphoria, after taking stimulant medications.^{15,34,46}

The use of stimulants for patients with chronic tics or Tourette's disorder has been controversial because of concern that stimulants may worsen tics or precipitate the development of new tics.^{1,17,25} Some studies found about 15% to 30% of children experience motor tics, most of which are transient, when treated with stimulants.^{17,25,45} A review of 7 studies comparing stimulants with placebo or with other medications found no increase in tics in ADHD children treated with stimulants.²⁵ Some researchers have suggested that low to moderate doses of stimulants may be used safely and effectively to treat children with ADHD and tic disorder. Nevertheless, others have suggested that stimulant must be used carefully for children with a family history of tic disorder.^{1,25,45}

Another side effect that has been encountered frequently by clinicians is the "rebound" phenomenon. This may resemble a deterioration of the original symptoms. Usually, this consists of increased excitability, irritability, activity, or insomnia that occurs in the late afternoon and evening when the last dose of the day wears off.^{3,15,34} Rebound effects may be managed by administration of a lower-dose medication in the late afternoon (provided that this does not lead to loss of appetite at dinnertime or insomnia), or use of a long-acting formulation.^{3,15,34}

Growth suppression is a possible long-term side effect that has been of concern. Present evidence, however, suggests that suppression in growth, primarily resulting from loss of appetite, is relatively transient and has no significant effect on eventual adult height or weight.^{15,25}

Concerns have also been raised about children's possible addiction to stimulants or increased risk of abusing other drugs as teenagers. Currently, there is little evidence to suggest that either children or adolescents with ADHD exhibit signs of addiction to the

stimulants when taken orally.^{1,50} However, existing studies offer conflicting conclusions as to whether use of stimulants increases or decreases the risk of substance abuse.^{1,15}

2.6.6 Discontinuation of Medication

There are no firm guidelines regarding when to discontinue stimulant treatment. It was once believed that treatment should be discontinued when a child reaches puberty given diminished efficacy. However, empirical research over the past several decades, has consistently demonstrated that the beneficial effect of the stimulants is similar for children and adolescents with ADHD.^{15,34,50} On average, the duration on medication for ADHD is 7 to 8 years for high school students, 4 to 5 years for middle school students and 2 years for elementary school students.⁴⁴

2.7 Compliance Issues

The failure of patients to comply with medical instructions is a major health care problem. Non-compliance results in loss of twenty million workdays and \$1.5 billion in earnings every year.⁵¹ Nearly 10% of hospital admissions and 23% of nursing home admissions are caused by noncompliance. The combination of direct and indirect cost of noncompliance with medication has been estimated at \$100 billion per year in the United States.^{51,52}

Compliance, which is defined as “the extent to which the patient’s behavior (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice,”⁵³ represents one of the most vulnerable links in the therapeutic chain. In clinical practice, the patient’s improvement is commonly taken as an

indication that medication was taken properly, and conversely, failure to improve is often assumed to reflect non-compliance.^{8,53} Although this may be true in some cases, it is obvious that lack of improvement may also result from improper diagnosis, ineffective medications, or failure to inform patient how to take the medication correctly. There are direct and indirect measures of compliance. Direct measure refers to the quantitative and qualitative analysis of body fluids such as urine and blood samples to determine presence or absence or actual levels of the prescribed medication. The direct measure, though seemingly perfect, is limited by variable bioavailability of the drug due to interactions with other medication, interference with food, or individual differences in rates of metabolism.^{53,54} The direct measurements can also be misleading if the patient takes the medication prior to testing.^{54,55} Indirect measures include therapeutic outcome, pill counts, patient's self-reporting, monitoring prescription renewal dates, as well as physician estimate of compliance. Just like direct measurement, each indirect means of measuring compliance has advantages and disadvantages. For instance, patient's self-reporting and pill counts tend to overestimate compliance. Monitoring prescription refill records has the advantage of being unobtrusive. However, it does not provide the actual pattern of medication consumption.^{54,55,56}

The reported rate of medication compliance for pediatric patients has been low among various published studies. It has been estimated that the overall noncompliance rate for a pediatric population is 50%, with a range of 20% to 80%.⁸ There is some evidence from compliance studies of patients on long-term medical regimens that adolescents generally are less compliant than younger children.^{53,57} For instance, in a study of pediatric renal transplant patients, Beck found that noncompliance with

immunosuppressive therapy was associated with adolescents.⁵⁸ Although compliance may vary according to regimen, it is typical that compliance to the long-term regimen in asymptomatic conditions usually follows the U-shaped curve, with approximately one-third of the patients taking almost all of the medication, one-third taking none, and one-third between these extremes.⁵³

As described previously, ADHD is a persistent condition, affecting children from preschool to schoolage, and continuing through adolescence into adulthood.^{1,3} This chronic illness may merit long-term pharmacotherapy treatment.^{2,15} Without good compliance, the best therapy is ineffective. Limited data indicate that non-compliance with stimulant regimen is a significant problem in children with ADHD. In an 18-week study of 12 boys between ages of 6 and 12, Kauffman (1981) compared compliance between methylphenidate and amphetamine. Compliance rate, which was measured by a positive drug urine test, was 67% for Methylphenidate and 60% for d-amphetamine.¹⁰ Firestone (1982) studied adherence to methylphenidate among 56 hyperactive children between 5 and 9 years of age and reported that 20% of the patients discontinued medication by the fourth month of the study and 44% by the tenth month. Fewer than 10% of those families consulted with the project staff before terminating medication treatment.⁶ Brown *et al.*(1987) randomly assigned 34 children with ADHD between the ages of 6 and 13 to methylphenidate or placebo and 3 months of cognitive behavioral treatment. Compliance rate as measured by pill counts for methylphenidate was 75%.¹¹ In the most recent study by Thiruchelvam (2001),⁷ 71 ADHD children between the ages of 6 to 12 were prescribed methylphenidate and evaluated for adherence to the medication on an annual basis for 3 years. Adherence was measured by pill counts as

well as telephone contacts with parents, teacher and children at 4,8,12 months after initiation of treatment. After 12 months, pill counts were discontinued and adherence was evaluated on an annual basis by telephone contact at 2 and 3 years. In this study, of the 63 subjects who remained in the study at 3 years, 81% adhered to stimulant for 12 months, 67% for 2 years and 52% for 3 years. Another recent survey estimated that 50% to 75% of teenagers with ADHD discontinue their medications.⁵ Poor compliance with stimulant medication poses a major difficulty in accurately assessing the efficacy of treatment for ADHD and may explain, in part, the variable and negative long-term treatment outcome.^{1,3}

Clinical investigators have attempted to describe factors related to noncompliance and a number of determinants have been reported consistently in the literature. Complexity of a drug regimen is negatively correlated with compliance. More drugs, as well as more frequent dosing, appear to have a negative effect on a patient's compliance. Patients are less likely to be compliant as the frequency of dosing increases.^{8,9,53,54} Another important factor in patient compliance is "a good treatment alliance".⁶⁷ Hack reported that patients who receive ongoing treatment or frequent follow-up appointments are more likely to be compliant.⁶⁷ It was reported, however, that 43% of the children on stimulant were not adequately monitored by a physician. (Firestone) This poor monitoring practice may have contributed to the low compliance with stimulants. Drug side effects of methylphenidate were not important in decision to stop taking medication by the nonadherents in the study by Firestone. Instead, the major reasons given were that parents did not feel comfortable medicating their children with stimulants or the children were reluctant to take stimulants.⁶ Other studies concerning

ADHD found that lower age of the patients and parents, male gender, being non-white, and lower IQs of patients and parents predicted noncompliance.^{6,11,12} Thiruchelvam reported that younger age, more teacher-rated ADHD symptoms, and absence of oppositional defiant disorder (ODD) predicted adherence.

Some developmental issues specific to adolescents put them at high risk for noncompliance. Adolescence is characterized by the emergence of greater personal freedom, autonomy, and the development of self-esteem.^{59,60,61} Many adolescents refuse taking medication which adults want them to take simply because they are rebellious. They may resist the diagnosis or indications for treatment because of their natural developmental tendency to resist external agents of control and their need to feel that nothing is wrong with them.^{2,31,60} Adolescents with ADHD may intend to be compliant but they either forget to take the pills or feel embarrassed to take the mid-day dose in school. In many adolescents, regular-release stimulants, such as methylphenidate, are absorbed rapidly, yet will not last more than 4 hours.^{34,46} In this case, twice daily administration (in the morning and at noon) is necessary to ensure adequate treatment effect for the whole day. More intensely treated adolescents will require 4 or more daily doses to prevent rebound phenomenon during the late afternoon.^{34,60,61,62} Multiple daily dosing, or taking midday medication may put adolescents at higher risk for noncompliance.^{53,59,60,62} The sustained-form of methylphenidate, which has the efficacy compared with the regular-release formulations, lasts up to 8 hours.^{15,34,46,62} Medication taken in the morning should provide adequate blood concentrations for the entire school day and therefore, midday dosing becomes unnecessary. Thus, the sustained-release form

of methylphenidate has the potential to improve compliance and positively affect the outcome of treatment in adolescents with ADHD.

To summarize, ADHD is one of the most commonly diagnosed behavioral disorder of childhood that represents a major public health problem. ADHD is a chronic disorder, affecting children and continuing through adolescence into adulthood. In the last two decades, there has been an increase in the number of adolescents diagnosed with and treated for ADHD. Although numerous studies have established the efficacy and safety of stimulant for treating adolescents with ADHD, noncompliance with pharmacotherapy is a significant problem among adolescents and it creates a huge barrier to the effective treatment. Data on compliance and persistence with stimulants among adolescents with ADHD are practically nonexistent. Given the chronic and debilitating nature of ADHD, it is very important to monitor compliance and persistence with therapeutic regimens when evaluating the effectiveness of the medication and identify factors that may affect the compliance and persistence among adolescents with ADHD.

CHAPTER 3

METHODOLOGY

A retrospective longitudinal review of Georgia Medicaid data was used to examine the compliance and persistence with stimulants among adolescents with ADHD. In this chapter, the source of data, the design of study, data extracting criteria and the method of statistical analysis will be discussed in turn.

3.1 Data source

The Georgia Medicaid claims were the data source for this study. This computerized database contains the records of all Georgia Medicaid recipients, and is currently housed at the University of Georgia. The database consists of the following three files:

- (1) Recipient eligibility file, which contains monthly records of eligibility and demographic characteristics;
- (2) Monthly medical history file, which contains information for all medical claims such as diagnosis codes, category of services etc., and
- (3) Monthly pharmaceutical history file, which provides prescription information for each Medicaid enrollee.

Medicaid records from January of 1993 to December of 1995 were summarized for this study. To capture all prescribed stimulants in the Medicaid prescription file, a list

of stimulant products from the Multum® Information Service was used (www.multum.com)

3.2 Design of the study

Phase I study, which began on January 1, 1993 and ended on December 31, 1994, was designed to identify the potential cohort for the compliance study. To be included in this group, recipients were between the ages of 10 to 16 as of January 1, 1993, and had at least one ICD-9 CM code for ADHD without any diagnosis for major mental disorders, at least one stimulant prescription was obtained during the 24-month period. The information obtained in phase I include diagnosis of ADHD, stimulant prescription, and age.

Compliance and persistence with stimulants were measured and analyzed in the phase II study, which began on January 1, 1995 and ended on December 31, 1995. The group identified from 93 and 94 were followed through 95. Those who developed major mental disorders in 95 were discarded from the cohort. Those who were not continuously eligible for 95 were also eliminated from the study.

3.3 Data extraction

Some operational definitions related to this research, as well as inclusion and exclusion criteria are provided in this section.

3.3.1 Operational definitions

I) **ADHD** is identified as any of the following ICD-9-CM codes:

314.01 - attention deficit/hyperactivity disorder, combined type

314.00 - attention deficit/hyperactivity disorder, predominantly inattentive type

314.01- attention deficit/hyperactivity disorder, predominantly hyperactive-impulsive type

3140 - attention deficit disorder

31480 - attention deficit disorder, residual type

314.9 - attention deficit/hyperactivity disorder not otherwise specified

314 - hyperkinetic syndrome

II) **Major mental conditions** are identified as any of the following ICD9-CM

codes:

293.xx - psychotic disorder

295.xx - schizophrenia

296.xx - bipolar disorder

297.xx - paranoid, delusional disorder

298.xx - psychotic disorder NOS

299.xx - pervasive developmental disorder, psychosis

300.xx - generalized psychogenic anxiety disorder

301.xx - personality disorder

303.xx, 304.xx, 305.xx - alcohol, drug, tobacco dependence and abuse

309.xx - adjustment disorder

311- depressive disorder NOS

312.xx - conduct disorder

313.xx - oppositional defiant disorder

317.xx, 318.xx, 319.xx – retardation

III) **Stimulant** prescriptions were defined as all generic, trade name forms of stimulant regardless of dosage form. These prescriptions were identified by using the information provided by Multum®, by merging Multum® with the National drug code (NDC) numbers of the Medicaid prescription files.

IV) **Compliance and Persistence**

Compliance is defined as the total days of prescription filled during the follow-up period. The Georgia Medicaid program encourages monthly prescription quantities for long-term therapy, especially controlled substances. Each date of service is considered as one 30-day stimulants prescribed and filled. If the interval between the subsequent date-of-service and the preceding date-of-service is less than 30, then the compliance days is equal to the interval; if the interval is equal or greater than 30, then the compliance days is equal to 30.

Persistence is defined as the number of days of continuous therapy during the follow-up period. If the same prescription was refilled within a window of 45 days from the beginning of the preceding prescription, the patient was considered persistent. If the interval between the subsequent date-of-service and the preceding date-of-service is less than or equal to 45, then the persistence days is equal to the interval; if the interval is greater than 45, the persistence days is zero.⁹

3.3.2 Inclusion and Exclusion criteria

3.3.2.1 Inclusion criteria

All Georgia Medicaid recipients who met the following criteria were included:

1. Adolescents: age as of January 1,1993 was between 10 to 16 years old
2. Individuals who had at least one ICD9 CM code for ADHD within the period of January 1993 to December 1994.
3. Individuals who filled at least a single stimulant prescription during the period from January 1993 to December 1995.
4. Individuals who were continuously enrolled in the Medicaid programs through 1995.

3.3.2.2 Exclusion criteria

1. Individuals who had at least one ICD9 CM code for major mental disorders during the period from January 1993 to December 1995
2. Individuals who had category of service for general inpatient hospitals or inpatient mental hospitals during 1995.
3. Individuals who had unknown gender.
4. Individuals who were not continuously eligible during 1995.

3.4 Statistical analysis

SAS version 8.2(SAS Institute, Cary, NC) was used throughout this study.

Descriptive statistics (frequency and percentage) were calculated for the potential factors defined in the study, including age, gender, race, and the dosage form of the medication. A logistic regression model was developed to test hypotheses and explore

the quantitative association between compliance and persistence and age, gender, race, as well as the dosage form of stimulants, and patient's behavior of changing stimulants. The dependent variable is $\log [P/(1-P)]$, where P is the probability of being compliant for 120 days or more, or being persistent for 60 days or more. The explanatory variables were demographic characteristics (age, gender, race), dosage form of the medication, and patient's behavior of changing stimulants. Measures of statistical significance (p-values) and odds ratios (OR) were computed for the predictor variables.

CHAPTER 4

STUDY RESULTS

4.1 Summary of the study population

Between January 1, 1993 and December 31, 1994, there were 2,876 individuals between the ages of 10 to 17 selected from the Georgia Medicaid Claim Database according to the inclusion criteria. Of these, 1,795 people were deleted from the study according to the exclusion criteria. Among the 1,795 excluded individuals, 774 were not continuously eligible for Georgia Medicaid for 1995, 448 were diagnosed with one of the major mental disorders in 1995, two had inpatient admission in either a general hospital or a mental hospital in 1995, and 571 stopped taking stimulant prescription in 1995. Therefore, 1,081 individuals were included as the study cohort. There were total 6,854 prescription records for the study population. The following table summarizes the characteristics for the study population

Table 2 Characteristics of the cohort and related variables

Characteristic	N (1081)	Mean Compliance (std. dev)	Mean Persistence (std. dev)	Median comply/persis
Sex				
Male (85%)	922	140 (87.47)	101 (93.79)	120/65
Female	159	140 (92.46)	103 (95.44)	120/67
Race				
Black(53%)	570	119 (75.18)	79 (71.55)	120/49.5
Non-black	511	164 (95.47)	126 (108.72)	150/75
Age				
12-15(83%)	899	143(86.71)	102(93.47)	120/66
16-18	182	128(94.29)	97(+/- 96.67)	90/59
Dosage Form				
Immediate-release (66%)	714	136(88.09)	96(94.50)	120/59
Other	367	148(87.95)	110(92.39)	140/74
Therapy Change				
Mono-drug (84%)	904	131(85.78)	91(89.34)	120/59
Multi-drug	177	187(85.24)	147(103.57)	180/115

The following observations can be obtained from the above table:

1. Males (85%) dominated the group. Looking at the median compliance and persistence, males and females were very similar.
2. Blacks (53%) outnumbered non-blacks. Blacks had lower median compliance and persistence, compared to non-blacks.
3. The mean age of the cohort was 13.7 years with a standard deviation of 1.32. Over 83% of the cohort were between the ages of 12-15. The median compliance/persistence for the older adolescents (16-18 group) were lower, compared to the group between 12-15.
4. In terms of the dosage form, “Immediate-Release” refers to the subjects who consumed only immediate-release stimulants (including methylphenidate tablet, Ritalin tablet, and Dexedrine tablet) during the entire course of the study period. “Other” refers to those subjects who exclusively consumed sustained-release

stimulants (including Cylert, Dexedrine Capsule, methylphenidate SR, and Ritalin-SR), and those who either took combination of both regular-release and sustained-release stimulants, or those who switched from immediate-release to sustained-release and vice versa. As shown from the table above, over 66% of the subjects consumed only immediate-release stimulants. Those who consumed only immediate-release had lower median compliance and persistence.

5. In terms of therapy change, “Mono-Drug” refers to those subjects who took the same stimulant (in terms of trade-name) for the entire study period, whereas “Multi-Drug” refers to the subjects who switched stimulants at least once during the study period. Therapy change was used as a proxy for physician-patient relationship in terms of physician monitoring and patient’s follow up. As noted from the table above, 94% of the study cohort consumed a single stimulant. Compared to those who switched at least once to other trade-name stimulants, the non-switch group had much lower median compliance and persistence.

4.2 **Univariate statistics of compliance and persistence**

Table 3

Statistics	Compliance (Days)	Persistence (Days)
Mean	140	101
Standard deviation	88.18	93.99
25 percentile	60	30
Median	120	65
75 percentile	183	135

The data is positively skewed, with a range from 30 days to 360 days for both compliance and persistence. In the chi-square and logistic regression analysis, the median for both compliance and persistence was used to dichotomize the group into two cohorts: compliance vs. non-compliance, and persistence vs. non-persistence.

4.3 Chi-square test for independence of outcomes and study variables

4.3.1 Chi-Square test for independence and relative risk of noncompliance

Table 4 Relative risk for non-compliance

Variables	Absolute Risk	Relative Risk	Prob>chisq
Sex			
Female	43.40	1.04	0.7181
Male *	41.87		
Age			
12-15 *	39.82	1.34	0.0008
16-18	53.30		
Race			
Black	49.82	1.49	<0.0001
Other *	33.46		
Dosage Form			
Immediate-release	43.70	1.12	0.1356
Other *	38.96		
Therapy Change			
Mono-drug	46.02	2.08	<0.0001
Multi-drug *	22.03		

* refers to the base comparator for relative risk calculation

- (1) The association between gender and compliance was not statistically significant.
- (2) The impact of age on compliance was statistically significant. Compared to those between the ages of 12-15, the group of 16-18 had a 34% increased risk of being non-compliant.
- (3) Race was significantly associated with compliance. Being black increased the risk of being non-compliant by 49%, compared to non-blacks.
- (4) Dosage form was not significantly associated with compliance.

(5) Whether or not the subjects switched the stimulants had a significant impact on compliance. Compared to those who switched the stimulant at least once, those who took a single stimulant were twice likely to be non-compliant.

4.3.2 Chi-Square test for independence and relative risk of non-persistence

Table 5 Relative risk for non-persistence

Variables	Absolute Risk	Relative Risk	Prob>chisq
Sex			
Female	44.03	0.94	0.5417
Male *	46.64		
Age			
12-15 *	45.38		
16-18	50.55	1.11	0.2024
Race			
Black	54.39	1.46	<0.0001
Other *	37.18		
Dosage Form			
Immediate-release	50.28	1.31	0.0002
Other *	38.42		
Therapy Change			
Mono-drug	50.66	2.13	<0.0001
Multi-drug *	23.73		

* indicates the base comparator for relative risk calculation

- (1) Gender was not significantly associated with persistence.
- (2) The effect of age on persistence was not statistically significant
- (3) Race was significantly associated with persistence. Being black increased the risk of being non-persistent by 46%.
- (4) The effect of dosage form on persistence was statistically significant. Those who consumed only immediate-release stimulants increased the risk of being non-persistent by 31%.
- (5) Change in stimulant therapy had a significant impact on persistence. Compared to those who changed the stimulant at least once, those who took the same stimulant had a 2-fold increased chance of being non-persistent

4.4 Logistic regression analysis

In this section, a logistic regression analysis was performed to test hypotheses and explore the quantitative association between compliance and persistence and age, gender, race, as well as the dosage form of stimulants, and change in therapy. The five hypotheses in Chapter 1 are reiterated for convenience:

H₀₁: Compliance and persistence with stimulants are not related to age

H₀₂: Compliance and persistence with stimulants are not related to gender

H₀₃: Compliance and persistence with stimulants are not related to race

H₀₄: Compliance and persistence with stimulants are not related to dosage form of the medication

H₀₅: Compliance and persistence with stimulants are not related to patient's behavior of changing stimulants

4.4.1 Variable definition

The variables of interest for the study are defined in Table 5.

Table 5 Variable names and definition

Variable Type	Name	Definition
Dependent	COMPLY	1 if compliance days ≥ 120 (median); 0 otherwise
Dependent	PERSIS	1 if persistence days ≥ 60 (median); 0 otherwise
Independent	AGE	Continuous variable, 12-18
Independent	FEMALE	1 if the subject is female; 0 otherwise
Independent	BLACK	1 if the subject is black; 0 otherwise
Independent	IMMEDIATE-RELEASE	1 if the subject took immediate-release only; 0 otherwise
Independent	MULT_DRUG	1 if the subject took more than 1 type of stimulants; 0 otherwise

4.4.2 Statistics measuring the fit of the model and predictive power

The Hosmer-Lemeshow Goodness-of-Fit statistic was calculated to measure how well the model fits the data. For both models of compliance and persistence, the p-values for the Goodness-of-Fit tests were greater than 0.3, indicating the models fit the data well. C-statistic was 0.669 for compliance model, indicating that the model correctly predicted the probability of being compliant 67 percent of times. Similarly, c-statistic for persistence was 0.652, implying that the model correctly predicted the probability of being persistent 65 percent of times.

4.4.3 Output from logistic regression analysis

A logistic regression model of compliance and persistence was employed on all the independent variables listed in the table above. Stepwise method with alpha of 0.1 was used to determine the best model and the most appropriate independent variables. The odds ratio for each variable is an estimated multiplicative effect of a one-unit increase in that variable on the odds of being compliant for ≥ 120 days or being persistent for ≥ 60 days, holding all the other covariates constant. Odds ratios, p-value, and 95% CI were displayed in the following table.

Table 6 SAS 8.2 output from logistic regression**Compliance****Odds Ratio Estimates**

Effect	Odds Ratio	95% Wald Confidence Limits		Pr >Chisq
AGE	0.783	0.711	0.861	<0.0001
BLACK	0.507	0.393	0.654	<0.0001
IMMEDIATE	0.867	0.660	1.140	0.0642
MULT_DRUG	2.828	1.920	4.166	<0.0001

Persistence**Odds Ratio Estimates**

Effect	Odds Ratio	95% Wald Confidence Limits		Pr >Chisq
AGE	0.853	0.775	0.938	<0.0011
BLACK	0.515	0.401	0.661	<0.0001
REGULAR	0.690	0.526	0.906	0.007
MULT_DRUG	2.758	1.899	4.006	<0.0001

From the above table, the following inferences can be made:

- (1) For each year increase in age from 12 to 18, adolescents were 22% less likely to be compliant.
- (2) Compared to non-black adolescents, blacks were about 50% less likely to be compliant.
- (3) The relationship between dosage form and compliance was not statistically significant.
- (4) Taking different stimulants increases the odds of being compliant by 183%.

- (5) With each year increase in age from 12 to 18, adolescents were 15% less likely to be persistent.
- (6) Black adolescents were 49% less likely to be persistent, compared to non-blacks.
- (7) Adolescents who consumed only immediate-release stimulants were 31% less likely to be persistent.
- (8) Adolescents who consumed different stimulants were 176% more likely to be persistent.

In the stepwise model, gender was not significantly related to either compliance or persistence.

CHAPTER 5

DISCUSSION

ADHD is one of the most commonly diagnosed behavioral disorders of childhood and adolescence that represents a major public health problem. In the last two decades, there has been an increase in the number of adolescents diagnosed with and treated for ADHD.^{1,2,25,61} However, there has been a limited number of studies reporting treatment results specific to adolescents with ADHD. Noncompliance with pharmacotherapy is a significant problem among adolescents and it creates a huge barrier to the effective treatment.^{53,57} Data on compliance and persistence with stimulants among adolescents with ADHD are practically nonexistent. Given the chronic and debilitating nature of ADHD, it is very important to monitor compliance and persistence with therapeutic regimens when evaluating the effectiveness of the medication and identify factors that may affect the compliance and persistence among adolescents with ADHD. This research addressed this objective. The present study may be the first retrospective follow-up of adolescents with a confirmed diagnosis of ADHD that has evaluated compliance and persistence with stimulants over a period of 12 months. The following sections of this chapter discussed the statistical inference of the results presented in chapter 4, the strength and limitations, and final conclusions of this study.

5.1 Statistical Inference

There were 1,081 adolescents with ADHD, but without any other major mental disorders, in the Georgia Medicaid population in 1995. The multiple logistic regression analysis was performed to quantify the association between compliance and persistence and age, gender, race, dosage form of the stimulant, as well as patients' follow-up, which was inferred by their behavior of changing stimulants.

The study results indicate that the overall compliance and persistence with stimulants are poor among adolescents with ADHD. Fifty percent of the adolescents are compliant for 120 days out of 360 days, while fifty percent of them remain persistent for 65 days out of 360 days. Given the chronic nature of ADHD, the low rate of compliance and persistence would appear to be a huge barrier to the long-term care of adolescents with ADHD.

The poor compliance reported in this study is consistent with other studies concerning compliance with stimulants among children with ADHD.^{6,7,10,11,13} The low persistence rate may be explained by the “drug holidays”. It is common that school-aged children and adolescents will not take stimulants during weekends, school holidays, and summer/winter breaks. In the study by Thiruchelvam, adherents were those who continuously consumed the stimulants for 190 days during one year period, when considering all the potential “drug holidays” in a year.⁷ The rates in this study, however, are lower than what was reported in previous studies. Firestone⁶ reported in his study, which lasted for 12 months, that 80% of the children were still taking their medications at 4 months, and 56% of the children were doing so at 10 months. Medication compliance was 75% by pill counts in the study by Brown¹¹, which monitored compliance with

methylphenidate for 3 months. In the most recent study by Thiruchelvam⁷, 81% of subjects continued to use stimulant at 12 months. Discrepancies between the current study and the earlier studies may be due to several factors: previous studies examined stimulant compliance among children between the ages of 5 to 13, and the subjects in this study are between the ages of 12 to 18. As the study results indicate, the increase in age is inversely related to compliance and persistence. If the subjects of the study were in the similar age group as other studies, the compliance and persistence rate may have been higher. The majority of the previous studies measured stimulant compliance with parent or patient report, or pill counts. Subjects in those studies were usually observed with their knowledge that compliance was being assessed. Therefore, these studies were potentially subject to the Hawthorne effect and compliance was mostly likely overestimated.^{53,63} Compared to 1,081 subjects in the current study, the sample sizes in previous studies are consistently small, ranging from 12 to 76 subjects with an average of 46 subjects per study. The small sample size would have made it easier for researchers to monitor the treatment progress, which in turn, may encourage the compliance with medication.

There are several developmental issues salient to adolescents that relate significantly to their compliance with medical advice. First, Adolescence is characterized by the emergence of greater personal freedom, autonomy, and the development of self-esteem.^{59,60,61} “which is often manifested as increased oppositionality toward authority”.⁶¹ Many adolescents may refuse to take medication which adults want them to take simply because they are rebellious. They exercise noncompliance in the attempt to assume some control. Coping mechanisms are used to avoid the anxiety resulting from identity formation, the establishment of greater independence, and physiological changes.

“The coping strategies in adolescents commonly include denial and acting out”.⁵⁷ They may resist the diagnosis or indications for treatment because of their natural developmental tendency to resist external agents of control and their need to feel that nothing is wrong with them.^{2,31,60} Also, the difficulties associated with increased independence and autonomy are typically met by a greater need for peer acceptance.⁶¹ Adolescents don’t want to be singled out or labeled as “the drugged ones”. Therefore, they may feel embarrassed to take the medication in school. Finally, “consolidation of body image is another dynamic area of development in the normal adolescent”.⁵⁷ Growth suppression is a possible long-term side effect of stimulants that has been of concern. Although present evidence suggests that suppression in growth resulted from taking stimulants is relatively transient and has no significant effect on eventual adult height or weight,^{15,25} adolescents may have concerns about the growth suppression and choose to discontinue stimulants.

Similar to previous compliance studies^{6,7,12}, younger age is positively related to compliance and persistence in the current study. This study indicates that with each year increase in age from 12 to 18, adolescents are 22% less likely to be compliant and 15% less likely to be persistent with stimulants. This phenomenon is explained by the developmental characteristics pertinent to adolescents discussed above. In addition, the misconception that ADHD is a self-limiting disorder of childhood with remission of symptoms after puberty may have contributed to the declining compliance and persistence among adolescents, especially as they age.^{6,61} Longitudinal studies have consistently documented the persistence of ADHD into adolescence and young

adulthood.^{15,21,23} It is true that the observable symptoms of ADHD change in quantity and quality across development. Hyperactivity diminishes faster than impulsivity and inattentiveness.¹ However, many adolescents who were diagnosed with ADHD during childhood continue to suffer from moderate to severe impairment in functioning even when they have subclinical levels of ADHD.^{15,61} As Firestone pointed out, “this change in the topography of the problematic behavior may lead to decreased adherence rates”.⁶

Consistent with the study by Brown¹¹, in which white subjects missed fewer pills, race is significantly related to stimulant compliance and persistence in the present study. Being blacks decrease the odds of being compliant and persistent by 50% and 49% respectively. The racial difference in medication compliance and persistence may be partially explained by the ethnic group differences in patterns of help-seeking behavior, which in turn is strongly influenced by cultural factors.⁶⁴ Research has indicated that African American and Latino families were 37% less likely to seek help from a health care professional than white families. A majority of the preclinic contacts of the non-white groups were with families and community residents, while majority of the white families contacted professionals. Even when families of minority background seek medical help from professionals and initiate treatment, they are more likely to terminate treatment prematurely compared with white families.⁶⁴ This implies that “families of African and Latino background may be reluctant to present their concerns in clinic settings and may have some level of mistrust toward behavioral health specialists”.⁶⁴

As previously reported,^{7,53} the current study does not show any statistical difference between males and females with respect to stimulant compliance and persistence. This may be because males and females have similar perceptions and

attitudes toward taking stimulants. When assessing the attitudes toward taking stimulants among hyperactive children, Sleator⁶⁵ indicated that change in attitude was related to age. However, the relationship between gender and attitude was not established.

The present study may be the first to assess the relationship between stimulant compliance and persistence and dosage form of the medication. As discussed in chapter 2, stimulants can be either immediate-release or sustained-release, depending on the half-life, and duration of action. In this study, methylphenidate SR, Ritalin® SR, Dexedrine® Spansule, and Cylert® are classified as sustained-release, methylphenidate, Ritalin®, and Dexedrine® Tab are classified as immediate-release. Immediate-release stimulants, such as methylphenidate, are absorbed rapidly, yet the effectiveness will not last more than 4 hours.^{34,46} In this case, twice daily administration (in the morning and at noon) is necessary to ensure adequate treatment effect for the whole day. More intensely treated adolescents will require 4 or more daily doses to prevent rebound phenomenon during the late afternoon.^{34,60,61,62} Multiple daily dosing, or taking midday medication may put adolescents at higher risk for noncompliance.^{53,59,60,62} The sustained-form of methylphenidate, which has the efficacy comparable to the immediate-release formulations, lasts up to 8 hours.^{15,34,46,62} Medication taken in the morning should provide adequate blood concentrations for the entire school day and therefore, midday dosing becomes unnecessary. Liptak⁶⁶ reported that, in a general pediatric population, once or twice-daily dosing achieves 70% to 80% compliance, whereas three or four times a day achieves only 40% to 50% compliance.

In the current study, dosage form of the stimulant was not found to have a significant impact on compliance. However, persistence is significantly related to the

dosage form of the medication. Those adolescents who consume only immediate-release stimulants are 31% less likely to be persistent. Compliance in this study is defined as taking stimulants for the treatment of ADHD, while persistence reflects the continuous or consistent pattern of taking the stimulants, which parallels more closely with the definition of compliance in other studies.^{7,8,53} In this regard, the finding of the current study agrees with previous studies. As mentioned earlier, multiple-daily dosing resulted from immediate-release stimulants makes it more difficult for adolescents to consistently maintain the therapy because they may forget to take the mid-day dose or feel embarrassed to take it in school. This finding has important clinical implication for medical providers who manage the care of adolescents with ADHD. Sustained-release stimulants have the potential to improve patient compliance and maximize the therapeutic outcomes. Therefore, if no other contraindications exist, providers should consider prescribing more sustained-release stimulants.

This study may also be the first to assess the association between stimulant compliance and persistence and physician-patient relationship. In the present study, we used the frequency of changing stimulants as a proxy of patients' consistently following up with medical providers and seeking the best treatment regimen. Stimulants are controlled substances. Therefore, making a change to another stimulant requires an appointment or consultation with the medical provider and a new hand-written prescription. In general, research has supported "the contention that the quality of the relationship between doctor and patient contributes significantly to compliance behavior".⁵⁷ Patients who receive ongoing treatment and more frequent appointments are more cooperative and more compliant.^{57,67} This study indicates that those who changed

stimulants at least once are 183% more likely to be compliant, and 176% more likely to be persistent. This result confirms the recommendation in the American Academy of Pediatric's clinical guideline for treatment of children with ADHD in which it states that "the clinician should periodically provide a systematic follow-up for the child with ADHD"²⁵, because "research on adherence to medical regimens in chronic disease highlights the importance of identifying patient and family concerns and goals and jointly designing a management plan in a way that addresses these concerns and promotes these goals".²⁵ Physicians can help improve patient compliance with treatment regimens by monitoring patients' treatment progress regularly and fostering a sound physician-patient relationship.

It is also conceivable that those who followed up with their medical providers and changed stimulants more frequently were likely to have more severe manifestations of ADHD symptoms. In that regard, our finding is consistent with the study by Thiruchelvam, in which increased frequency of teacher-reported ADHD symptoms were positively related to adherence.⁷

5.2 Strength of the study

The strength of the study is the uniqueness of the study, the sample size, and the study method. This study may be the first compliance study specifically for adolescents with ADHD. It may also be the first one to quantify the relationship between stimulant compliance and persistence and dosage form of the medication, as well as physician-patient relationship. The results of the study provide medical providers with valuable information to guide treatment decisions to adolescents with ADHD. Secondly, this may

be the largest cohort of adolescents with ADHD that has been investigated to determine stimulant compliance and persistence. Each year, over one million Georgia residents are eligible for the Medicaid benefits. Therefore, it can be assumed that the study population included a variety of medical conditions, and health beliefs.⁵⁶ Compliance and persistence in this study were assessed retrospectively by review of prescription refill records. This method does not rely on patient participation or observation. Hence, the Hawthorne effect may be avoided and the findings of compliance and persistence are more valid.⁶³

5.3 Limitations of the study

Several limitations should be noted for this study. One is the operational definitions of compliance and persistence, which were completely based on prescription records, “for which there were no data to verify that recipients actually consumed the agents”.⁵⁶ Therefore, it cannot be ensured that the medication is actually taken, or taken properly, even though refills may have occurred at proper times. Additionally, although a database can reveal that patients are no longer receiving a particular prescription, it does not indicate the reason for discontinuation (eg, adverse events, lack of efficacy) or other influencing factors (eg, severity of illness, comorbidities).⁹

The design of this study was static group comparison. Potential selection bias exists due to lack of randomization and equivalent control group. Those who were prescribed immediate-release stimulants may be inherently different from those who were prescribed non-immediate release stimulants. Although multiple logistic regression was used to control for some of the confounding variables such as demographic

characteristics, other confounding factors such as severity and duration of disease, education level, family characteristics may still bias the measurement because these variables don't exist in the claims data and therefore can not be modeled.

Finally, the subjects in this study were both left and right censored. Some of our subjects had received stimulant prescription in the months before the study started, and prescription consumption was left censored because we could not observe this behavior. Other subjects might continue therapy for many months after the last month of our study, and some may have discontinued stimulants after completion of the study. Because we could not observe this behavior, compliance and persistence with stimulants beyond 12 months of observation are right censored.⁵⁶

5.4 Conclusions

The study results demonstrate that compliance and persistence are poor among adolescents with ADHD in the Medicaid population. Fifty percent of the adolescents are compliant with stimulant treatment for 120 days, and fifty percent of them consistently take the medication for 60 days out of 360 days. Poor compliance with stimulant medication poses a major difficulty in accurately assessing the efficacy of treatment for ADHD. Future studies of the long-term efficacy of drugs in treating ADHD should include objective assessment of medication compliance. The long-term care of adolescents with ADHD must include interventions to maintain and improve compliance with medication.

The results of this analysis indicate that including sustained-release stimulants in the treatment regimen increases the chance of being persistent, and having more frequent

follow-up with physicians significantly increase the odds of being compliant and persistent among adolescents with ADHD.

Considering the results of the current study and previous stimulant compliance studies in pediatric population, it may be suggested that health care providers adopt the following two interventions to improve patient compliance with stimulants. The first is trying to reduce the dosing frequency and simplify medication regimen whenever possible by taking advantage of the available sustained-release form of stimulants. The second is building a sound physician-patient relationship by monitoring patients' progress regularly and working with patients and their families to find the best medication regimen tailored to individual patient's needs.

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APPENDIX

DSM-IV Criteria for ADHD

A. Either 1 or 2(or both):

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:
 - a. often fails to give close attention to details or makes careless mistakes in schoolwork, 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 schoolwork, 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 often 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:
 - 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 restless)
 - 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
 - g. often blurts out answers before the question has been completed
 - h. often has difficulty awaiting turn
 - i. often interrupts or intrudes on others (e.g. butts into conversations or games)

Additional criteria:

B. The behavioral symptoms of ADHD must be present for at least 6 months, across 2 or more settings (e.g., at home and in school), ensuring that persistent rather than transient symptoms shall be included.

C. At least some of the symptoms must have been present before the age of 7. The symptoms must be maladaptive and inconsistent with developmental level and intellectual ability of the patient.

D. The symptoms are of sufficient severity to cause clinically significant impairment in social, academic, or occupational functioning.

E. The symptoms are not better explained by another disorder such as pervasive developmental disorder (autism), mood disorder, or psychosis.

Adapted from American Psychiatric Association¹³

Goldman, L.S., Genel, M., Bezman, R.J., et al¹

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