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A study of incidence, prevalence, treatment patterns, healthcare utilization, and costs of treatment of Attention Deficit Hyperactivity Disorder (ADHD) among Texas Medicaid preschoolers

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A STUDY OF INCIDENCE, PREVALENCE, TREATMENT PATTERNS, HEALTHCARE UTILIZATION, AND COSTS OF TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AMONG TEXAS MEDICAID PRESCHOOLERS

by

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Dedication

To my Mom and Dad.

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A study of incidence, prevalence, treatment patterns, healthcare utilization, and costs of treatment of Attention Deficit Hyperactivity Disorder (ADHD) among Texas Medicaid preschoolers

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Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurobehavioral disorder diagnosed in children and adolescents, affecting approximately 11% of children in the United States in 2011. Children are often diagnosed with ADHD before seven years of age. Yet, there is very little information about the diagnoses, treatments, healthcare utilization, and costs associated with ADHD in preschool children.

The American Academy of Pediatrics recommends behavioral therapy as the first-line therapy for preschoolers, with a recommendation to prescribe medications only if behavioral therapy is unsuccessful in alleviating ADHD-related symptoms. For children in elementary school, combination therapy is recommended. Thus, the goal of the current study was to assess the epidemiology (i.e., prevalence and incidence), treatment patterns (i.e., adherence, persistence, augmentation, and switching), healthcare utilization, and costs in preschoolers diagnosed with ADHD using the Texas Medicaid dataset.

Patients < 6 years of age diagnosed with ADHD (ICD-9 codes 314.00, 314.01) with continuous enrollment for a 6-month pre-index period and a 12-month post-index period between

2008 and 2013 were identified from the Texas Medicaid dataset. Epidemiology estimates were calculated for all the patients < 6 years of age diagnosed with ADHD. Treatment patterns, healthcare utilization, and costs were estimated for patients between 2 – 6 years of age. Based on the study inclusion criteria, we identified 10,877 patients in the overall cohort. A subsample from the overall cohort was selected for inclusion in the treatment pattern cohort (n = 8,833). The index date for the overall cohort was the ADHD diagnosis date. The index date for the treatment pattern cohort was the date of the first ADHD prescription. Prevalence and incidence estimates were calculated for all the patients < 6 years of age. Time-to-initiation, healthcare utilization, and costs were analyzed using the overall cohort. Treatment pattern outcomes (i.e., adherence, persistence, augmentation, and switching) were evaluated using the treatment pattern cohort. The study sample was further subcategorized into pharmacotherapy only, psychotherapy only, and combination therapy groups. The study covariates included patient demographic (i.e., age, gender, race/ethnicity, and urban/rural status), clinical (i.e., other psychotropics, other mental health diagnosis, medication duration of action, and medication class), and prior utilization (i.e., pre-index total costs, pre-index psychiatric visits, and pre-index non-psychiatric visits) characteristics. Bivariate and multivariate analyses were used to analyze the data.

The prevalence of ADHD in preschoolers was estimated to be between 2.1% and 8.5% from years 2008 to 2012. Incidence estimates were stable and were estimated to be between 2.4% and 2.1% from years 2009 to 2012. Medication adherence, augmentation, and switching rates were higher in the combination therapy group as compared to the pharmacotherapy group. The combination therapy group had significantly higher healthcare utilization in all resource utilization categories except ADHD-related prescriptions, other mental health-related office-based, and inpatient visits. Similarly, medical, prescription, and total healthcare costs were also

significantly higher in the combination therapy group as compared to the pharmacotherapy group except for the other mental health-related medical costs.

In summary, the prevalence and incidence of ADHD in preschoolers is significant. Most of the patients received medication therapy followed by combination therapy and psychotherapy. A comparison of treatments revealed that combination therapy group had a higher healthcare burden as compared to the pharmacotherapy group. This study adds to the existing literature regarding ADHD in preschoolers, from a Medicaid perspective. Also, since Texas Medicaid provides coverage for nearly 50% of children in Texas these results have important implication for the state of Texas. The results of the current study will help identify the more important healthcare utilization and cost categories so as to develop a more targeted intervention approach for patients with ADHD. Further research is needed to understand the long-term effects of pharmacotherapy, psychotherapy, and combination therapy in preschoolers. More evidence is needed to identify the best treatment option for the management of ADHD in preschoolers.

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CHAPTER 1: INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders diagnosed in children. Although symptoms of ADHD decline with age, a vast majority of patients show developmental delays and associated mental health problems later in life. The Diagnostic and Statistical Manual Fifth Edition (DSM-V) emphasizes that the onset of impulsivity or inattentiveness can start manifesting in children earlier than 7 years of age (i.e., during kindergarten and preschool years).[1] Although there is a lack of more recent prevalence estimates of ADHD in preschoolers, previous studies during the 1990s and 2000s have estimated the prevalence rate of ADHD in preschool children (< 6 years of age) to vary between 0.5% and 6.5%.[2–6] These ADHD prevalence estimates are lower (11%) compared to those in children (6 – 12 years of age) and adolescents (13 – 17 years of age) and vary based on the referral source, diagnostic criteria, and diagnostic instruments used in the studies.[2–6] Preschoolers who are referred to psychiatrists and other healthcare professionals are more likely to have a higher healthcare burden, frequent behavioral issues, comorbidities, aggressive and disruptive behavior, inattentiveness and impulsivity compared to their peers. They are more likely to suffer from injuries, are developmentally more challenged, have problems in maintaining peer-to-peer relationships, are at higher risk of expulsion from school or daycare, and are at-risk for poor educational outcomes.[7,8] In addition, children with developmental delays are more likely to continue on the same developmental trajectory leading to mental health problems as they grow older.

Previous developmental theories have postulated two basic mechanisms of developmental delays characterized by “cardinal basic deficits” and a “specific developmental

trajectory" of ADHD.[9–11] The temperamental precursors of ADHD emerge early on during childhood, which is related to basic deficits in the executive and motivational deviations that involve prefrontal (dorsolateral and orbitofrontal), cingular (dorsal anterior cingulate cortex), and striatal regions that are integrated predominantly by dopamine pathways. With an increase in age, the prefrontal structures and their connectivity attain maturity; however, the most rapid changes occur in the first five years of brain development. Garon et al. (2008) assimilated existing research on the developmental functions and distinguished two distinct developmental periods. The authors suggested that in the first developmental period (i.e., the first three years of a child's life) skills such as holding a representation in mind, inhibiting a response using a rule held in mind, and consequently the capacity to suppress a motivationally-determined motor response develop in children. Between 22 and 33 months of age, most children master simple tasks like suppressing a response. Similarly, between three and five years of age, a child's brain continues to develop in a non-linear fashion and more complex skills are acquired. Yet, a majority of the past research on ADHD has focused on school-aged children and adolescents. Understanding the pattern of disease development early on in life might help achieve better outcomes, as the child grows older. In addition, the problem is further compounded due to the lack of treatment options for ADHD in preschoolers.

CHAPTER 2: LITERATURE REVIEW

Chapter overview

The chapter provides a detailed overview of the literature pertaining to ADHD. It briefly discusses the historical evolution of ADHD as a condition, prevalence of ADHD in the general population as well as in preschoolers, diagnosis criteria for ADHD, age-of-onset and prognosis of ADHD, treatment options available for the management of ADHD, utilization of treatment options, and comorbidities in patients with ADHD. This chapter also provides a brief overview of the Texas Medicaid program. This chapter concludes with the study rationale and the objectives that were examined in the study. It also provides a list of hypotheses that were tested to answer the research questions.

2.1 History of ADHD

The symptoms of ADHD are described in their contemporary form in the Diagnostic and Statistical Manual Fifth Edition (DSM-V). However, a description of symptoms similar to ADHD was made more than two centuries ago in 1798 by Sir Alexander Crichton, a Scottish physician born in Edinburgh.[12] His observations were compiled together into a book titled "*An Inquiry into the Nature and Origin of Mental Derangement: Comprehending a Concise System of the Physiology and Pathology of the Human Mind and a History of the Passions and their Effects.*" His work was one of the early studies where mental health conditions were formally discussed as medical conditions. In the second chapter of his book titled "*On Attention and its Disease*," Crichton provided a detailed account of the challenges that a few young students

experience while focusing on daily school activities.[12] These observations were similar to the characteristics of children diagnosed with inattentive type ADHD.

Almost eight decades later in 1884, a German physician, Heinrich Hoffmann, provided a detailed description of symptoms that were also similar to ADHD in his storybook titled "*Der Struwwelpete."*[13] This pictorial storybook designed for his 3-year-old son discusses some of the characteristics of ADHD based on a popular character "*Zappelphilipp"* (Fidgety Philip). The descriptions provided in the book are starkly similar to the diagnosis of hyperactive subtype in children diagnosed with ADHD.

Dr. George Still's early discussions of abnormal defect of moral control in children are considered by scholars to be the clinical starting point of ADHD. The symptoms that were first observed by Dr. Still in 1902 were collectively labeled as "morbid defect of moral control."[14] He observed certain traits that were peculiar to individuals diagnosed with this disorder including over activity, inattention, and poor inhibitory regulation. In addition to these traits, he also observed that these behaviors were not easily modifiable through corrective measures. Since then, the term has gone through numerous modifications and was subsequently labeled as "postenchephalitic behavior disorder" (1922), "hyperactive child syndrome" (1950s), "hyperkinetic reaction of childhood" (1968), and "attention deficit disorder" (1980) before it was established as attention deficit hyperactivity disorder in the year 1987.[14] These initial observations became the core characteristics for diagnosis of patients with ADHD almost eight decades later and were incorporated in the Diagnostic and Statistical Manual Fourth Edition (DSM-IV).

2.2 Etiology and risk factors of ADHD

The etiology of ADHD is very complex and research is still underway to determine the possible causes of ADHD. Nevertheless, environmental and genetic factors are widely accepted as probable causes of ADHD. Genetic predisposition and family history of ADHD have been identified as possible explanations for the occurrence of ADHD in certain populations. Previous clinical research has shown that reduction in the size of the prefrontal cortex, the caudate nucleus, and the globus pallidus results in lack of connectivity between the regions that moderate attention, stimulus processing, and impulsivity.[15]

Genetic studies have identified and established the role of genetic influences on occurrence of ADHD. Previous studies based on observations in family, adoption, and twin populations have identified family history of ADHD as a predictor for ADHD occurrence in offspring and siblings.[16,17] Previous studies have identified the role of "familiality trait" in the etiology of ADHD. A study by Faraone et al. (2000) showed that the risk of being diagnosed with ADHD is 6-to 8-fold higher in siblings exposed to similar familial risk factors.[18] In order to control for similar environmental exposure within the same household, Biederman et al. (1990) conducted a study where they controlled for gender, intactness of family, and socioeconomic status.[17] The results from these studies show that familiality is certainly associated with an increased likelihood of being diagnosed with this condition. However, since members of the same family are more likely to experience the same genetic and familial environmental influences, twin studies and adoption studies were needed to delineate the relative contributions of each factor.

Adoption studies have been conducted to address the confounders associated with the family studies. Adoption studies offer a unique perspective where environmental factors can be studied while controlling for biological effects. More specifically, biological relatives are genetically similar but are exposed to different environmental factors whereas adoptive relatives are exposed to the same environmental factors but are genetically dissimilar. Thus, examining the relative risk of ADHD in these two cohorts provided pointers towards probable causes of ADHD. Adoption studies showed that risk of ADHD occurrence in children of parents with a history of ADHD was higher in biological siblings than adopted siblings.[20–22]

Faraone et al. (2005) conducted an extensive review of studies conducted on twins to identify and confirm the heritability trait of ADHD diagnosis.[23] Twin studies are conducted in order to disentangle and identify the heritability parameter that might not be easily recognizable in population studies. The central idea of twin studies is that monozygotic twins (i.e., twins that are identical and share nearly 100% of the gene composition) will have a higher likelihood of being diagnosed with ADHD compared to dizygotic twins (i.e., non-identical or fraternal twins who share 50% of the gene composition). Both monozygotic and dizygotic twins will have a higher likelihood of inheriting the disease than the general population. The authors calculated the heritability factor at 76%, thus indicating that ADHD is a highly heritable disease.

Previous studies have also discussed the role of molecular genetics in the etiology of ADHD. In individuals with ADHD, the prefrontal cortex, caudate nucleus and globus pallidus are typically smaller than in people without ADHD, which suggests a lack of connectivity between the brain regions that moderate attention, stimulus processing and impulsivity.[15] A faulty dopamine receptor D4 (DRD4) gene and over expression of dopamine transporter-1

(DAT-1) could be a possible explanation for the lack of attention and impulsivity observed in ADHD patients.[15] Additionally, individuals with the DRD4-7 dopamine risk allele show a greater chance of having the same severity of ADHD in adulthood.[24]

Some environmental factors that have been implicated as secondary causes of ADHD are a high degree of social stress, maternal mental disorders, paternal criminality, low socioeconomic status, and being in foster care. In addition to this, some studies indicate that exposure to cigarette smoke, brain injuries and a high level of sugar intake have been linked to ADHD symptoms.[25–27]

2.3 Diagnosis of ADHD

ADHD is considered to be one of the most common mental health disorders diagnosed in children. A thorough evaluation of symptoms should be conducted prior to the initiation of treatment for a patient diagnosed with ADHD. Symptoms of ADHD are classified into three major categories: inattention, hyperactivity, and impulsivity, or a combination of these factors.[28] Inattention is characterized by loss of attention to detail and inability to follow or comprehend instructions. Hyperactivity is characterized by increased fidgeting, increased talking, or the constant need to be in motion. Impulsivity is characterized by impatience and constant interruption of activities.

As expected, it is normal for young children to be inattentive, hyperactive, and impulsive; therefore, necessary precautions should be taken by the physician to avoid misdiagnosis. Although there is general agreement that ADHD is a real mental health condition, there are some challenges surrounding the diagnosis of ADHD. Three major sets of guidelines are used to assess and establish the diagnosis of ADHD in children. Diagnosis guidelines are published by the American Academy of Pediatrics (AAP), the American Academy of Child and Adolescent Psychiatry (AACAP), and the Diagnostic and Statistical Manual, which is considered to be the gold standard for diagnosis of ADHD. The AAP and AACAP diagnostic guidelines were published from a primary care physician's perspective, owing to their increased involvement in the assessment and treatment process for ADHD.

2.3.1 AAP diagnostic evaluation guidelines

The AAP diagnostic guidelines were published for establishing diagnosis of ADHD in children between six and twelve years of age. These guidelines were updated in 2011 to broaden the age range from 4 to 18 years.[29] The AAP recommends that relevant diagnosis information be obtained using behavioral rating scales to establish a diagnosis of ADHD based on DSM-IV criteria (**Table 2.1**). The AAP asserts that broadening the age range from 4 to 18 years will result in early detection and therefore, increase the chances of better outcomes. The AAP has developed 4 key action statements for establishing a diagnosis of ADHD in children. First, the AAP recommends initiating evaluation of ADHD in any child between the ages of 4 and 18 years who presents behavioral and academic problems along with a concurrent symptom of inattention, hyperactivity, or impulsivity. Second, to establish a diagnosis of ADHD, the AAP recommends that the primary care physician verify that the individual meets the diagnostic criteria specified in the DSM-IV. The DSM criteria should have been met in more than one setting and should be based on evidence obtained from caregivers, teachers, and other school and mental health clinicians involved in the child's care. Third, the physician should also examine the patient for other comorbidities such as disruptive behavior disorder, mood disorder, and anxiety as well as learning disabilities that might be responsible for symptoms similar to ADHD. It is important to rule out other causes before establishing a diagnosis of ADHD. Fourth, use of other diagnostic tools such as blood lead levels, thyroid hormone levels, brain imaging, and electroencephalography to ascertain a diagnosis of ADHD is not supported by evidence.[30]

Table 2.1: Behavior rating scales recommended by the AAP[29,30]

Behavior Rating Scales
Conner's Parent Rating Scale 3 ADHD Index (DSM-IV)
Conner's Parent Rating Scale - 1997 Revised Version: Long Form, DSM-IV Symptoms Scale
Barkley's Home and School Situations Questionnaire-Original Version

ADHD – Attention Deficit Hyperactivity Disorder
DSM-IV – Diagnostic and Statistical Manual Fourth Edition
DSM-V – Diagnostic and Statistical Manual Fifth Edition
(Source: APA 2000)

2.3.2 AACAP diagnostic evaluation guidelines

The diagnostic evaluation criteria adopted by the AACAP include recommendations that are similar to those of the AAP. The AACAP recommends that a thorough evaluation of developmental, medical, psychiatric, and family history should be undertaken, in addition to the systematic assessment of the DSM-IV symptoms.[31] The AACAP recommendations are tailored for each age group (i.e., preschoolers 3-5 years of age; children 6-12 years of age; and adolescents 13-17 years of age).[32]

The AACAP recommends that screening for ADHD should be conducted irrespective of the nature of the complaint associated with the visit. Evaluation should focus on the core parameters as outlined by the DSM-IV (i.e., inattention, hyperactivity, and impulsivity). A brief preliminary evaluation based on the rating scales and questionnaires listed in the DSM-IV should be conducted (**Table 2.2**). If the symptom requirements are met, then a detailed account of each of the 18 symptoms listed in the DSM-IV criteria must be obtained for that patient. The physician should ascertain the presence of symptoms, age-of-onset, frequency, and severity of the symptoms.[32] The patient must report at least six of the nine symptoms listed in the inattention cluster or six of the nine symptoms listed in the hyperactivity/impulsivity cluster. The physician should also ascertain that the symptoms being observed are not transient in nature and were detected in early childhood.

After the presenting symptoms have been assessed, evidence regarding the academic and intellectual functioning of patients in a daycare setting (for preschoolers) and in a school setting (for school-aged children and adolescents) should be obtained.[32] DSM-IV requires that impairment should be present in more than one setting (either home, school, or job); however,

clinicians also agree that significant impairment in one setting can be an indicator for starting treatment. Assessment of the patient's parents based on standardized behavior rating scales should also be conducted to confirm the diagnosis. Since DSM-IV criteria state that ADHD symptoms should be present in two settings, assessment of other caregivers can also be conducted to confirm the diagnosis of ADHD.

Following functional impairment assessment, ADHD patients should be evaluated for other coexisting psychiatric disorders.[32] Assessment of underlying psychiatric diagnoses should be conducted to rule out symptoms that are inconsistent with the ADHD diagnosis. Because ADHD is strongly associated with genetic inheritability, a detailed review of family history as well as the social history should be carried out. In addition, physicians should obtain information regarding the patient's perinatal history, developmental milestones, medical history, and mental health history. The AACAP, however, does not recommend laboratory or neurological testing in cases where a discreet family history information cannot be ascertained.[32] Additional psychological and neurological tests are recommended for situations where patients have low cognitive ability or achievement in language and mathematics compared to their overall intelligence quotient.

Table 2.2: Behavior rating scales recommended by the AACAP

Behavior Rating Scales
Academic Performance Rating Scale (APRS)
ADHD Rating Scale-IV
Brown ADD Rating Scales for Children, Adolescents, and Adults
Child Behavior Checklist (CBCL)
Conner's Parent Rating Scale-Revised (CPRS-R)
Conner's Teacher Rating Scale-Revised (CTRS-R)
Conner's Wells Adolescent Self-Report Scale
Home Situations Questionnaire-Revised (HSQ-R), School Situations Questionnaire-Revised (SSQ-R)
Inattention/Overactivity With Aggression (IOWA) Conners Teacher Rating Scale
Swanson, Nolan, and Pelham (SNAP-IV), Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP)
Vanderbilt ADHD Diagnostic Parent and Teacher Scales

ADHD – Attention Deficit Hyperactivity Disorder; ADD – Attention Deficit Disorder;
Source AACAP 2007

2.3.3 DSM-IV and the DSM-V diagnostic evaluation guidelines

According to the DSM-IV guidelines, diagnosis of ADHD is subjective and should be considered only if the symptoms of inattention, hyperactivity or impulsivity persist for more than 6 months (**Table 2.3**).[28] More recently, the diagnosis criteria for ADHD were updated to address the age group-related concerns raised by some of the experts in the clinical field. According to the assessment criteria specified in DSM-IV, ADHD diagnosis can be ascertained if the patient presenting these symptoms meets at least five of the criteria. The first criterion is that the patient should present at least 6 of the 9 symptoms in the inattention and/or hyperactivity domains for at least six months to an extent that it is developmentally maladaptive and inconsistent with the overall intellectual ability of the child (**Table 2.3**). Second, these symptoms must be manifested in the patient before 7 years of age. This criterion has been slightly relaxed in the DSM-V where a patient can be diagnosed with ADHD between 4 and 12 years of age. Third, functional impairment affecting behavior and development should be present in more than one setting (i.e., either school, home or both for school-aged children and home, daycare or both for preschoolers). Fourth, observed impairment should be substantial so that it hinders normal development or behavior in school, social, and work place settings. Fifth, the observed symptoms should not be attributable to other coexisting mental health conditions and should be clearly associated with ADHD. Evidence regarding functional impairment can be obtained from the clinical interviews of parents, teachers, and other caregivers in school. Although, behavioral rating scales provide much valuable information, they should be supplemented with other indicators to establish a positive diagnosis.

Table 2.3: List of symptoms for diagnosis of Attention Deficit Hyperactivity Disorder as defined in the Diagnostic and Statistical Manual Fourth Edition (DSM-IV)

	Inattentive Symptoms	**Hyperactive/Impulsive Symptoms**
1.	Often fails to give close attention to details or makes careless mistakes	Often fidgets with hands or squirms in seat
2.	Often has difficulty sustaining attention in tasks or play activities	Often leaves seat in classroom or in other situations in which remaining seated is expected
3.	Often does not seem to listen when spoken to directly	Often runs about or climbs excessively in situations in which it is inappropriate
4.	Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace	Often has difficulty playing or engaging in leisure activities quietly
5.	Often has difficulty organizing tasks and activities	Is often "on the go" or often acts as if "driven by a motor"
6.	Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort	Often talks excessively
7.	Often loses things necessary for tasks or activities	Often blurts out answers before questions have been completed
8.	Is often easily distracted by extraneous stimuli	Often has difficulty awaiting turn
9.	Is often forgetful in daily activities	Often interrupts or intrudes on others

Standardized rating scales, such as Conner's Rating Scales for parents and teachers, may be utilized to document baseline symptom severity (**Table 2.4**).[33] Other behavioral symptoms that are prevalent in preschool kids could be erroneously labeled as ADHD in this population. In such cases, precautions should be taken in establishing the diagnosis of ADHD in preschoolers because their ability to use and respond to language for moderating behavior may be limited. Similarly, behavioral interventions might not be as effective because of potential challenges in communicating the treatment. Young children might not notice the differences between instructions and rules and the consequences of violating them.

Table 2.4: Behavior rating scales recommended by the Diagnostic and Statistical Manual Fourth Edition (DSM-IV)

Behavior Rating Scales
ADHD Rating Scale-IV (ADHD-RS)
Swanson, Nolan, and Pelham-IV (SNAP-IV)
Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)
Connors Rating Scales (Long or Short Version)
Vanderbilt ADHD Rating Scales
Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Scale (SWAN)
Inattention/Overactivity with Aggression Connors Teacher Rating Scale (IOWA)
Brown Attention - Deficit Disorder Scales (BADDS)

ADHD – Attention Deficit Hyperactivity Disorder

2.4 Prevalence of ADHD and other behavioral disorders in children and adolescents

ADHD is a neurobehavioral disorder primarily characterized by impairment of executive functioning leading to developmentally inappropriate level of inattention, hyperactivity, and impulsivity.[19,20] The proportion of children in the U.S. aged 4 to 17 years with a parent-reported ADHD diagnosis increased from 7.8% in 2003 to 9.5% in 2007. A more recent study (2011) using the National Health Interview Survey indicated that nearly 8.4% of parents reported that their children had a history of ADHD diagnosis.[36] The prevalence rate was higher in males (13.2%) as compared to females (5.6%) and a higher proportion of patients were in the 15 to 17 years age range. Compared to the national average, the prevalence of ADHD in children between 4 and 17 years of age was lower in Texas and was estimated to be 10.1% in 2007.[37]

Symptoms in ADHD often overlap with symptoms from other psychiatric disorders. Irrespective of the age when ADHD is diagnosed, ADHD exhibits a high rate of comorbidity and substantial role impairment. Previous studies assessing comorbidities in ADHD patients were conducted in clinical and community samples. Wilens et al. (2002) conducted a systematic review of all the clinical characteristics in preschool children (4-6 years of age) and in school-aged children (7-9 years age).[38] Psychiatric comorbidity was reported in 74% of the preschoolers and 79% of the school-aged children diagnosed with ADHD. Oppositional defiant disorder (ODD) and Major Depressive Disorder (MDD) were the most common comorbidities in the preschool group as well as the school age group.

Recently, a large-scale study was conducted to determine the comorbidities commonly occurring in respondents diagnosed with ADHD. The study was conducted on a birth cohort of patients born between January 1, 1976 and December 31, 1982. The study cohort, before study

criteria were applied, consisted of 5,718 children (2,956 boys and 2,762 girls). After inclusion and exclusion criteria were applied, the final cohort consisted of 343 children with ADHD. Occurrences of psychiatric disorders were higher in the ADHD group as compared to the non-ADHD group. Moreover, 62.1% of the children in the ADHD cohort were reported as having more than one psychiatric disorder while 34.4% were reported as having more than two psychiatric disorders.[39]

Diagnosis of ADHD in patients with comorbid psychiatric disorders is difficult and the similarities of symptoms often obscure the diagnosis process. More recently, comorbid autism spectrum disorder (ASD) in ADHD patients has generated considerable debate. ASDs are a group of pervasive developmental disabilities characterized by impairments in socialization, communication, and the presence of restricted, repetitive behaviors or interests.[40] Establishing diagnosis of ADHD in preschoolers is difficult and may be at times preceded by symptoms of ODD or conduct disorder (CD). ODD and CD are classified together as disruptive behavior disorder (DBD). Conversely, preschoolers might be labeled with a DBD diagnosis that may or may not develop into ADHD as the patients' ages increase.

2.5 Prevalence of ADHD and other behavioral disorders in preschoolers < 6 years of age

Prevalence of ADHD in preschoolers has not been adequately reported in the literature. One of the early studies estimating the prevalence of ADHD and other psychiatric disorders in preschoolers was conducted in 1982. The study reported the prevalence of ADHD in preschool children to be around 2% for ADHD, 4% for oppositional defiant disorder (ODD), and 5% for anxiety.[41] A study by Keenan et al. (1997) studied 104 mother-child dyads recruited from the Women, Infant and Children Program (WIC) of Allegheny County, Pennsylvania who were living in poverty. The authors reported that nearly 5.7% of the sample had ADHD, 8.0% of the participants were considered to be suffering from oppositional defiant disorder, 1.1% were estimated to be suffering from depression, and 2.3% from anxiety disorder.[3]

Lavigne et al. (1996) conducted a large-scale epidemiologic study to estimate the prevalence of psychiatric disorders in pre-school-aged children outside the psychiatric setting. Data for the study were collected through the use of the Child Behavior Checklist (CBCL) which was administered to 3,860 parents of children aged 2 to 5 years visiting 68 pediatricians residing in the Chicago area. The children who scored 90% or above on the CBCL were invited for a second evaluation. The authors reported that in this sample, the proportion of patients diagnosed with ODD was 16.8% and nearly 50% of these cases were classified as severe. Additionally, the authors reported that the prevalence of ADHD was around 2% in the preschool-aged population. Prevalence of separation anxiety disorder (0.5%) and depression (0.3%) were also reported by the authors.[4] A study by Angold et al. (2006) conducted on a sample of 307 children between the ages of 2 to 5 years after administration of the Preschool Age Psychiatric Assessment (PAPA) also reported similar results. The authors reported that the prevalence of ODD was

approximately 6.6% followed by ADHD (2.1%), separation anxiety disorder (2.4%), and general anxiety disorder (6.5%).

More recently, Lavigne et al. (2009) conducted a study to estimate the prevalence of ODD, anxiety, depression, and ADHD in young children. Parents of children from 13 Chicago public schools preschool programs and 23 primary care pediatric practices throughout Cook County, including inner city clinics and schools, were approached and detailed about the intervention program. Parents were selected for further questioning if: their children were 4 years old at the time of assessment and had no psychiatric disorders which included ODD symptoms; the child and parent both spoke either English or Spanish; the child had the same caretaker for six months; the child obtained a standard score on a language screen of 70 or greater at baseline; the child was not enrolled in the school as mentally retarded; and he/she did not have a school IQ test below 70. Of all the cases in the study, the rate of ADHD with any kind of impairment was 12.8%, and the rate of ODD with any kind of impairment was 13.4%.[42] Previous studies on preschoolers were confined to particular geographic locations and included very few cases. A review of the literature showed that no national studies have been conducted to estimate the prevalence of ADHD in the preschool population.

2.6 Economic burden of ADHD

ADHD also imposes a significant economic burden on society. A systematic review by Doshi et al. (2012) showed that the direct and indirect medical costs for children diagnosed with ADHD were mostly attributable to healthcare and educational expenditures, respectively. The same study reported that the indirect cost due to special educational arrangements for children with ADHD was approximately $15 to $25 billion in 2010.[43] Additionally, the authors reported that the total ADHD-related cost for children and adolescents from the ages of 7 to 18 years was around $72 billion in 2010.[43] Healthcare costs of preschoolers with ADHD have not been estimated in the literature. This study aimed to fill this gap in the literature by providing medical, prescription, and total cost estimates in preschoolers with ADHD.

2.7 ADHD treatments

ADHD is a chronic condition; however, it is possible to manage symptoms and help individuals cope with the disorder. The goal of current treatment is to achieve symptomatic control of ADHD and to improve daily functioning. Successful management options for ADHD involve use of psychotherapy/psychosocial interventions, medications or a combination of both.[44]

2.7.1 Psychosocial interventions

Psychosocial interventions are usually considered ideal for preschool children before initiating medications. In the case of children diagnosed with ADHD, the AACAP emphasizes the role of family in treatment. Support and education of parents, including parent training, can increase parent competence and overall adherence, as well as improve parent-child interactions. Some standardized parental behavior training interventions such as the Positive Parenting Program (Triple P), the Incredible Years (IY) parenting program, Parent-Child Interaction Therapy (PCIT), and New Forest Parenting Program (NFPP) have been developed to address the issue of disruptive behavior in preschoolers. Similarly, studies that determined the impact of parental behavior therapy reported improvement in children's interaction scores across all levelsof functioning.[45,46]

2.7.1.1 Parent training intervention

Parental training can be effective in managing behavior in children diagnosed with ADHD. The parental training component includes behavior modifying techniques such as deploying antecedents (giving instructions and establishing rules) and consequences (providing

rewards and timeouts). Parental training programs focus either on the didactic and interaction component or the parent-child relationship component. In the didactic component, Barkley and colleagues developed a parent training program where parents were trained and participated in one-on-one training or group trainings.[47] Parents also actively participate in role-play practice sessions and have assignments that can be practiced at home. In the parent-child relationship component, interventions focus on the intricacies of parent-child relationships and offer an in-class parent-child interaction where parents are given active feedback from the counsellor and trained on skills that they can later incorporate in their interactions with their children. Programs such as the New Forest Parenting Package offer a combined modality of both programs.[48]

2.7.1.2 Classroom training intervention

Behavioral interventions initiated in the classroom setting have been found to be beneficial in improving school-related outcomes in ADHD patients. Barkley et al. (2000) conducted a study to evaluate the impact of kindergarten classroom intervention including direct child instruction in anger management, social skills, and self-control in children.[47] The authors also evaluated the role of contingency management procedures such as token economies, a response-cost system, and a daily report card. The authors evaluated these children at the end of the school year and reported that the interventions were effective and led to improvement in the overall behavior. In a follow-up study, the authors reported that the observed benefit diminished in effect even after the schools were willing to provide support.[49]

2.7.1.3 Multimodal psychosocial intervention

Multimodal treatments developed by Barkley et al. (2000), and the Incredible Years training program (IY) have shown some evidence of benefit. The IY program developed by Webster-Stratton has proven to be effective in managing symptoms of ADHD.[50] It was also found to be effective in improving parents' skills, improving parent-child interaction and controlling other negative behaviors in the classroom and at home.[50–52] The IY program has a child component, a parent component, and a teacher component. Parents are trained in a group setting in a collaborative environment using role plays and videotapes. Child training encompasses emotional regulation, social skills training, and problem-solving strategies in a clinic setting as well as a classroom-based setting. The teacher training component is similar to the parent training component; however, it is tailored for management of a child's behavior in a classroom setting.[50]

2.7.1.4 Utilization of psychosocial interventions in children <6 years old

Psychosocial intervention with a primary focus on parental and family training has been recommended as the first-line treatment for preschoolers with ADHD.[53] Several studies have demonstrated the effectiveness of parental intervention in ADHD preschoolers. A study by Lakes et al. (2011) evaluated the impact of parental intervention on 154 predominantly low-income and Latino preschoolers. The parents participated in a community-based parent-training model intervention (COPE). One year later, the parents were asked to answer questions covering 10 domains (praise, ignoring problem behavior, start chart, time-outs, physical punishment, take away privileges, rewards, transitional statement, when-then statements and planning ahead). The post-intervention evaluation of parents showed that they demonstrated improvements on at least

1 of the 10 domains. Also, children in the study showed significant behavioral improvement in the post-intervention assessment that was measured using the Strengths and Difficulties Questionnaire (SDQ).[54]

Another study by Huang et al. (2003) studied the impact of parent behavioral training in 23 preschoolers (3-6 years of age). The intervention consisted of 10 sessions and the data was collected at multiple (first, fourth, sixth, seventh, and tenth) sessions using the Disruptive Behavior Rating Scale-Parent Form, Child Attention Profile, and Home Situation Questionnaire. The results showed that ADHD/ODD symptoms as well as the level of severity improved for 14 children post treatment.[55]

More recently, Kern et al. (2007) studied the effect of parent education alone and individualized assessment along with parent education in children 3-5 years of age at-risk for ADHD. The authors reported that the intervention group was better off post intervention as compared to the no-intervention group.[56] Matos et al. (2009) evaluated the impact of Parent-Child Interaction Therapy (PCIT) for Puerto Rican preschool children aged 4-6 years with a diagnosis of ADHD. Participants were randomly assigned to the intervention group or the control group and were assessed for ADHD symptoms and behavior problems, parent or family functioning, and parents' satisfaction with treatment before and after treatment. The authors concluded that the parental intervention was effective for Puerto Rican families that have young children with significant behavior problems.[57]

2.7.2 Pharmacotherapy of ADHD

The most common treatment option for individuals diagnosed with ADHD is the use of stimulant medications (**Table 2.5**). In addition to stimulant medications, non-stimulants are available for patients who do not tolerate or respond to stimulants. Availability of the stimulants and non-stimulants in various delivery dosage forms (i.e., liquid, sprinkle, tablet, capsule or patch) and duration of action (i.e., long-acting, short-acting) offer physicians an opportunity to tailor the medication therapy according to each patient's needs.[58]

Although intuitively, stimulant medications should lead to exacerbated activity, the evidence for ADHD patients is to the contrary. Administration of stimulant medications such as amphetamines (e.g., Adderall and Vyvanse) and methylphenidates (e.g., Ritalin and Concerta) increases the ability of ADHD patients to concentrate, be more attentive and less aggressive.[28] Preclinical studies have demonstrated that stimulants increase the release of monoamines into the extra-neuronal space thereby inhibiting dopamine and norepinephrine transporter proteins. [59,60] Lack of these transporters leads to lower levels of dopamine (DA) and norepinephrine (NE) into the presynaptic neuron.[61–64] Catecholamine uptake transporter is an important mediator for action of amphetamine and methylphenidate.[61,62] Amphetamine binds to the dopamine transporter protein thus blocking the reuptake of dopamine from the synapse into the cell. Amphetamine subsequently moves into the cell and exchanges with dopamine via the dopamine transported protein. Cytoplasmic dopamine moves from the interior of the cell through the sodium dependent transport mechanism thus increasing the concentration of dopamine in the synapse.[61,62] Methylphenidate, on the other hand, is hydrolyzed in the intestine before reaching the systemic

circulation and acts by increasing the dopamine concentration in the synapse by interacting with dopamine transport protein in a way similar to other sympathomimetic enzymes.[59,61,65]

Non-stimulant medications are also used to manage the symptoms of ADHD (**Table 2.5**). One FDA-approved non-stimulant medication to be used in hyperactive children is atomoxetine, which inhibits pre-synaptic norepinephrine reuptake and leads to increased synaptic norepinephrine.[66–68] Atomoxetine numbs the posterior attentional symptoms resulting in lowered response to stimuli and also improves problem solving skills.[66–68]

Other non-stimulant medications approved for use in ADHD patients include guanfacine and clonidine. Clonidine, a derivative of imidazoline, is an alpha-adrenergic agonist and was originally formulated for use in hypertensive patients.[69] Clonidine acts centrally as well as peripherally and has demonstrated benefit in the ADHD population. It affects the alpha-1 and alpha-2 receptors located in presynaptic and postsynaptic neurons. Clonidine blocks the release of norepinephrine from the central catecholaminergic nerve terminal.[70] Guanfacine also acts by mimicking norepinephrine at alpha-2a receptor sites. Thus, both clonidine and guanfacine lead to elevated norepinephrine levels in the prefrontal cortex by modulating the norepinephrine in the pre-synaptic and post-synaptic membrane leading to better executive functioning in patients with ADHD.[71]

Other medication classes that have shown some evidence of benefit in these patients are bupropion, tricyclic antidepressants, monoamine oxidase inhibitors [MAOIs], and selective serotonin reuptake inhibitors [SSRIs].[31,72] Bupropion, an aminoketone derivative, was originally approved for use as an antidepressant. It has a dual mechanism of action and inhibits dopamine and norepinephrine reuptake.[73] Tricyclic antidepressants' effect on norepinephrine, mediated

thorough catecholamine pathways, is assumed to be the primary mechanism of action of tricyclic antidepressants in ADHD patients.[60] Modafinil's primary mechanism of action is the attenuation of cholinergic and monoaminergic components through its action on the hypothalamus. However, its effect in ADHD patients is attributed, although debatably, to its effect on the dopaminergic and noradrenergic systems.[74] Other alternative explanations for modafinil's mechanism of action have also been explored in the literature. Previous studies have shown that modafinil acts on 4 distinct sites in the brain: gamma-aminobutyric acic (GABA) located in ventrolateral preoptic nucleus; noradrenergic neurons of the locus ceruleus; the histamine neurons of the tuberomammillary nucleus; and the mesencephalic dopaminergic neurons.[75] Modafinil is also thought to regulate the reuptake of dopamine in the cerebral cortex and caudate nucleus by activating the postsynaptic alpha-1 adrenergic receptors.[76]

Table 2.5: Types of medications used for the management of ADHD in school-aged children, adolescents, and adults[77]

Class	Generic name, formulation and brands	Daily dosage	Duration
Stimulants			
Methylphenidate	Immediate-release/short-acting (Ritalin, Methylin, Desoxyn)	Initial 5-18 mg; increase as needed until beneficial effects peak or unacceptable side effects develop Two to three times daily; can titrate as needed as long as beneficial effects are greater than side effects	3-6 hours
	Intermediate-acting (Metadate ER, Metadate CD, Methyllin ER, Ritalin LA, Ritalin SR)	One to two times daily	3-8 hours
	Extended release/long-acting (Concerta, Daytrana Patch)	Once daily	8-12 hours
Dexmethylphenidate	Short-acting (Focalin)	Two to three times daily; initial dose half that of IR MPH	4-5 hours
	Extended-release/long-acting (Focalin XR)	Once daily	8-12 hours
Amphetamines	Immediate-release/short-acting (Dexedrine, DextroStat, Adderall)	Initial dose half that of IR MPH; two to three times daily	4-6 hours
	Intermediate-acting (Dexedrine Spansule)	One to two times daily	6-10 hours
	Extended-release/long-acting (Adderall-XR)	Once daily	8-12 hours
Prodrug Amphetamines	Lisdexamfetamine (Vyvanse)	Initial 4 × IR MPH once daily	8-12 hours

Table 2.5: Types of medications used for the management of ADHD in school-aged children, adolescents, and adults (continued)

Class	Generic name, formulation and brands	Daily dosage	Duration
Non-stimulants			
Norepinephrine Reuptake Inhibitors	Atomoxetine (Strattera)	Initial 0.5 mg/Kg; Increase to 1.2-1.8 mg/Kg one to 2 times a day	18-24 hours
Alpha$_{2A}$ agonists			
Guanfacine	IR Guanfacine (Tenex)	Initial 1 mg daily; titrate as needed up to 4 mg twice daily	12-24 hours
	ER Guanfacine (Intuniv)	Initial 1 mg; up to 4 mg; once daily	~24 hours
Clonidine	ER Guanfacine **(**Kapvay)	1 mg QD; 1 mg/day every week	8 – 14 hrs; up to 24 hrs in higher doses

D = Dopamine; N = Norepinephrine; S = Serotonin; IR = Immediate Release; MPH = Methylphenidate; mg/kg = milligrams/kilogram; QHS = before bed; TTS = Transdermal Therapeutic System; EKG = Electrocardiogram; Serotonin Norepinephrine Reuptake Inhibitors; Adapted from: Antshel et al. BMC Medicine 2011 9:72 doi:10.1186/1741-7015-9-72

2.7.2.1 Medication utilization and treatment patterns in children and adolescents

Determining medication utilization patterns is important for effective management of disease. Previous studies have assessed utilization of medications in the private as well as Medicaid ADHD populations. Of the children between 4 and 17 years of age with current ADHD diagnosis, rate of medication use was higher in Texas (71.9%) as compared to the national rate (66.3%). Furthermore, of all the children (between 4 and 17 years of age) with a lifetime diagnosis of ADHD, medication use was lower in Texas (3.4%) as compared to the national rate (4.8%).[78] According to the yearly reports published by the Texas Health and Human Services Commission, stimulants had the second highest expenditure ($168,023,838) among drug groups in 2012. Garfield et al. studied the trend in use of stimulants and other therapies in individuals < 18 years of age diagnosed with ADHD.[79] The overall proportion of ADHD patients with stimulant medication use declined in the last decade from 98% (n= 5,511) in 2000 to 87% (n = 8,631) in 2010. The authors observed an increase in the use of guanfacine after an ER form (Intuniv) was launched. The authors also observed that the decline in the use of short-acting (SA) forms of stimulants was almost parallel to the increase in the use of long-acting (LA) forms. Utilization of LA forms of stimulants increased from 14% of patients (n= 771) to 87% (n= 7,508) between 2000 and 2010. Another study that explored treatment patterns in patients between the ages of 6 and 12 years using multi-state Medicaid data reported that 45% of the children and adolescents diagnosed with ADHD were initiated on psychotherapy, nearly 41% were initiated on pharmacotherapy on at least one type of stimulant medication and 14% of the children and adolescents were initiated on combination therapy (i.e., psychotherapy along with pharmacotherapy).[80] The authors also noted that the presence of comorbid mental conditions increased the chances of being initiated on combination therapy. Another study conducted

among ADHD patients enrolled in a commercial health plan revealed that 78.4% of the patients were initiated on stimulants as their index therapy.[81] Molife et al. (2012) reported that patients (≥ 6 years of age) insured through Medicaid had a higher proportion of monotherapy and combination therapy (> 1 medication) users as compared to the commercial population.[82]

Medication use patterns in patients diagnosed with ADHD in the Texas Medicaid population have also been assessed by previous studies. A study by Barner et al. (2011) that assessed medication use among Texas Medicaid children between 3 and 18 years of age with ≥ 2 ADHD prescriptions reported that a majority (86.4%) of the subjects were prescribed stimulant medications.[83] Another study by Lawson et al. (2012) using Texas Medicaid data on patients between 6 and 63 years of age showed that the overall proportion of patients initiated on methylphenidates was higher (71.1%) as compared to amphetamines (28.9%). Among children, a higher proportion of patients were initiated on LA methylphenidates (66.2%) followed by LA amphetamines (23.3%). Similarly in adolescents, 64.4% were initiated on LA methylphenidates as compared to 29.4% being initiated on LA amphetamines.[84]

In a study conducted using Medicaid managed care program data to examine whether care processes or severity varied according to practice settings (i.e., primary or specialty mental health) in children between 5 and 11 years of age, Zima et al. (2010) reported that over 80% of children in the primary care setting received stimulants as compared to 33% in specialty health care clinics.[85] However, medication adherence was low in both the primary care and mental specialty health clinics. Differences in medication utilization patterns have been reported according to the level of severity, place of residence, race and ethnicity of the individuals diagnosed with ADHD.[86]

Treatment patterns of ADHD medications have also been discussed in the literature. In a retrospective claims database study conducted using medical, pharmacy, and enrollment information from an insurance claims data, Christensen et al. (2010) reported that patients in the stimulant cohort, methylphenidate group or LA medication group were more adherent as compared to those in the non-stimulant, amphetamine, or SA groups.[81] Similarly, a retrospective study was conducted using Texas Medicaid data to determine the utilization patterns of stimulant medications in the ADHD population.[84] Adherence was measured as the days in possession ratio defined as the proportion of days with medication in the 180-day post-index period. Persistence was assessed as the sum of the number of days with medication without a 30-day gap in a 150-day post-index period. Additionally, the study also reported that children and adolescent patients on LA formulations had better adherence as compared to those initiated on SA forms. Conversely, adherence to SA forms of amphetamine was better in adults as compared to LA forms of methylphenidate. Another study by Sanchez et al. (2005) also noted that patients on extended release methylphenidate had better persistence (defined as number of days of continuous medication therapy without a 15-day gap period over a period of 180 days) and medication possession ratios (defined as days supplied/days in treatment period) as compared to patients on amphetamines or immediate-release methylphenidates.[87]

Previous studies have also shown that switching to alternative forms of treatment takes place in the ADHD population. Stein et al. (2012) reported that 28% (n=238) of the children who were initiated on medication treatment added a psychosocial intervention and 42% (n=392) of the children who were initiated on a psychosocial intervention added medication to their treatment regimen.[80] In addition, of the patients receiving combination therapy, nearly half were

switched to medication therapy alone. In the Texas Medicaid population with ADHD, switching was observed between the SA and LA forms of medications.[84]

Psychotropic medications in general including antipsychotics are also being used in ADHD patients to achieve symptomatic control even though their use is not supported by evidence. A recent systematic review by Birnbaum et al. (2013) concluded that 30.5% of patients treated with antipsychotics were reported to have a diagnosis of ADHD. Additionally, the authors reported that 11.5% of ADHD youth received antipsychotics.[88] Furthermore, there is evidence that antipsychotic use among ADHD patients in increasing. A study by Fullerton et al. (2012) examining the trend of psychotropic drug utilization in Medicaid patients with ADHD from 1996 to 2005 reported that the probability of filling at least one antipsychotic medication in 2005 was two times that in 1996. Another study using the Medicaid population from 2001 to 2005 was conducted to identify children newly initiated on second-generation antipsychotics. The authors reported that ADHD was the most frequently diagnosed disorder in children. Furthermore, nearly half the children identified in the study were receiving antipsychotics for indications that were not supported by strong evidence.[89] Other psychotropic drug use has also been reported in the literature. In a study using US managed care claims data, Van Brunt et al. (2005) reported the use of bupropion, antidepressants, antipsychotics, antimanics, and anxiolytics in patients diagnosed with ADHD.[90] In light of the current therapeutic evidence and practice pattern trends, it is important to examine the utilization of other psychotropic medications in preschoolers.

2.7.2.2 Medication utilization in children < 6 years old

Medications are often the treatment of choice for physicians even though there is very little evidence supporting medication use in preschoolers. Olfson et al. (2002) conducted a study using the Medical Expenditure Panel Survey (MEPS) data for the period 1987 to 1996, and gathered information regarding the psychotropic medications (stimulants, antidepressants, anticonvulsants, sedative/hypnotics, benzodiazepines, miscellaneous anxiolytics, and lithium) used in children less than 18 years of age. Although not the focus of the study, the researchers found that the rate of ADHD declined in the population <6 years of age from 35.5% in 1987 to 32.0% in 1996. Conversely, the use of psychotropic medications in children <6 years of age increased from 0.46% in 1987 to 0.82% in 1996. Stimulant medication use also increased from 0.22% in 1987 to 0.31% in 1996.[91]

Zito et al. (2000) conducted a population-based analysis to estimate the prevalence of psychotropic medication (stimulants, antidepressants and neuroleptics) use in preschool-aged youths and to determine their utilization trends across a 5-year span based on prescription data from two Medicaid programs and a salaried group model health maintenance organization (HMO). The authors reported that in the 2 to 4 year age group, the use of stimulants increased almost 3-fold for the Midwest Medicaid program and the HMO and almost 2-fold for the Mid-Atlantic Medicaid program. Furthermore, the authors also stated that the use of methylphenidate, antidepressants, tricyclic antidepressants (TCAs), clonidine and neuroleptics increased in the 5-year span. The authors also graphed the trend of methylphenidate prevalence per 1,000 enrollees by age for the Midwestern State Medicaid program and reported that the prevalence of methylphenidate use increased from 6.9 per 1,000 enrollees to 20.8 per 1,000 enrollees between

1991 and 1995.[92] Conversely, a study by Zuvekas et al. (2012) observed that the stimulant medication use in children 0 to 5 years old for the period 1987 to 2008 remained low in the population.[93] However, previous literature on the use of medications other than methylphenidate in the preschool ADHD population is limited.

2.8 Age-of-onset and prognosis of ADHD

ADHD is a chronic condition that is usually detected in early childhood.[94] Prior to the publication of DSM-V, all previous versions of the DSM criteria for ADHD diagnosis required symptom presentation before 7 years of age. The criterion of age-of-onset of < 7 as defined in DSM-IV and earlier versions was criticized in the literature; however, it also was established as the de facto standard for identification of ADHD. A report by Barkley and Biederman (1997) suggests that the criteria for diagnosis specified in DSM-III was based on clinical observations of a few experts in the field.[95] In an effort to address the widespread debate regarding the age-of-onset of ADHD, the most recent version of the DSM (version V published in 2011) changed the age-of-onset from < 7 years to < 12 years for certain types of ADHD.

Biederman et al. (1996) used a longitudinal sample to examine the remission patterns of ADHD patients. The authors categorized 14 DSM-III-R symptoms of ADHD according to inattentive, hyperactive, and impulsive types. The authors reported that age was a significant factor associated with all forms of remission for ADHD and with the three-symptom clusters (i.e., inattentive, hyperactive, and impulsive).[96] Langberg et al. (2008) used data from the multisite Multimodal Treatment Study of Children with ADHD to examine manifestations of ADHD symptoms before, during, and after transition to middle school.[97] The authors reported a transient reversal in ADHD symptoms associated with transitioning to middle school.[97] A number of similar studies in the past have assessed the clinical course of ADHD symptoms; however, most of the studies have focused on school-aged children.[98]

Previous studies found that behavioral problems often manifest in ADHD patients before elementary school. Preschool children are usually referred, evaluated, and treated for ADHD.

Lahey et al. (2004) reported that a majority of children diagnosed with ADHD in preschool, kindergarten, or first grade continue to exhibit symptoms and impairments as they mature.[99] Additionally, the subtypes (hyperactive, impulsive, inattentive, and combined) within ADHD differ in prognosis as well. Children with disruptive behaviors are frequently identified in preschool, while identification of individuals with the inattentive subtype often occurs later.[100] Very few studies have examined the course of ADHD in children after it is identified at an early age. The lack of valid instruments to accurately diagnose ADHD in children between 1 and 6 years of age makes diagnosis challenging. Furthermore, uncertainty regarding treatment options and lack of treatment alternatives in children < 6 years of age could also be challenging. However, numerous studies have demonstrated that a majority of children diagnosed with behavioral abnormalities at an early age exhibit long-term negative behavioral change. A 12-year follow-up study conducted by McGee et al. (1991) on preschool hyperactive children reported that only 25% of the children recovered as they aged and about 33% of children met the DSM-III criteria for ADHD at follow-up.[101] Lahey et al. (2004) reported that nearly 79% of the patients diagnosed with ADHD in the initial phase of the study continued to exhibit symptoms of ADHD over a three-year period.[99] A recent study by Riddle et al. (2013) examined the stability of symptom severity 6 years after the completion of a cohort study conducted earlier. The study utilized participants from their previous preschool ADHD treatment follow-up study that consisted of patients in the 3 to 5 years age group and in the 9 to 12 years age group. The study reported that six years after completion of the initial cohort study, nearly 90% of the clinically referred preschoolers initially diagnosed with mild to severe ADHD continued to be diagnosed with ADHD in mid- to late-childhood.[102]

Information regarding the clinical course, treatment patterns, and the costs of preschool kids diagnosed with ADHD at a very young age is sparse. The rise in prevalence of ADHD in preschoolers has gained attention and thus, it is important to understand the treatment utilization patterns and costs in this population.

2.9 Texas Medicaid program

The Medicaid program is a means-tested entitlement program established through the Social Security Act of 1965 and is jointly funded by the federal and state governments.[97] The Medicaid program is administered by the states, with federal oversight through the Centers for Medicare and Medicaid Services (CMS). It was initially designed to provide healthcare coverage to low-income children deprived of parental support, related caretakers of dependent children, the elderly, the blind, and individuals with disability. The program was later broadened in the late 1980s and early 1990s and included mandates for pregnant women (deemed eligible for participation in the program). Around the same time, provisions for prescription drugs rebates were also introduced. Through this program, the states manage a master list of drugs, generic substitutes, and alternative treatment options. Participating states are mandated by the CMS to provide a set of basic healthcare services to enrollees and since it is an entitlement program, there is no restriction on the number of people who can be enrolled provided they meet the eligibility criteria for the program. Based on the most recent available data, the Texas Medicaid program provided health insurance coverage for approximately 4 million non-elderly residents (i.e., 64 years of age and below).[103] Examples of services provided by the Texas Medicaid program include: physician services, inpatient and outpatient hospital services, long-term care, lab and X-ray services, and pharmacy services.

2.10 Study rationale, purpose, and objectives

2.10.1 Study rationale

ADHD is a chronic condition often diagnosed in children before the age of 7 years, which may have a long-term impact on social functioning, school performance, cognitive abilities, and/or behavior problems. Optimal treatment of ADHD must be multidisciplinary, multimodal and maintained over a long period of time. The most effective treatment options for managing symptoms related to ADHD involve use of medications, behavioral therapies, combination of medications and behavioral therapies, and environmental techniques. A study by the MTA co-operative demonstrated that medication and psychotherapy work collaboratively better than medication alone. Yet, use of medication alone is highly prevalent according to the literature and often viewed as the most effective alternative in treating children diagnosed with ADHD. A similar trend in the utilization of medications in preschoolers has also been reported. Nevertheless, scientists argue that extensive use of medications to treat ADHD during the early brain developmental phase might impede brain development and may be associated with long-term behavior modifications. Preschool children are at increased risk of bearing the consequences of excessive medication use, which may lead to future developmental problems.

In light of evidence supporting combination therapy, benefits of pharmacotherapy over psychotherapy for treatment of patients with ADHD are inconclusive and need further investigation. Furthermore, investigation of treatment patterns in preschoolers diagnosed with ADHD might provide insights into clinical practice. Additionally, current evidence regarding the use of treatments in preschoolers with ADHD in the Texas Medicaid population is sparse and/or inconclusive. In addition to understanding the current clinical practice for preschoolers with

ADHD, it is also important to evaluate their healthcare utilization and cost burden. Previous studies that estimated healthcare utilization and costs included a wide range of age categories. A review of the literature indicated that very few studies have estimated the healthcare utilization and costs in preschool children (< 6 years of age) diagnosed with ADHD.

2.10.2 Study purpose

The present study was conducted with three main purposes; 1) to characterize the prevalence and incidence of ADHD among preschoolers in the Texas Medicaid population; 2) to investigate the pharmacotherapy, psychotherapy, and combination therapy use patterns in preschoolers diagnosed with ADHD and to investigate adherence, persistence, switching, and augmentation patterns of pharmacologic agents; 3) to assess healthcare utilization (office-based, inpatient, outpatient hospital, ED visits, and prescription medications) and direct medical, prescription, and total costs of ADHD among preschoolers.

2.10.3 Study objectives and hypotheses

Objective 1 – To determine the annual prevalence and incidence of ADHD in the Texas Medicaid preschool population.

1a: To determine the treated prevalence of ADHD in preschoolers <6 years of age enrolled in Texas Medicaid.

No hypothesis – descriptive statistics were reported.

1b: To determine the treated incidence of ADHD in preschoolers <6 years of age enrolled in Texas Medicaid.

No hypothesis – descriptive statistics were reported.

Objective 2 – To determine and compare the study characteristics between pharmacotherapy only (RX), psychotherapy only (PSY), and pharmacotherapy + psychotherapy (RX+PSY) groups.

2a: To determine and compare the baseline demographic, clinical, physician, and prior utilization characteristics between the RX, PSY, and RX+PSY groups.

No hypothesis - inferential statistics were used to make the comparisons.

Objective 3 – To assess the treatment patterns of preschoolers (2 to <6 years of age) diagnosed with ADHD.

3a: To determine the time to "first pharmacotherapy," "first psychotherapy," and "first combination therapy."

No hypothesis – descriptive statistics were reported.

3b: To compare the time to first pharmacotherapy, psychotherapy, and combination therapy in preschoolers with ADHD and to compare time-to-pharmacotherapy with respect to gender, race/ethnicity, medication duration of action, and physician specialty.

> **$H_0(3b)_1$:** There is no significant difference in time-to-initiation of first pharmacotherapy ("first RX"), first psychotherapy ("first PSY"), and first combination therapy ("first RX+PSY.")
>
> **$H_0(3b)_2$:** There is no significant difference in the time-to-initiation of RX in **male vs. female** ADHD patients.
>
> **$H_0(3b)_3$:** There is no significant difference in the time-to-initiation of RX in different **race/ethnicity** groups diagnosed with ADHD.
>
> **$H_0(3b)_4$:** There is no significant difference in the time-to-initiation of RX with respect to **long-acting (LA) vs. short-acting (SA)** medications in ADHD patients.
>
> **$H_0(3b)_5$:** There is no significant difference in the time-to-initiation of RX by **physician specialty**.

3c: To assess the factors associated with receiving RX, PSY, or RX+PSY treatments, after controlling for covariates.

No hypotheses - inferential statistics were used to make the comparisons.

3d: To compare adherence, persistence, augmentation, and switching of pharmacotherapy agents between the RX and the RX+PSY groups.

> **$H_0(3d)_1$:** There is no significant difference in the likelihood of medication **adherence** between the RX and the RX+PSY groups, after controlling for covariates.
>
> **$H_0(3d)_2$:** There is no significant difference in **time to discontinuation** of index therapy between the RX and the RX+PSY groups, after controlling for covariates.
>
> **$H_0(3d)_3$:** There is no significant difference in the likelihood of **augmentation** between the RX and the RX+PSY groups, after controlling for covariates.
>
> **$H0(3d)_4$:** There is no significant difference the likelihood of **switching** between the RX and the RX+PSY groups, after controlling for covariates.

Objective 4 – To determine and compare healthcare utilization between the RX and the RX+PSY groups.

4a: To determine and compare the healthcare utilization frequencies for all-cause office-based, inpatient, outpatient hospital, emergency department (ED) visits, and prescriptions between the RX and the RX+PSY groups.

H(4a)$_1$: The number of **all-cause office-based visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

H(4a)$_2$: The number of **all-cause inpatient visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

H(4a)$_3$: The number of **all-cause outpatient hospital visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

H(4a)$_4$: The number of **all-cause ED visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

H(4a)$_5$: The number of **all-cause prescriptions** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

4b: To determine and compare the healthcare utilization frequencies for ADHD-related office-based, inpatient, outpatient hospital, ED visits, and prescriptions between the RX and RX+ PSY groups.

H(4b)$_1$: The number of **ADHD-related office-based visits** is significantly higher in the RX+ PSY group as compared to the RX group, after controlling for covariates.

H(4b)$_2$: The number of **ADHD-related inpatient visits** is significantly higher in the RX+ PSY group as compared to the RX group, after controlling for covariates.

H(4b)$_3$: The number of **ADHD-related outpatient hospital visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

H(4b)$_4$: The number of **ADHD-related ED visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

H(4b)$_5$: The number of **ADHD-related prescriptions** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

4c: To determine and compare the healthcare utilization frequencies for other mental health-related office-based, inpatient, outpatient hospital, ED visits, and prescriptions between the RX and RX+ PSY groups.

H(4c)$_1$: The number of **other mental health-related office-based visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

H(4c)$_2$: The number of **other mental health-related inpatient visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

H(4c)$_3$: The number of **other mental health-related outpatient hospital visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

H(4c)$_4$: The number of **other mental health-related ED visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

H(4c)$_5$: The number of **other mental health-related prescriptions** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

Objective 5 – To determine and compare the healthcare costs between the RX and the RX+PSY groups.

5a: To determine and compare the all-cause medical (office-based, inpatient, outpatient hospital, and ED), prescription, and total costs between the RX and RX+ PSY groups.

H(5a)$_1$: The **all-cause medical costs** are significantly higher in the RX+ PSY group as compared to the RX group, after controlling for covariates.

H(5a)$_2$: The **all-cause prescription costs** are significantly higher in the RX+ PSY group as compared to the RX group, after controlling for covariates.

H(5a)$_3$: The **all-cause total costs** are significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

5b: To determine and compare the ADHD-related medical (office-based, inpatient, outpatient, and ED), prescription, and total costs between the RX and RX+PSY groups.

H(5b)$_1$: The **ADHD-related medical costs** are significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

H(5b)$_2$: The **ADHD-related prescription costs** are significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

H(5b)$_3$: The **ADHD-related total costs** are significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

5c: To determine and compare the other mental health-related medical (office-based, inpatient, outpatient, and ED), prescription, and total costs between the RX and RX+PSY groups.

H(5c)$_1$: The **other mental health-related medical costs** are significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

H(5c)$_2$: The **other mental health-related prescription costs** are significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

H(5c)$_3$: The **other mental health-related total costs** are significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates.

CHAPTER 3: METHODOLOGY

Chapter Overview

This chapter provides a detailed description of the study methodology, which includes information pertaining to the study design, data source, study population, data extraction, study timeframe, inclusion and exclusion criteria, and the study variables. This chapter also discusses operational definitions, the coding structure, sample size assumptions and calculations, and the statistical analyses that were employed for testing the hypotheses listed in the previous chapter.

Institutional Review Board (IRB) approval

Before commencement of the study, approval was sought from the Institutional Review Board of The University of Texas at Austin and Texas Medicaid. Approval with a waiver of informed consent was granted because this was a retrospective database study containing de-identified data, which presents no more than a minimal risk to the welfare and privacy of subjects.

3.1 Data source

This retrospective study used data from Texas Medicaid. Information pertaining to patient demographics, medical services, and prescription claims from the years 2008 – 2013 was utilized for the purpose of this study. Data files included the patient eligibility file, medical claims file, inpatient claims file, and prescription claims file. The following components for each of the files listed below were extracted:

Patient eligibility file: Person-level file with unique identification number, gender, year of birth, race/ethnicity, county of residence, and enrollment periods for the beneficiaries enrolled in Texas Medicaid.

Medical claims file: Event-level file with information pertaining to office-based visits, hospital outpatient visits, ED visits, diagnoses (e.g., ICD-9 codes), procedure codes (e.g., CPT codes), date of service, amount paid, and provider type.

Inpatient claims file: Event-level file with information pertaining to inpatient stays, diagnoses, admission and discharge dates, and amount paid.

Prescription claims file: Event-level file with information pertaining to the prescription medications dispensed, dispense dates, quantity dispensed, number of authorized refills, number of days supplied, National Drug Code (NDC), physician identifier, and amount paid.

3.2 Study design

This study utilized the Texas Medicaid database to conduct a retrospective analysis of medical and pharmacy claims data. Based on the information provided by Texas Medicaid, nearly 6 million children < 6 years of age were eligible to be included in this study. Different patient selection criteria were used for prevalence and incidence calculations (i.e., for objectives 1a and 1b).Two patient cohorts were used for objectives 2 to 5. The overall cohort was used to assess time-to-initiation, utilization, and cost (i.e., for objectives 2, 3a-c, 4, and 5). The treatment pattern cohort was used to assess adherence, persistence, augmentation, and switching (i.e., for objective 3d). The patient selection processes for all the cohorts are described below.

3.2.1 Patient selection – Prevalence

The treated prevalence rate of ADHD among preschool children with continuous enrollment in Texas Medicaid for a 12-month period was estimated for objective 1a. The patients included in the numerator (the prevalent ADHD cases) for this estimate were selected if they met the following criteria:

i. had a diagnosis of ADHD (ICD-9 code = 314.00 or 314.01) recorded in the medical claims file during a specific year – 2008, 2009, 2010, 2011, or 2012;
ii. had at least two paid claims for an ADHD medication in the same year;
iii. were < 6 years of age at the end of each year; and
iv. had continuous enrollment in Medicaid for a full 12 months of each year noted in (i) and (ii).

Since it is difficult to establish a diagnosis of ADHD in preschoolers we included an additional criterion of two paid ADHD prescription claims to validate the ADHD diagnosis. Also, enrollment data for 2013 (provided by Texas Medicaid) were incomplete; thus, the prevalence estimate for 2013 was not calculated. The denominator for calculating prevalence was the total number of preschoolers < 6 years of age covered by Medicaid in each year (2008 – 2012). An estimated annual enrollment of 1.2 million children < 6 years of age was provided by Texas Medicaid and used as the denominator for each year's prevalence calculations based on the assumption that enrollment was relatively stable during this period as indicated by Texas Medicaid personnel.

3.2.2 Patient selection – Incidence

The treated incidence rate of ADHD among preschool children with continuous enrollment in Texas Medicaid for a 24-month period was estimated for objective 1b. The patients included in the numerator (the incident ADHD cases) for this estimate were selected if they met the following criteria:

i. had a diagnosis of ADHD (ICD-9 code = 314.00 or 314.01) recorded in the medical claims file during a specific year – 2008, 2009, 2010, 2011, or 2012 but with no claims associated with ADHD in the previous 12-month period;
ii. had at least two paid claims for an ADHD medication in the same year;
iii. were < 6 years of age at the end of each year; and
iv. had continuous enrollment in Medicaid for a full 12 months during the year in which the diagnosis was recorded and for the previous 12-month period.

The same denominator figure that was used in the prevalence rate calculation described above (1.2 million enrollees) was used in the incidence rate calculation.

3.2.3 Patient selection – Overall cohort

The base population consists of patients enrolled in Texas Medicaid between January 01, 2008 and August 01, 2013 (the observation period). Texas Medicaid enrollees who met the following eligibility criteria were included in the overall cohort for the study:

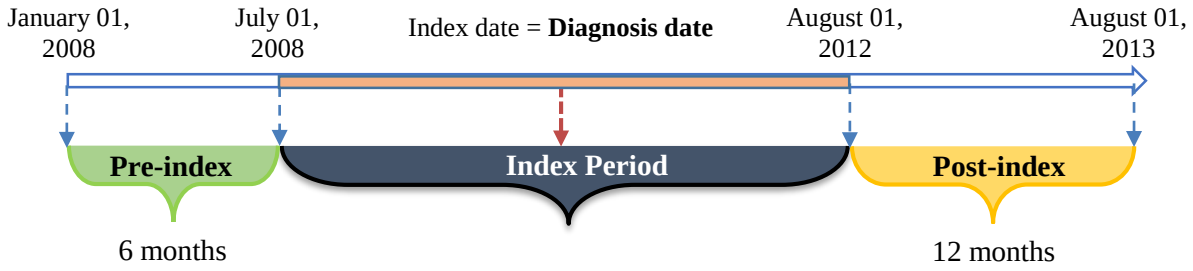
i. had at least one ADHD diagnosis based on ICD-9 codes – (314.00, 314.01);
ii. was 2 to < 6 years of age at the index date;
iii. had continuous Medicaid enrollment for at least 6 months before and 12 months after the index date; (see section 3.2.3.1)
iv. had at least two ADHD medication claims (e.g., for brand or generic formulations of amphetamines, methylphenidates, guanfacine, clonidine, or atomoxetine) or at least one psychotherapy visit (e.g., see Appendix I) indicated for the treatment of ADHD during the index period; and
v. had no ADHD medication claim or psychotherapy visit in the 6-month pre-index period.

3.2.3.1 Index date – Overall cohort

The index date is the date of the first ADHD diagnosis within the index period. The pre-index period was defined as the 6-month period before the first ADHD diagnosis (index date). The post-index period was defined as the 12-month period after the first ADHD diagnosis (index

date). Index dates between July 01, 2008 and August 01, 2012 were included in the study (**Figure 3.1**).

Figure 3.1: Study time frame – overall cohort



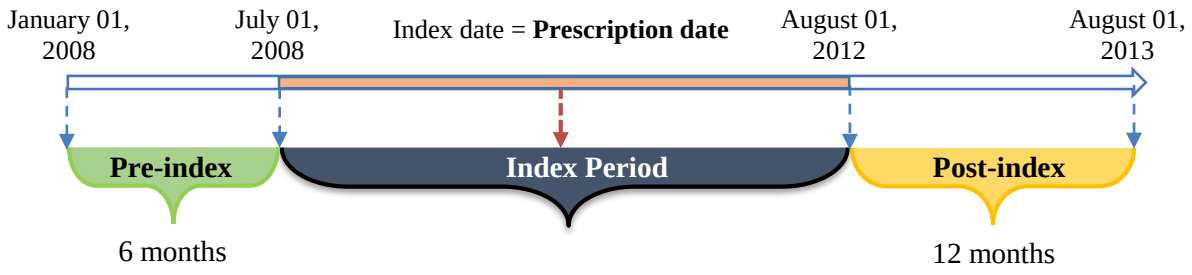
3.2.4 Patient selection – Treatment pattern cohort

A sub-sample of patients from the overall cohort were included in the treatment pattern cohort to study adherence, persistence, augmentation, and switching. The patient selection criteria used for the overall cohort were in effect for the treatment pattern cohort; however, a different index date was used for this cohort as described below.

3.2.4.1 Index date – Treatment pattern cohort

The index date is the date of the first ADHD prescription within the index period. The pre-index period was defined as the 6-month period before the first ADHD prescription (index date). The post-index period was defined as the 12-month period after the first ADHD prescription (index date). The index dates between July 01, 2008 and August 01, 2012 were included in the study (**Figure 3.2**).

Figure 3.2: Study time frame – treatment pattern cohort



3.2.5 Data collection/study timeframe

Information extracted from the Texas Medicaid files consisted of: patient demographics (i.e., age, gender, race/ethnicity, enrollment dates, and county of residence [used to determine urban/rural status]), diagnoses, NDC codes, dispense dates, quantity dispensed, number of authorized refills, number of days supplied, physician specialty, and the amount paid for prescription medications and medical services. Additional information related to generic sequence (GCN codes), American Hospital Formulary Service (AHFS codes), medication class, label name, medication duration of action were appended to the prescription claims file using a crosswalk file. Data between January 01, 2008 and August 01, 2013 were extracted for the purpose of this study. Subjects were identified during the index period from July 01, 2008 to August 01, 2012 (i.e., allowing for 6-month pre-index and 12-month post-index periods).

3.2.6 Treatment groups

The study population was sub-divided in three treatment groups based on the type of therapy received:

i) **Pharmacotherapy only (RX only):** Pharmacotherapy only group (i.e., RX only) included patients with claims for ADHD stimulant or non-stimulant medications in the follow-up period

who did not have a psychotherapy visit. Stimulant medications included brand and generic formulations for amphetamine and its derivatives, and methylphenidate and its derivatives. Non-stimulant medications included brand and generic formulations for atomoxetine, clonidine, and guanfacine. Brand and generic names along with their medication class and duration of action for the ADHD medications included in the study are shown in Appendix I.

ii) **Psychotherapy only (PSY only):** Patients with psychotherapy visits associated with ADHD but no ADHD medication claims during the follow-up period were assigned to the psychotherapy only group. Appendix II contains a list of the psychotherapy codes used in the study.

iii) **Combination therapy (RX+PSY)**: The combination therapy group included patients who received ADHD pharmacotherapy as well as psychotherapy anytime (i.e., concurrently or separately) during the follow-up period.

3.3 Study variables

3.3.1 Dependent variables

The dependent variables included: prevalence and incidence; time-to-initiation of pharmacotherapy, time-to-initiation of psychotherapy, time-to-initiation of combination therapy, medication adherence, persistence, augmentation, and switching; number of office-based visits, inpatient visits, outpatient hospital visits, ED visits, and prescription medications (all-cause, ADHD-related, and other mental healthcare-related); and medical, prescription, and total costs (all-cause, ADHD-related, and other mental health-related). Definitions of study measures are provided in **Table 3.1**.

3.3.1.1 Prevalence estimate of ADHD in preschoolers

The numerator for the prevalent cases was identified based on the patient selection criteria enlisted in section 3.2.1. We assumed enrollment of 1.2 million preschool patients (each year) as the denominator. The prevalence rates were calculated and expressed as cases per 1,000 preschoolers. Enrollment data for 2013 (provided by Texas Medicaid) were incomplete; thus, the prevalence estimate for 2013 was not calculated.

3.3.1.2 Incidence estimate of ADHD in preschoolers

The numerator for the incident cases was identified based on the patient selection criteria enlisted in section 3.2.2. We assumed enrollment of 1.2 million preschool patients (each year) as the denominator. The incidence rates were estimated as the number of new cases per 1,000

preschoolers. Enrollment data for 2013 (provided by Texas Medicaid) were incomplete; thus, the incidence estimate for 2013 was not calculated.

3.3.1.3 Treatment patterns

Treatment pattern analyses that were conducted included determining the time-to-initiation of treatment (RX, PSY, or RX+PSY) and investigating the relationships between time-to-initiation of RX and gender, race/ethnicity, and medication duration of action. Use of physician specialty was planned; however, physician specialty information was incomplete and potentially inaccurate. Therefore, physician specialty was dropped from all analyses. The relationships between treatment group membership (RX, PSY, or RX+PSY) and patient demographic, clinical, and prior utilization characteristics were also assessed. Finally, analyses evaluated adherence and persistence to ADHD pharmacotherapy, as well as medication augmentation and switching.

3.3.1.3.1 Time-to-initiation of RX, PSY, or RX+PSY

Time-to-initiation of ADHD treatment was measured as the number of days between the first ADHD diagnosis (index date) and the date of receiving the first ADHD-related treatment (i.e., ADHD medication, ADHD-related psychotherapy, or medication + psychotherapy). Differences in time-to-initiation of pharmacotherapy were tested with respect to race/ethnicity (White, African American, Hispanic, and other/unknown), gender (male and female), and medication duration of action (LA and SA). Patients initiating both LA and SA medications on the same date were categorized in the LA group as it was speculated that the SA formulation may have been prescribed on an "as needed" basis.

3.3.1.3.2 Factors associated with receiving RX, PSY, or RX+PSY

Previous research has shown that differences in treatment occur in children and adolescents according to patient age, gender, race/ethnicity, and urban/rural status. Since similar differences might exist in the preschool population, the likelihood of receiving ADHD treatment (RX, PSY, or RX+PSY) was assessed while controlling for covariates. Patients were categorized into RX, PSY, or RX+PSY groups based on the type of therapy received.

3.3.1.3.3 Measurement of medication adherence

Medication adherence can be defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen."[104] The most widely used insurance claims-based methods for measuring medication adherence are the medication possession ratio (MPR) and the proportion of days covered (PDC). While the PDC and MPR calculations will yield almost identical results when assessing adherence to a single medication as is the case in the current study, the PDC was selected for use in this study because it has been endorsed by the Pharmacy Quality Alliance (PQA).[105] The PDC was calculated as follows: the numerator was calculated by summing the number of days with medications; the denominator was calculated by summing the number of days in the follow-up period (**Figure 3.3**). PDC was used to measure adherence in the current study over a 365-day period. Patients with < 80 % PDC value were categorized as non-adherent and patients with ≥ 80% PDC value were categorized as adherent.[106]

Figure 3.3: Proportion of Days Covered (PDC)

$$PDC = \frac{(\Sigma \text{ Days of drug available})}{(\text{Days in follow-up period})}$$

3.3.1.3.4 Measurement of medication persistence

Medication persistence can be defined as "the duration of time from initiation to discontinuation of therapy."[104] Medication persistence was assessed for patients receiving RX and was defined as the time between treatment initiation and discontinuation of the index ADHD-related medication.[104,107–109] A continuous variable measuring the number of days a patient diagnosed with ADHD was on the index ADHD medication without a gap of > 30 days. Medication persistence was measured over a 365-day observation period. A 30-day allowable gap period has been used in previous studies to estimate medication persistence in patients with ADHD.[81,83,110–112] Since "drug holidays" cannot be identified using claims data, a sensitivity analysis with 60-, and 90-day gap was conducted to test for variability that might be accounted for by "drug holidays" and other factors that might be directly or indirectly associated with patients' medication therapy behavior. Previous studies have used these gap periods to study medication persistence in the ADHD population. Persistence with medications in preschoolers has not been assessed in the past and thus, the current study provides insight into their persistence rates with ADHD medications.

3.3.1.3.5 Measurement of medication augmentation and switching

Augmentation was defined as initiation of a new ADHD medication (i.e., a different chemical entity) with a continuous overlap of at least 30 days with the index medication. Switching was defined as having a prescription claim for an alternative ADHD medication (i.e., a different chemical entity) to the index ADHD medication (received on or after the index date), before or within 30 days of discontinuation of the index medication. Index medication

discontinuation was defined as no subsequent dispensing for ≥ 60 days. The "switched-to" medication must have had a days supply of at least 30 days to be considered switching.

3.3.1.4 Healthcare utilization and costs

Healthcare resource utilization and expenditure variables associated with office-based visits, inpatient stays, outpatient hospital visits, ED visits, and prescription fills are the main outcomes for this component of the study.

3.3.1.4.1 Healthcare utilization – Medical visits

All-cause utilization and ADHD-related utilization were analyzed, with services associated with primary or secondary ADHD diagnosis being defined as ADHD-related. Other mental health-related visits were included if associated with the following primary diagnoses (ADHD could not be a secondary diagnosis for this group of services): pervasive developmental disorders (ICD-9 codes: 299.xx), conduct disorder (ICD-9 codes:312.0x, 312.1x, 312.2x, 312.4, 312.8, 312.8x, and 312.9) , oppositional defiant disorder (ICD-9 code: 313.81), developmental delays (ICD-9 codes: 307.0, 307.9, 315.x, 315.0x, 315.3x, 317, 318.0, 318.1, 318.2, 319, V400, and V401) listed as the primary diagnosis without ADHD as one of the secondary diagnosis were included in this category.

3.3.1.4.2 Healthcare utilization – Prescription medications

All-cause prescriptions: Prescription claims for all medications were included in this category.

ADHD-related prescriptions: Prescription claims for ADHD medications were included in this category.

Other mental health-related prescriptions: Prescription claims for other mental health-related medications were included in this category (defined later in the methods).

3.3.1.4.3 Healthcare costs

Costs (all-cause, ADHD-related, and other mental health-related) reflect costs to the Texas Medicaid program and are based on "paid amount" variable for each claim. Medical costs (i.e., sum of office-based, inpatient, outpatient hospital, and ED visits), prescription costs, and total costs (medical + RX + other) were calculated. All costs were converted to 2013 dollars based on the medical consumer price index (CPI).

Table 3.1: Operational definitions for the dependent variables included in the study

Dependent Variables	Operational Definitions
Prevalence and Incidence	
Prevalence rate	Ratio of the number of preschoolers who meet the inclusion criteria for prevalent cases each year/estimated total number of preschoolers < 6 years of age enrolled in Texas Medicaid each year (proportion).
Incidence rate	Ratio of the number of preschoolers who meet the inclusion criteria for incident cases each year/estimated total number of preschoolers < 6 years of age enrolled in Texas Medicaid each year (proportion).
Treatment patterns	
Time-to-initiation[a]	Number of days between the first ADHD diagnosis (index date) and the first therapy (i.e., pharmacotherapy, psychotherapy, or combination therapy).
Treatment adherence[b]	ADHD medication adherence measured in the post-index period using PDC. **0** = Non-Adherent (PDC < 0.8 or 80%) **1** = Adherent (PDC ≥ 0.8 or 80%)
Treatment persistence[b]	Number of days of continuous therapy without a gap of >30 days in the post-index period. Sensitivity analyses with 60-, and 90-day gap periods were conducted.
Treatment augmentation[b]	Prescription claims for new ADHD medication in addition to the index medication with an overlap of at least 30 days. **0** = Did not add medications to the index treatment **1** = Added medications to the index treatment
Treatment switching[b]	Prescription claim for an ADHD medication (different chemical entity) other than the index medication before or within 30 days of discontinuation of the index medication with no subsequent dispensing of the index medication for ≥ 60 days. "Switched-to" drug should be taken for at least 30 consecutive days. **0** = Did not switch from index treatment **1** = Switched from index treatment

Table 3.1: Operational definitions for the dependent variables included in the study (continued)

Dependent Variables	Operational Definitions
Healthcare utilization[a]	
All-cause	
Office-based visits	Number of all-cause office-based visits in the post-index study period (frequency count).
Outpatient hospital visits	Number of all-cause outpatient hospital visits in the post-index study period (frequency count).
Inpatient hospital visits	Number of all-cause inpatient visits in the post-index study period (frequency count).
Emergency department visits	Number of all-cause ED visits in the post-index study period (frequency count).
Prescriptions	Number of all-cause prescriptions in the post-index study period (frequency count).
ADHD-related	
Office-based visits	Number of ADHD-related office-based visits in the post-index study period (frequency count).
Outpatient hospital visits	Number of ADHD-related outpatient hospital visits in the post-index study period (frequency count).
Inpatient hospital visits	Number of ADHD-related inpatient visits in the post-index study period (frequency count).
Emergency department visits	Number of ADHD-related ED visits in the post-index study period (frequency count).
Prescriptions	Number of ADHD-related prescriptions in the post-index study period (frequency count).
Other mental health-related	
Office-based visits	Number of other mental health-related office-based visits in the post-index study period (frequency count).
Outpatient hospital visits	Number of other mental health-related outpatient hospital visits in the post-index study period (frequency count).
Inpatient hospital visits	Number of other mental health-related inpatient visits in the post-index study period (frequency count).
Emergency department visits	Number of other mental health-related ED visits in the post-index study period (frequency count).
Prescriptions	Number of other mental health-related prescriptions in the post-index study period (frequency count).

Table 3.1: Operational definitions for the dependent variables included in the study (continued)

Dependent Variables	Operational Definitions
Healthcare costs[a]	
All-cause	
Post-index medical costs	Sum of costs related to office-based, inpatient, outpatient hospital, and ED visits in the post-index study period adjusted to 2013 dollars using the medical CPI (continuous).
Post-index prescription medication costs	Sum of prescription-related costs in the post-index study period adjusted to 2013 dollars using the medical CPI (continuous).
Post-index total costs	Total (medical + prescription + other[c]) costs in the post-index study period adjusted to 2013 dollars using the medical CPI (continuous).
ADHD-related	
Post-index medical costs	Sum of ADHD-related costs for office-based, inpatient, outpatient hospital, and ED visits in the post-index study period adjusted to 2013 dollars using the medical CPI (continuous).
Post-index prescription medication costs	Sum of ADHD-related prescription costs in the post-index study period adjusted to 2013 dollars using the medical CPI (continuous).
Post-index total costs	Sum of ADHD-related total (medical + prescription + other[c]) costs in the post-index study period adjusted to 2013 dollars using the medical CPI (continuous).
Other mental health-related	
Post-index medical costs	Sum of other mental health-related costs for office-based, inpatient, outpatient hospital, and ED visits in the post-index study period adjusted to 2013 dollars using the medical CPI (continuous).
Post-index prescription medication costs	Sum of other mental health-related prescription costs in the post-index study period adjusted to 2013 dollars using the medical CPI (continuous).
Post-index total costs	Sum of other mental health-related total (medical + prescription + other[c]) costs in the post-index study period adjusted to 2013 dollars using the medical CPI (continuous).

CPI = Consumer Price Index; ADHD = Attention Deficit Hyperactivity Disorder; ED = Emergency Department; PDC = Proportion of Days Covered;

[a] Conducted on the overall cohort [i.e., patients with 1 year follow-up after the first ADHD diagnosis (index date = diagnosis date)];

[b] Conducted on treatment pattern cohort patients [i.e., patients with 1 year follow-up after the first ADHD-related prescription (index date = date of first prescription)]

[c] Other costs included cost that could not be captured in the medical or prescription-related categories (e.g., Ultrasound procedures, culture coding, routine venipuncture, thyroid function tests, X-ray, or psychotherapy without place of service code)

3.3.2 Independent variables

The primary independent variable was type of therapy (i.e., pharmacotherapy, psychotherapy, and combination therapy). Covariates included in the study were age, gender, race/ethnicity, urban/rural status, number of pre-index visits (psychiatric and non-psychiatric office-based visits), number of pre-index psychotropic prescription claims, other mental health diagnosis, pre-index total healthcare costs, medication duration of action, and medication class. Definitions of study measures are provided in **Table 3.2**.

3.3.2.1 Patient demographics

Patient demographic characteristics included age at the index date (diagnosis date), gender, race/ethnicity (White, African American, Hispanic, other/unknown). Urban/rural status was defined based on the patient's county of residence.

3.3.2.2 Physician specialty

Use of physician specialty was planned; however, physician specialty information was incomplete and potentially inaccurate. Therefore, physician specialty was dropped from all analyses.

3.3.2.3 Clinical and prior utilization characteristics

Patients' pre-index utilization of psychiatric office-based visits, non-psychiatric office-based visits, and psychotropic medications, as well as pre-index all-cause total healthcare costs served as independent variables. Psychotropic medications were identified based on AHFS codes

28:16.04 (antidepressants), 28:16.08 (antipsychotics), 28:24 (anxiolytics/sedatives/hypnotics), 28:28 (antimanics), and 28:12 (anticonvulsants).

Clinical characteristics included were other mental health diagnoses, medication class, and medication duration of action. Other mental health diagnoses were identified based on the ICD-9 codes of the most commonly-occurring mental health conditions in patients with ADHD. Other mental health diagnoses are listed in section 3.3.1.4.1.

With respect to medication class, index medications were classified as stimulants and non-stimulants. The stimulant medications include amphetamine and its derivatives, and methylphenidate and its derivatives. The non-stimulant medications include atomoxetine, clonidine, and guanfacine.

With respect to medication duration of action, ADHD medications were classified as short-acting or long-acting depending on their product names and product literature. See Appendix I for a listing of medications by medication class and duration of action.

Table 3.2: Operational definitions for the independent variables included in the study

Variables	Operational Definitions
Treatment group	Categorized as **0** = Pharmacotherapy only (RX only) **1** = Psychotherapy only (PSY only) **2** = Combination therapy (RX+PSY)
Age	Age of the respondent at the index date (continuous)
Gender	Dichotomized as **0** = Female **1** = Male
Race/Ethnicity	Categorized as **0** = White **1** = African American **2** = Hispanic **3 =** Other/Unknown
Urban/rural status	Categorized as **0** = Urban **1** = Rural
Pre-index psychiatric office-based visits	Visits with a other mental health diagnosis as a primary diagnosis in the pre-index period (frequency count)
Pre-index non-psychiatric office-based visits	Visits without other mental health diagnosis as a primary diagnosis in the pre-index period (frequency count)
Pre-index psychotropic prescription claims	Presence of psychotropic medication claims for one of the following Antipsychotics (AHFS code – 28:16.08) Antidepressants (AHFS code – 28:16.04) Anxiolytics/Sedatives/Hypnotics (AHFS code – 28:24) Antimanics (AHFS code – 28:28) Anticonvulsants (AHFS code – 28:12) Categorized as **0** = No psychotropic medication claim **1** = Psychotropic medication claim
Pre-index all-cause total healthcare costs	Total costs in the pre-index period for patients diagnosed with ADHD (adjusted to 2013 dollars using medical CPI) (continuous)

Table 3.2: Operational definitions for the independent variables included in the study (continued)

Variables	Operational Definitions
Other mental health diagnosis	Presence of mental health diagnoses for one of the following Pervasive developmental disorders[a] Conduct disorder[b] Oppositional defiant disorder[c] Developmental delays[d] Categorized as **0** = Absence of other mental health diagnosis **1** = Presence of other mental health diagnosis
Medication class	Presence of claims for stimulants and non-stimulants. Stimulant medications included methylphenidate and its derivatives and amphetamines and its derivatives. Non-stimulant medications include atomoxetine, clonidine, and guanfacine. Categorized as **0** = Stimulant **1** = Non-stimulant
Medication duration of action	Presence of claims for long-acting or short-acting medications. Long-acting medications included Concerta, Ritalin LA, Ritalin SR, Metadate CD, Metadate ER, Methylin ER, Daytrana, Adderall XR, Focalin XR, Intuniv, Kapvay, and Vyvanse. Short-acting medications include Ritalin, Methylin, Focalin, Dexedrine, Dextrostat, Procentra, Strattera, and Adderall. Categorized as **0** = Long-acting [LA] **1** = Short-acting [SA]

ADHD = Attention Deficit Hyperactivity Disorder; ICD-9 = International classification of disease, 9th revision; AHFS = American Hospital Formulary System; RX = Pharmacotherapy only; PSY = Psychotherapy only; RX+PSY = Combination therapy;

[a] pervasive developmental disorders (ICD-9 codes: 299.xx);

[b] conduct disorder (ICD-9 codes: 312.0x, 312.1x, 312.2x, 312.4, 312.8, 312.8x, and 312.9);

[c] oppositional defiant disorder (ICD-9 code: 313.81);

[d] developmental delays (ICD-9 codes: 307.0, 307.9, 315.x, 315.0x, 315.3x, 317, 318.0, 318.1, 318.2, 319, V400, and V401)

3.4 Statistical analyses

Preliminary analyses involved basic descriptive statistics to identify patient baseline characteristics. Preliminary tests were used to identify potential outliers in the data and to assess the statistical test assumptions proposed for each analysis. All analyses were two-tailed with an a priori significance level of 0.05.

Frequencies and percentages were used to summarize categorical variables (i.e., gender, race/ethnicity, urban/rural status, pre-index psychotropic prescriptions, medication class, medication duration of action, other mental health diagnoses, adherence status, switching status, and augmentation status). Mean, median, and distribution statistics were used to summarize continuous variables (i.e., age, pre-index psychiatric office-based visits, pre-index non-psychiatric office-based visits, time-to-initiation, adherence, persistence, office-based visits, inpatient visits, outpatient hospital visits, ED visits, prescriptions, and costs).

Data management and analyses were performed using SAS® for Windows version 9.3 (SAS Institute, Cary, NC) and Stata Version 12 (TX).

3.4.1 Objective 1: Prevalence and incidence

Proportions were used to describe the prevalence and incidence statistics. The annual prevalence and incidence rates were calculated as described in sections 3.3.1.1 and 3.3.1.2, and reported as ratios.

3.4.2 Objective 2: Comparing demographic and patient, clinical, and prior utilization characteristics between RX, PSY, and RX+PSY groups

Baseline patient demographics, pre-index psychiatric office-based visits, pre-index non-psychiatric office-based visits, pre-index psychotropic prescription claims, pre-index all-cause total healthcare costs, other mental health diagnosis, medication class, and medication duration of action were assessed and compared across the pharmacotherapy only (RX), psychotherapy only (PSY), and pharmacotherapy + psychotherapy (RX+PSY) groups. Categorical variables were compared using chi-square tests and continuous variables were compared using ANOVA or Kruskal-Wallis tests (for data violating normality assumption).

3.4.3 Objective 3: Treatment patterns of preschoolers between 2 and < 6 years of age

Objective 3a: Time-to-initiation of RX, PSY, or RX+PSY

In this study, median times to initiate each type of therapy were estimated from the time of the first ADHD diagnosis (index date) to the date of receiving the first treatment (i.e., first RX, first PSY, or first RX+PSY). Kaplan-Meier curves were plotted to estimate the time-to-initiation of "first PSY," "first RX," and "first RX+PSY." Patients not receiving RX (in the estimation of time-to-initiation of "first RX"), patients not receiving PSY (in the estimation of

time-to-initiation of "first PSY"), and patients not receiving RX+PSY (in the estimation of time-to-initiation of "first RX+PSY") were 'censored.' Unadjusted Cox proportional hazards models were used to compare time-to-initiation among the three treatment groups.

Objective 3b: Time-to-initiation of RX according to gender, race/ethnicity, and medication duration of action

Time from diagnosis of ADHD (index date) to initiation of first RX was assessed in this objective. Log-rank tests were conducted to test differences in time-to-initiation of "first RX" in relation to gender and medication duration of action. Cox proportional hazards regression models were used to assess time-to-initiation of "first RX" by race/ethnicity. Patients not receiving pharmacotherapy were 'censored.'

Objective 3c: Factors associated with receiving RX, PSY, or RX+PSY

Multinomial logistic regression models were used to assess the relationships of patient demographics, clinical, and prior utilization characteristics with the likelihood of receiving RX, PSY, or RX+PSY in the post-index period, while controlling for the covariates.

Objective 3d: Adherence, persistence, augmentation, and switching

The adherence rates of the index medication therapy were calculated for patients in the RX and RX+PSY treatment groups. Chi-square tests were used to compare proportions of adherent patients (PDC $\geq$ 80%), and proportions of patients augmenting and switching between the RX and RX+PSY groups. An independent groups t-test was used to compare adherence (PDC) and persistence between the RX and RX+PSY groups. Multiple linear regression was also

used to compare the adherence and persistence between RX and RX+PSY groups, while controlling for covariates. Logistic regression analysis was used to compare the likelihood of adherence, augmentation, and switching between the RX and RX+PSY groups, while controlling for covariates.

Persistence was compared between the RX and RX+PSY groups using a Kaplan-Meier estimator curve. Cox proportional hazards regression analysis was used to compare time to discontinuation of pharmacotherapy between the RX and RX+PSY groups while controlling for covariates. Patients who still persist with their initial therapy at the end of the follow-up period were 'censored.'

3.4.4 Objectives 4 & 5: Healthcare utilization and costs

Healthcare utilization data are often recorded as counts whereas healthcare cost data are the absolute dollar value for a particular service. Since utilization data usually violate the normality distribution assumption, it is important to account for non-normality by fitting appropriate models.[113] Because the data do not always satisfy the normality assumption, analysis of healthcare data based on OLS regression assumptions may not be warranted. Analyzing healthcare data using OLS regression may increase the type I error rate due to erroneous standard errors and confidence intervals. Also, healthcare utilization data tends to have a higher number of zero values (e.g., few patients incur hospitalization costs because it is very rare to be hospitalized for a particular condition) and are highly skewed (e.g., a few patients incur disproportionately higher costs relative to a majority of the patients). Additionally, utilization data may be highly correlated especially for chronic conditions. Also, previous studies have shown that utilization data is rarely homoscedastic.

Inadequacy of the OLS regression in handling count outcomes can be overcome by use of Poisson regression models. Poisson regressions may provide a more appropriate alternative for analyzing count data (e.g., inpatient, outpatient, and ED visits) often encountered in healthcare research. Poisson regression models assume that the variance of the population is equal to the mean. However, Poisson distributions could be over-dispersed (i.e., where the variance is greater than the mean), thus violating the assumption of equidispersion. In such cases, the negative binomial models would be appropriate to model over-dispersed count data with unobserved heterogeneity. Alternatively, data could be skewed or lumped due to the presence of excessive zeros. When the data have an excessive number of zero observations, zero-inflated regression models or hurdle models are recommended. The choice between zero-inflated regression models and hurdle models is based on identifying the source of zeros. The excessive zeros observed in the zero-inflated model could be due to a chance occurrence (known as 'sampling zeros') or due to the method of data collection (known as 'structural zeros') (e.g., lack of hospitalizations because everyone in the cohort is healthy). On the other hand, hurdle models have an important distinction and assume that all the zeros observed in the data are structural. Zero-inflated Poisson regression models were used to model utilization data for this study because the data included a high number of zero values in all the utilization categories, except for all-cause ADHD-related prescriptions. All-cause and ADHD-related prescriptions were modelled using Poisson regression.

Objective 4: To determine and compare healthcare utilization between the RX and the RX+PSY groups

Objectives 4a-c: To determine and compare the healthcare utilization frequencies for all-cause, ADHD-related, and other mental health-related office-based, inpatient, outpatient hospital, ED visits, and prescriptions between the RX and RX+PSY groups

Based on the distribution of the data, Possion regression and zero-inflated regression models were used to compare the number of all-cause, ADHD-related, other mental health-related office-based, inpatient, outpatient hospital, ED visits, and prescriptions between the RX and the RX+PSY groups while controlling for patient demographics and treatment covariates.

Objective 5: To determine and compare healthcare costs between the RX and the RX+PSY groups

Objective 5a-c: To determine and compare all-cause, ADHD-related, and other mental health-related medical costs (office-based, inpatient, outpatient hospital, and ED), prescription drug costs, and total costs between the RX and RX+PSY groups

Means and median all-cause, ADHD-related, and other mental health-related medical, prescription, and total costs were reported for the RX and RX+PSY groups. A Modified Park test was conducted to identify the distribution and select the appropriate functional form and link function. Separate generalized linear regression models with a gamma distribution and a log-link were used to compare all-cause, ADHD-related, other mental health-related costs between the RX and RX+PSY groups while controlling for covariates. Cost data were adjusted to 2013 dollars using the medical CPI index for 2013 (published by the Bureau of Labor Statistics.)

Table 3.3 provides a list of objectives and the corresponding statistical tests that were carried out.

Table 3.3: Summary of study objectives, hypotheses, variables, and statistical analyses

Objectives and Hypotheses	Dependent Variables	Measurement Levels	Independent Variables	Measurement Levels	Statistical Analyses
Objective 1 – To determine the annual prevalence and incidence of ADHD diagnosis in the Texas Medicaid preschool population					
1a: To determine the treated prevalence of ADHD in preschoolers <6 years of age enrolled in Texas Medicaid	Prevalence (number of preschoolers diagnosed with ADHD)	Count	N/A	N/A	Descriptive
1b: To determine the treated incidence of ADHD in preschoolers <6 years of age enrolled in Texas Medicaid	Incidence (number of newly diagnosed preschoolers with ADHD)	Count	N/A	N/A	Descriptive
Objective 2 – To determine and compare the baseline characteristics between RX, PSY, and RX+PSY groups					
2a: **To determine and compare the baseline demographic, clinical, and prior utilization characteristics between the pharmacotherapy only (RX), psychotherapy only (PSY), and pharmacotherapy + psychotherapy combined (RX+PSY) groups**	Age, gender, race/ethnicity, urban/rural status, pre-index psychiatric office-based visits, pre-index non-psychiatric office-based visits, pre-index all-cause total healthcare costs, pre-index psychotropic medication use, other mental health diagnosis, medication class, and medication duration of action	Continuous and categorical	Treatment groups (RX, PSY, and RX+PSY)	Categorical	Chi-square tests for categorical variables and ANOVA (Kruskal-Wallis in case of non-normality) for continuous variables

Table 3.3: Summary of study objectives, hypotheses, variables, and statistical analyses (continued)

Objectives and Hypotheses	Dependent Variables	Measurement Levels	Independent Variables	Measurement Levels	Statistical Analyses
Objective 3 – To assess the treatment patterns of preschoolers (2 to <6 years of age) diagnosed with ADHD					
3a: To determine the time to "first pharmacotherapy," "first psychotherapy" and "first combination therapy"	Pharmacotherapy (time to "first pharmacotherapy") Psychotherapy (time to "first psychotherapy") "first combination therapy" (time to combination therapy)	Continuous	**Pharmacotherapy** (Yes, No) **Psychotherapy** (Yes, No) **"Combination therapy"** (Yes, No)	Categorical	Kaplan-Meier estimation curve
3b: To compare the time to first pharmacotherapy, psychotherapy, and combination therapy in preschoolers with ADHD and to compare time to pharmacotherapy with respect to gender, race/ethnicity, medication duration of action, and physician specialty					
$H_0(3b)_1$: There is no difference in time-to-initiation of pharmacotherapy ("first RX"), psychotherapy ("first PSY"), or "first combination therapy"	Time to therapy (first pharmacotherapy, first psychotherapy, or first combination therapy)	Continuous	**Type of therapy** ("first RX," "first PSY," or "first RX+PSY")	Categorical	Cox Proportional Hazards (Cox PH) regression
$H_0(3b)_2$: There is no significant difference in the time-to-initiation of RX in **male vs. female** ADHD patients	Time to "first pharmacotherapy"	Continuous	**Gender** (Male, Female)	Continuous and categorical	Log-rank test
$H_0(3b)_3$: There is no significant difference in the time-to-initiation of RX in different **race/ethnicity** groups diagnosed with ADHD	Time to "first pharmacotherapy"	Continuous	**Race/ethnicity** (White, Black, Hispanic, and Other)	Continuous and categorical	Cox PH regression
$H_0(3b)_4$: There is no significant difference in the time-to-initiation of RX with respect to **long-acting (LA) vs. short-acting (SA) medications** in ADHD patients	Time to "first pharmacotherapy"	Continuous	**Medication duration of action** (short-acting [SA], long-acting [LA])	Continuous and categorical	Log-rank test

Table 3.3: Summary of study objectives, hypotheses, variables, and statistical analyses (continued)

Objectives and Hypotheses	Dependent Variables	Measurement Levels	Independent Variables	Measurement Levels	Statistical Analyses
$H_0(3b)_5$: There is no significant difference in the time-to-initiation of RX by **physician specialty**	Time to "first pharmacotherapy"	Continuous	**Physician specialty** (Psychiatrist, Primary care, Other and Missing)	Continuous and categorical	Cox PH regression
3c: To assess the factors associated with receiving RX, PSY, or RX+PSY, after controlling for covariates	Received pharmacotherapy or psychotherapy (RX = 1, PSY = 2, or RX+PSY = 3)	Nominal	Covariates[a]	Continuous and categorical	Multinomial Logistic regression
3d: To compare adherence, persistence, augmentation, and switching of pharmacotherapy between the RX and the RX+PSY groups					
$H_0(3d)_1$: There is no significant difference in the likelihood of medication **adherence** between the RX and the RX+PSY groups, after controlling for covariates	Medication adherence (PDC) [Yes = 1 (PDC $\geq$ 80), No = 0 (PDC < 80)]	Dichotomous/ categorical	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	Logistic regression
$H_0(3d)_2$: There is no significant difference in **time to discontinuation** between the RX and the RX+PSY groups, after controlling for covariates	Medication persistence (time to discontinuation)	Continuous	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	Log-Rank test Cox PH regression
$H_0(3d)_3$: There is no significant difference in the likelihood of medication **augmentation** between the RX and the RX+PSY groups, after controlling for covariates	Medication augmentation (Yes = 1, No = 0)	Dichotomous/ categorical	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	Logistic regression
$H_0(3d)_4$: There is no significant difference in the likelihood of **switching** between the RX and the RX+PSY groups, after controlling for covariates	Medication switching (Yes = 1, No = 0)	Dichotomous/ categorical	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	Logistic regression

Table 3.3: Summary of study objectives, hypotheses, variables, and statistical analyses (continued)

Objectives and Hypotheses	Dependent Variables	Measurement Levels	Independent Variables	Measurement Levels	Statistical Analyses
Objective 4 – To determine and compare healthcare utilization between the RX and the RX+PSY groups					
4a: To determine and compare healthcare utilization frequencies for all-cause office-based, inpatient, outpatient hospital, emergency department (ED) visits, and prescription medications between the RX and the RX+PSY groups					
H(4a)$_1$: The number of **all-cause office-based visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	Number of all-cause office-based visits	Count	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	Zero-Inflated Poisson regression (ZIP)
H(4a)$_2$: The number **of all-cause inpatient visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	Number of all-cause inpatient visits	Count	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	ZIP
H(4a)$_3$: The number of **all-cause outpatient hospital visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	Number of all-cause outpatient hospital visits	Count	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	ZIP
H(4a)$_4$: The number **of all-cause ED visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	Number of all-cause ER visits	Count	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	ZIP
H(4a)$_5$: The number **of all-cause prescriptions** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	Number of prescription fills	Count	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	Poisson regression

Table 3.3: Summary of study objectives, hypotheses, variables, and statistical analyses (continued)

Objectives and Hypotheses	Dependent Variables	Measurement Levels	Independent Variables	Measurement Levels	Statistical Analyses
4b: To determine and compare healthcare utilization frequencies for ADHD-related office-based, inpatient, outpatient hospital, ED visits, and prescription medications between the RX and RX+PSY groups					
H(4b)$_1$: The number of **ADHD-related office-based visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	Number of ADHD-related office-based visits	Count	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	ZIP
H(4b)$_2$: The number of **ADHD-related inpatient visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	Number of ADHD-related inpatient visits	Count	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	ZIP
H(4b)$_3$: The number of **ADHD-related outpatient hospital visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	Number of ADHD-related outpatient hospital visits	Count	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	ZIP
H(4b)$_4$: The number of **ADHD-related ED visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	Number of ADHD-related ED visits	Count	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	ZIP
H(4b)$_5$: The number **of ADHD-related prescriptions** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	Number of prescription fills	Count	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	Poisson regression

Table 3.3: Summary of study objectives, hypotheses, variables, and statistical analyses (continued)

Objectives and Hypotheses	Dependent Variables	Measurement Levels	Independent Variables	Measurement Levels	Statistical Analyses
4c: To determine and compare healthcare utilization frequencies for other mental health-related office-based, inpatient, outpatient hospital, ED visits, and prescription medications between the RX and RX+PSY groups					
H(4c)$_1$: The number of **other mental health-related office-based visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	Number of other mental health-related office based visits	Count	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	ZIP
H(4c)$_2$: The number of **other mental health-related inpatient visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	Number of other mental health-related inpatient visits	Count	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	ZIP
H(4c)$_3$: The number of **other mental health-related outpatient hospital visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	Number of other mental health-related outpatient hospital visits	Count	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	ZIP
H(4c)$_4$: The number of **other mental health-related ED visits** is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	Number of other mental health-related ER visits	Count	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	ZIP
H(4c)$_5$: The number of other mental health-related prescriptions is significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	Number of prescription fills	Count	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	ZIP

Table 3.3: Summary of study objectives, hypotheses, variables, and statistical analyses (continued)

Objectives and Hypotheses	Dependent Variables	Measurement Levels	Independent Variables	Measurement Levels	Statistical Analyses
Objective 5: To determine and compare the healthcare costs between the RX and the RX+PSY groups					
5a: To determine and compare the all-cause medical costs (office-based, inpatient, outpatient hospital, and ED), prescription drug costs, and total costs between the RX and RX+PSY groups					
H(5a)$_1$: The **all-cause medical costs** are significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	All-cause medical costs	Continuous	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	Generalized Linear Models (GzLM)
H(5a)$_2$: The **all-cause prescription costs** are significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	All-cause prescription costs	Continuous	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	GzLM
H(5a)$_3$: The **all-cause total costs** are significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	All-cause total costs	Continuous	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	GzLM
5b: To determine and compare the ADHD-related medical costs (office-based, inpatient, outpatient hospital, and ED), prescription drug costs, and total costs between the RX and RX+PSY groups					
H(5b)$_1$: The **ADHD-related medical costs** are significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	ADHD-related medical costs	Continuous	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	GzLM

Table 3.3: Summary of study objectives, hypotheses, variables, and statistical analyses (continued)

Objectives and Hypotheses	Dependent Variables	Measurement Levels	Independent Variables	Measurement Levels	Statistical Analyses
H(5b)$_2$: The **ADHD-related prescription costs** are significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	ADHD-related prescription costs	Continuous	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	GzLM
H(5b)$_3$: The **ADHD-related total costs** are significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	ADHD-related total costs	Continuous	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	GzLM
5c: To determine and compare the other mental health-related medical costs (office-based, inpatient, outpatient hospital, and ED), prescription drug costs, and total costs between the RX and RX+PSY groups					
H(5c)$_1$: The **other mental health-related medical costs** are significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	Other mental health-related medical costs	Continuous	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	GzLM
H(5c)$_2$: The **other mental health-related prescription costs** are significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	Other mental health-related prescription costs	Continuous	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	GzLM
H(5c)$_3$: The **other mental health-related total costs** are significantly higher in the RX+PSY group as compared to the RX group, after controlling for covariates	Other mental health-related total costs	Continuous	**Treatment groups** (RX or RX+PSY) & Covariates[a]	Continuous and categorical	GzLM

ZIP = Zero-Inflated Poisson regression; GzLM = Generalized Linear Models; ADHD = Attention Deficit Hyperactivity Disorder; PDC = Proportion of Days Covered;

[a] Covariates include age, gender, race/ethnicity, urban/rural status, pre-index psychiatric office based visits, pre-index non-psychiatric office-based visits, pre-index total healthcare costs, other mental health diagnosis, medication class, and medication duration of action

3.5 Statistical assumptions and sample size calculations

The sample size calculations were done a priori for each objective of the study. The sample sizes were based on four parameters: (i) type I error rate or alpha of 0.05; (ii) type II error rate or power of 0.80; (iii) effect size depending on the type of statistical test performed; and (iv) prevalence rates in the population (previous studies have estimated a prevalence rate ranging from 2 – 5 %. A conservative estimate of 3% was utilized in this study).[3,4]

3.5.1 Kaplan-Meier estimators

A Kapan-Meier (KM) curve generates survival probabilities within a given time frame.[114,115] KM curves are usually an estimate of probability of experiencing the event plotted against time. The proportion of patients surviving until the end of the specified period is given by[114,115]

Figure 3.4: Kaplan-Meier equation

$$S_t = \frac{(r_i - d_i)}{r_i}$$

Where

S_t = survival probability

r_i = number entering the cohort at the beginning of the study period

d_i = number of people experiencing the event during the specified follow-up time

3.5.2 Log-Rank test

To help understand the treatment patterns, time-to-initiation of pharmacotherapy with respect to gender and medication duration of action were tested using log-rank tests. The log-rank test was also used to compare time-to-discontinuation (persistence) between the RX and

RX+PSY treatment groups. The curves for each treatment group were compared statistically by testing the null hypothesis that there is no difference between time to discontinuation of these therapies. The log-rank test statistic requires that the proportional hazards assumption is met.[114,115] The test statistic is calculated as follows:

Figure 3.5: Log-rank equation

$$x^2 \text{ (log rank)} = \frac{(O_1 - E_1)}{E_1} + \frac{(O_2 - E_2)}{E_2}$$

Where

O_1 = Total number of observed events in group 1

O_2 = Total number of observed events in group 2

E_1 = Total number of expected events in group 1

E_2 = Total number of expected events in group 2

Sample sizes for the log-rank test were estimated using Stata software. A range of values were entered and the largest sample size was chosen as the sample size for analyzing objective 2.

Table 3.4 represents the sample size estimates for different input parameters. An estimated sample size of 887 patients were required for two-sample comparisons of survivor functions.

Table 3.4: Sample size estimates for log-rank test

Sample Size (N)	Pharmacotherapy	Combination Therapy	Events	Prob1	Prob2	Hazard Ratio
1,326	663	663	1,272	0.03	0.05	0.854
1,516	758	758	1,456	0.03	0.05	0.854
1,774	**887**	**887**	1,704	0.03	0.05	0.854

3.5.3 Cox Proportional-Hazards regression (Cox PH)

Cox Proportional-Hazards regression (Cox PH) models are similar to multiple regression models. In Cox PH regression models, no assumption regarding the probability distribution is made, but it does assume that the hazard ratios (i.e., conditional probability of having the event at time 't' given that the event has not occurred until that time) are constant over time.[114,115]

Assumptions of the proportional-hazards models can be tested based on Schoenfelds' residual plots to detect possible departures from the assumptions.[116] Also, since the hazard function in the Cox model assumes a log-linear relationship with its covariates, it is important to test this assumption. This linearity assumption can be tested by plotting the deviance residuals and the Martingale residuals against the covariates.[114–116]

Sample sizes for Cox PH regressions were estimated using PASS 13 software. A range of parameters (power = 0.80; α = 0.05, log hazard = [1.5-2.0], R^2 = 0.1 – 0.3) were entered into the sample size calculations and the largest sample size was chosen for the analyses.

Table 3.5 represents the sample size estimates required for the Cox PH regression analyses. Based on the sample size estimates, a total sample size of 1,662 patients were required for the Cox PH regression analysis.

Table 3.5: Sample size estimates for Cox proportional hazards regression models

Parameters					
B (log hazard ratio)[a]	1.50	1.50	1.50	1.50	1.50
P (overall event rate)[b]	0.30	0.35	0.40	0.45	0.50
R-squared[c]	0.10	0.10	0.10	0.10	0.10
Total sample size	**1,292**	**1,108**	**969**	**862**	**776**
B (log hazard ratio)	1.50	1.50	1.50	1.50	1.50
P (overall event rate)	0.30	0.35	0.40	0.45	0.50
R-squared	0.20	0.20	0.20	0.20	0.20
Total sample size	**1,454**	**1,246**	**1,091**	**969**	**873**
B (log hazard ratio)	1.50	1.50	1.50	1.50	1.50
P (overall event rate)	0.30	0.35	0.40	0.45	0.50
R-squared	0.30	0.30	0.30	0.30	0.30
Total sample size	**1,662**	**1,424**	**1,246**	**1,108**	**997**
B (log hazard ratio)	2.00	2.00	2.00	2.00	2.00
P (overall event rate)	0.30	0.35	0.40	0.45	0.50
R-squared	0.10	0.10	0.10	0.10	0.10
Total sample size	**727**	**623**	**546**	**485**	**437**
B (log hazard ratio)	2.00	2.00	2.00	2.00	2.00
P (overall event rate)	0.30	0.35	0.40	0.45	0.50
R-squared	0.20	0.20	0.20	0.20	0.20
Total sample size	**818**	**701**	**614**	**546**	**491**
B (log hazard ratio)	2.00	2.00	2.00	2.00	2.00
P (overall event rate)	0.30	0.35	0.40	0.45	0.50
R-squared	0.30	0.30	0.30	0.30	0.30
Total sample size	**935**	**801**	**701**	**623**	**561**

$\alpha = 0.05$ (two tailed); $\beta = 0.20$ (power = 80%);

[a] Known as the regression coefficient defined as the predicted change in log(base e) hazards at one unit change in X1 when the other covariates are held constant;

[b] Denotes the proportion of subjects in which the event of interest occurs during the duration of the study (Based on values reported in the across studies in the literature). The modeled event was medication discontinuation over a 12-month follow-up period;

[c] The value achieved when X1 is regressed on the other IVs or covariates in the regression

3.5.4 Logistic regression models

Logistic regression models allow for controlling the effects of confounders and are a common technique used for modelling binary dependent variables.[117] The model is specified as follows:

Figure 3.6: Logistic regression equation

$$\textbf{Log odds [Outcome]} = \beta_0 + \beta_1 X_1 + \beta_n X_n + \varepsilon$$

Where

Outcome is a binary variable indicating type of therapy received.

β_0 = estimate for the intercept (i.e., when all the other variables are controlled for in the model)

$X_1 \ldots X_n$ = Variables to be included in the model (demographic, physician, clinical characteristics, and prior utilization characteristics)

$\beta_1 \ldots \beta_n$ = Corresponding predicted values associated with each variable

Logistic regression analysis overcomes the restrictions posed by linear regression models that use OLS estimation principles. Logistic regression assumptions require that the variables should be nonlinear, independent variables are measured without error, and dependent variables are mutually exclusive and dichotomous in nature. Logistic regression uses a maximum likelihood estimation technique as opposed to the OLS technique used in linear regression models.[117]

Model fit was tested based on the R^2, Chi-square goodness of fit statistics, deviance test, and Hosmer-Lemeshow test. Chi-square tests help to determine if the model is correctly specified. R^2 is a measure of how well the independent variables specified in the model explain the dependent variable.[117] The Hosmer-Lemeshow test is similar to the Chi-square test where the observations are partitioned into deciles based on the predicted probabilities, thus making equal groups of observed and expected frequencies. [117] A statistically significant difference between the observed and the expected frequencies indicates poor model fit.

Sample size estimations for logistic regressions were performed using the G*Power software. A wide range of parameters were tested and the largest sample size was chosen as the required sample size for logistic regression.

Table 3.6 represents the sample sizes for different parameters. Based on the values tested, a total sample size of 4,248 patients (power = 0.80; $\alpha = 0.05$) were required for conducting a logistic regression analysis.

Table 3.6: Sample size estimates for logistic regression analysis

Parameters				
Odds Ratio	1.50	2.00	2.50	3.00
Pr (Y=1|X=1)Ho[a]	0.05	0.05	0.05	0.05
R-squared	0.10	0.10	0.10	0.10
Total sample size	**3,766**	**1,158**	**615**	**405**
Odds Ratio	1.50	2.00	2.50	3.00
Pr (Y=1|X=1)Ho[a]	0.05	0.05	0.05	0.05
R-squared	0.20	0.20	0.20	0.20
Total sample size	**4,237**	**1,303**	**692**	**456**
Odds Ratio	1.50	2.00	2.50	3.00
Pr (Y=1|X=1)Ho[a]	0.05	0.05	0.05	0.05
R-squared	0.30	0.30	0.30	0.30
Total sample size	**4,248**	**1,489**	**791**	**521**

Y = dependent variable; X = independent variables (IV); $\alpha = 0.05$ (two tailed); $\beta = 0.20$ (power = 80%); a binomial distribution was assumed for the IV of interest (X1);

[a] Denotes the probability of an event under H_o

3.5.5 Multinomial logistic regression

Multinomial logistic regressions (MLR) are used to predict likelihood of group membership relative to other groups based on multiple predictor variables.[118] It is an extension of the logistic regression (with dichotomous outcomes) and accommodates two or more categories in the dependent variable. Similar to logistic regression, MLR uses maximum likelihood estimation technique to evaluate the probability of group membership. MLR does not assume normality, linearity, and homoscedasticity of the data. However, similar to regular logistic regression, it does require that the data meets the requirement for independence among dependent variable membership.

The model is specified as follows:

Figure 3.7: Multinomial logistic regression model

$$\textbf{Log odds [Outcome]} = \beta_0 + \beta_1 X_1 + \beta_n X_n + \varepsilon$$

Where

Outcome is an ordinal variable indicating type of therapy received.

β_0 = estimate for the intercept (i.e., when all the other variables are controlled for in the model)

$X_1 \ldots X_n$ = Variables to be included in the model (demographic, clinical, and prior utilization characteristics)

$\beta_1 \ldots \beta_n$ = Corresponding predicted values associated with each variable

Because no procedure for calculating sample sizes needed for multinomial logistic regression was found, the sample size estimates for binomial logistic regression (estimated in

section 3.5.4) were used.[119,118] Therefore, a sample size of 4,248 patients was required for multinomial logistic regression analysis.

3.5.6 Generalized Linear Models (GzLM)

Cost data were analyzed using generalized linear models. GzLM is an extension of the traditional linear model and consists of three components:[120]

First, the linear component defined similar to the traditional linear model:

$$\eta_i = x'_i\beta$$

Where

x_i = column vector of covariates for observation i

β = column vector of unknown coefficients.

Second, a monotonic differentiable link function 'g' which describes how the expected value of a response 'y_i' is related to the linear predictor:

$$g(\mu_i) = x'_i\beta$$

Where

$\mu_i = E(y_i)$ and

Third, the response variables y1; y2; . . . are independent, each having a probability distribution from an exponential family:

$$Var\,(y_i) = \sigma_i^2 = \emptyset V(\mu_i)$$

Where

$\emptyset$ = constant known as the dispersion parameter

***V* = function of the mean response**

The exponential family of probability distributions includes the normal (Gaussian), the binomial, the Poisson, the gamma, and the inverse Gaussian distributions.

A Modified Park test was conducted to identify the distribution. A Vuong test was conducted to identify select the best model to model the healthcare utilization outcomes.[121] The Vuong test measure uses the Kullback-Leibler information criterion to measure the closeness of the estimated model to the true model. Since we speculated that the source of zeros in the healthcare utilization could be a chance occurrence, ZIP and Poisson regression models were compared to identify the best fit model.

Sample size estimation for the Poisson regression models used to model healthcare utilization was conducted using G*Power software. A range of baselines rates (5 to 20%) were tested to estimate the final sample size. The sample size required to detect at least 10% difference in healthcare utilization is listed in **Table 3.7**. Based on the values tested, a total sample size of 1,056 patients (power = 0.80; α = 0.05,) was required for conducting a Poisson regression analysis.

Table 3.7: Sample size estimates for Poisson regression analysis

Parameters			
Base rate	0.05	0.1	0.2
R-squared	0.1	0.1	0.1
Total sample size	**821**	**411**	**206**
Base rate	0.05	0.1	0.2
R-squared	0.2	0.2	0.2
Total sample size	**924**	**462**	**231**
Base rate	0.05	0.1	0.2
R-squared	0.3	0.3	0.3
Total sample size	**1,056**	**528**	**264**

A Modified Park test was conducted to identify the distribution and select the appropriate functional form and link function for cost outcomes as well.[122] Cost data were adjusted to 2013 dollars using the medical CPI index for 2013 (published by the Bureau of Labor Statistics.)

Sample sizes for the GzLM were estimated using the linear regression test in the G*power software. Estimates were calculated using the fixed effects linear multiple regression model with R^2 deviation from zero. Based on the number of predictor variables (n = 11), with a power = 0.80, and α = 0.05, a sample size of 850 patients were required to test objective 5.

3.6 Sensitivity analyses

School-aged children may be given drug holidays to evaluate the therapeutic need and side-effect profile of ADHD medications. Previous research has shown that ADHD medications were associated with side-effects in school-aged children including stunted growth, reduced appetite, and difficulty falling asleep. These side-effects may be more pronounced in preschoolers than in school-aged children thus warranting a break in therapy to evaluate the therapeutic and side-effect profiles of ADHD medications. Moreover, parents may choose to avoid medications during holidays and weekends due to apprehension related to medication therapy management in preschoolers. To circumvent issues related to drug holidays, we conducted sensitivity analyses of medication persistence with 60- and 90-day allowable gap periods.

CHAPTER 4: RESULTS

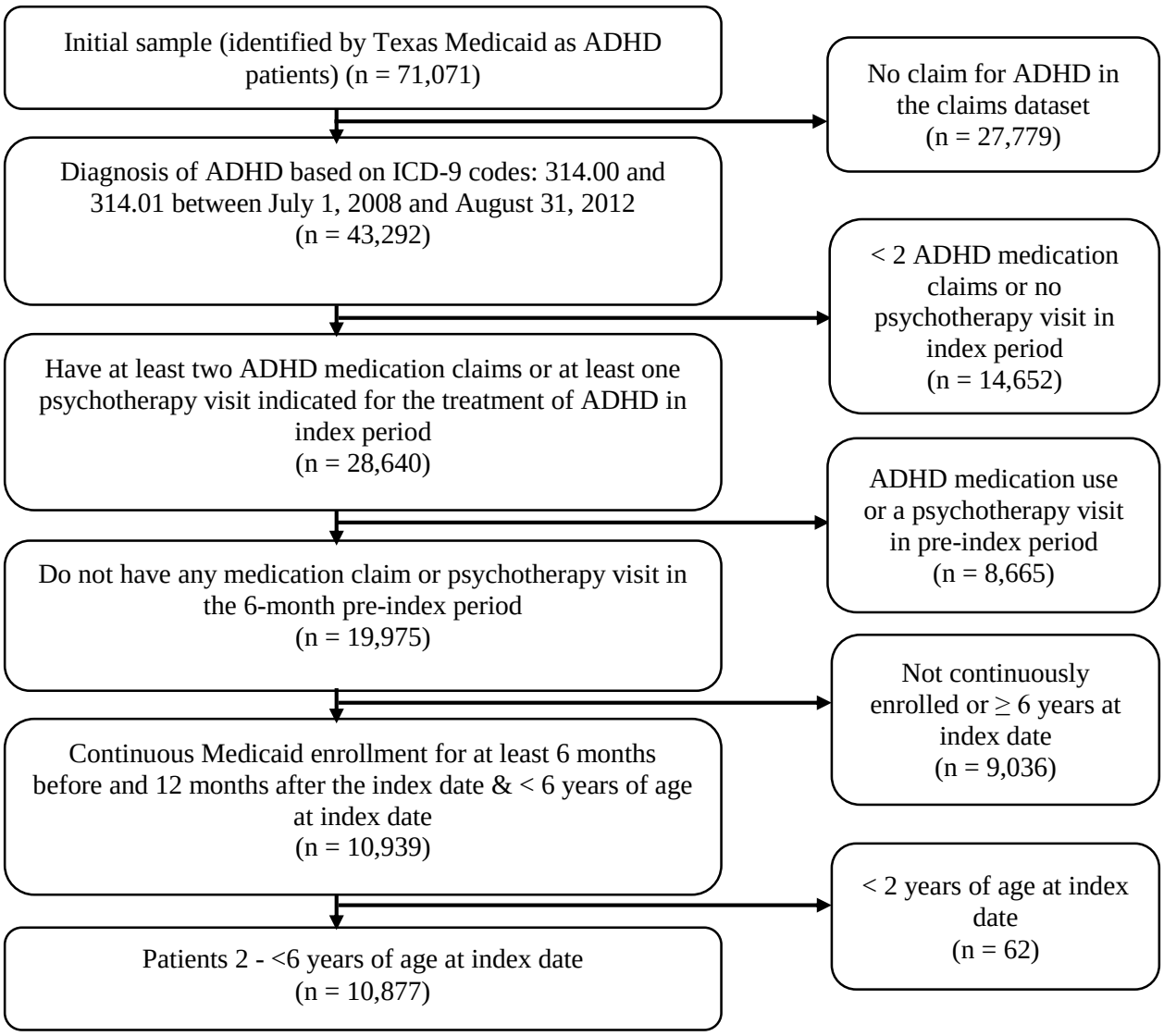
Chapter overview

This chapter presents the study results describing the incidence, prevalence, treatment patterns, healthcare utilization, and costs in preschoolers with ADHD. Baseline demographic, clinical, and prior utilization characteristics are discussed for the "overall cohort" and the "treatment pattern cohort." The results are discussed in the order stated in the methods section. Within each section, the hypotheses and associated statistical analyses are presented.

4.1 Sample selection

There were 7.2 million pediatric beneficiaries enrolled in Texas Medicaid across the six study years, 2008-2013. Overall, 71,071 patients with a diagnosis of ADHD between 2008 and 2013 were eligible to be included in the study. After applying the inclusion and exclusion criteria, a total sample of 10,877 preschoolers between 2 and 6 years of age were identified. Objectives 2, 3a-c, 4 and 5 were analyzed using the "overall cohort." **Figure 4.1** shows the study selection flowchart for the overall cohort. A subsample of this population, the "treatment pattern cohort" (n = 8,833), was selected to address the treatment pattern objective 3d (i.e., adherence, persistence, augmentation, and switching).

Figure 4.1: Study selection flowchart – Overall cohort



4.2 Descriptive statistics

The following paragraph provides a detailed description of the baseline characteristics in the "overall cohort" (n = 10,877) and the "treatment pattern cohort" (n = 8,833). The results for comparison of patient demographic, clinical, and prior utilization characteristics are also presented.

4.2.1 Patient demographic, clinical, and prior utilization characteristics – overall cohort

Demographic, clinical, and prior utilization characteristics of 10,877 preschoolers diagnosed with ADHD who were enrolled in Texas Medicaid are presented in **Table 4.1**. Overall, the mean age of preschoolers at diagnosis was 4.7(± 0.9) years. A higher proportion of patients were males (72.9%), Hispanics (51.1%), residing in urban areas (68.2%), without other mental health diagnosis (69.0%), without pre-index psychotropic medication use (95.2%), on long-acting medications (80.0%), and taking stimulants (89.0%). The patients in the overall group had 3.3 (± 4.4) pre-index non-psychiatric visits on average (±SD). The average (±SD) number of pre-index psychiatric visits in the overall cohort was 1.4 (± 6.7). The average (±SD) total pre-index cost in the overall cohort was $2,372.16 (± 4,999.66). The physician specialty variable was not included in the analysis due to questions regarding the validity of the data.

4.2.2 Patient demographic, clinical, and prior utilization characteristics – treatment pattern cohort

Demographic, clinical, and prior utilization characteristics of 8,833 preschoolers diagnosed with ADHD who were enrolled in Texas Medicaid and in the treatment pattern cohort are also presented in **Table 4.1**. Similar to the overall cohort, a higher proportion of patients

were males (72.9%), Hispanics (50.4%), residing in urban areas (68.3%), without other mental health diagnosis (64.8%), without pre-index psychotropic medication use (88.1%), taking long-acting medications (68.6%), and taking stimulants (89.8%). The patients in the treatment cohort had 4.6 (± 5.3) pre-index non-psychiatric visits on average (± SD). The average (± SD) number of psychiatric visits in the treatment pattern cohort was 1.8 (± 7.6). The average (± SD) total pre-index cost in the treatment cohort was $2,525.42 (± 4,131.37).

Table 4.1: Descriptive. Patient demographic, clinical, and prior utilization characteristics for the overall cohort and treatment pattern cohort

Characteristics	Overall cohort[a] (n = 10,877)		Treatment pattern cohort[b] (n = 8,833)	
Age (Mean +/- SD)	4.7	0.9	4.7	0.9
Gender				
Female	2,944	27.1%	2,393	27.1%
Male	7,933	72.9%	6,440	72.9%
Race/Ethnicity				
White	2,584	23.8%	2,088	23.6%
African American	1,657	15.2%	1,374	15.5%
Hispanic	5,556	51.1%	4,447	50.4%
Other/unknown	1,080	9.9%	924	10.5%
Urban/rural status				
Urban	7,419	68.2%	6,035	68.3%
Rural	3,458	31.8%	2,798	31.7%
Pre-index psychotropic medications				
Yes	526	4.8%	1,049	11.9%
No	10,351	95.2%	7,784	88.1%
Other mental health diagnosis				
Yes	3,370	31.0%	3,108	35.2%
No	7,507	69.0%	5,725	64.8%
Long-acting medications[c]				
Yes	8,698	80.0%	6,059	68.6%
No	2,179	20.0%	-	-
Short-acting medications[d]				
Yes	4,391	40.4%	2,774	31.4%
No	6,486	59.6%	-	-
Stimulants				
Yes	9,681	89.0%	7,931	89.8%
No	1,196	11.0%	902	10.2%

Table 4.1: Descriptive. Patient demographic, clinical, and prior utilization characteristics for the overall cohort and treatment pattern cohort (continued)

Characteristics	Overall cohort[a] (n = 10,877)		Treatment pattern cohort[b] (n = 8,833)	
Pre-index psychiatric visits (Mean ± SD)	1.4	6.7	1.8	7.6
Pre-index non-psychiatric visits (Mean +/- SD)	3.3	4.4	4.6	5.3
Total pre-index costs (Mean +/- SD)	$2,372.16	$4,999.66	$2,525.42	$4,131.37

[a] Overall cohort includes patients with a diagnosis of ADHD identified between July 01, 2008 and August 01, 2012 and followed for a 12-month period after the first ADHD diagnosis;
[b] Treatment pattern cohort includes a subset of the overall cohort patients followed for a 12-month period after the first ADHD-related prescription;
[c,d] Long-acting medication non-users in the treatment pattern cohort by default use short-acting medications, which differs from the definition used in the overall cohort;
Cost adjusted to 2013 dollars

4.3 Objective 1: Prevalence and incidence of ADHD in preschoolers

This part of the results provides insight into the epidemiology (i.e., prevalence and incidence) of ADHD in the Texas Medicaid preschool population between the years 2008 and 2012.

4.3.1 Prevalence

Objective 1a: *To determine the prevalence of ADHD in preschoolers <6 years of age enrolled in Texas Medicaid*

Table 4.2 presents the prevalence estimates of ADHD in preschoolers stratified by each year. The numbers of ADHD patients as defined for the prevalence estimates were 2,511 (2008), 4,717 (2009), 7,049 (2010), 9,168 (2011), and 10,238 (2012). Prevalence rates for ADHD were estimated at 2.1, 3.9, 5.9, 7.6, and 8.5 per 1,000 enrollees for the years 2008, 2009, 2010, 2011, and 2012, respectively.

Table 4.2: Descriptive. Estimated prevalence rates of ADHD in preschoolers enrolled in Texas Medicaid – stratified by year

Year	Number of ADHD patients	Prevalence/1,000[a,b]
2008	2,511	2.1
2009	4,717	3.9
2010	7,049	5.9
2011	9,168	7.6
2012	10,238	8.5

ADHD = Attention deficit hyperactivity disorder;
[a] Numerator for the prevalence calculation included all the patients < 6 years of age diagnosed with ADHD with 12 months of continuous enrollment in Texas Medicaid and taking at least 2 ADHD medications in the same year;
[b] Denominator for the prevalence calculation was assumed to be 1.2 million enrollees each year based on a 2-year (2012-2013) average enrollment rate provided by Texas Medicaid (actual numbers from Texas Medicaid were not available)

4.3.2 Incidence

***Objective 1b**: To determine the incidence of ADHD in preschoolers <6 years of age enrolled in Texas Medicaid*

Table 4.3 presents the incidence estimates of newly diagnosed ADHD (as defined for the incidence estimates) in preschoolers stratified by year. The numbers of incident ADHD patients were 2,814 (2009), 3,154 (2010), 3,216 (2011), and 2,562 (2012). Incidence rates for ADHD were estimated at 2.4, 2.6, 2.7, and 2.1 per 1,000 enrollees for the years 2009, 2010, 2011, and 2012, respectively.

Table 4.3: Descriptive. Estimated incidence rates of ADHD in preschoolers enrolled in Texas Medicaid – stratified by year

Year	Number of newly diagnosed patients with ADHD	Incidence/1,000[a,b]
2009	2,814	2.4
2010	3,154	2.6
2011	3,216	2.7
2012	2,562	2.1

ADHD = Attention deficit hyperactivity disorder;
[a] Numerator for incidence calculation included all the newly diagnosed ADHD patients < 6 years of age with 24 months of continuous enrollment in Texas Medicaid and taking at least 2 medications in the same year (i.e., year of diagnosis);
[b] Denominator for incidence calculation was assumed to be 1.2 million enrollees each year based on a 2-year (2012-2013) average enrollment rate provided by Texas Medicaid (actual numbers from Texas Medicaid were not available)

4.4 Objective 2: Comparison of treatment groups with respect to patient demographics, clinical, and prior utilization characteristics

Objective 2a: *To determine and compare the patient demographic, clinical, and prior utilization characteristics between the pharmacotherapy only (RX), psychotherapy only (PSY), and pharmacotherapy + psychotherapy combined (RX+PSY) groups*

4.4.1 Overall cohort

Table 4.4 provides a detailed description and comparison of patient demographic, clinical, and prior utilization characteristics between the pharmacotherapy, psychotherapy and combination therapy groups. Comparison of the pharmacotherapy, psychotherapy, and combination therapy groups revealed a similar trend in all the covariate categories. In all groups, a higher proportion of patients were male (72.9% vs. 74.1% vs. 72.9%; $p = 0.79$), Hispanic (50.8% vs. 60.6% vs 50.0%; $p < 0.0001$), residing in urban areas (68.3% vs. 73.1% vs. 67.3%; $p = 0.01$), did not have other mental health diagnosis (69.8% vs. 62.2% vs. 68.9%; $p < 0.01$), and were without pre-index psychotropic medication use (95.4% vs. 96.1% vs. 94.8%; $p = 0.19$). Chi-square tests revealed that the differences in proportions of race/ethnicity, urban/rural status, and other mental health diagnosis were statistically significant. Within race/ethnicity, a chi-square test revealed that the proportion of Hispanics was relatively higher in the psychotherapy group as compared to the pharmacotherapy and combination therapy groups. The same relationship was seen for urban/rural status. Conversely, proportion of patients with other mental health diagnosis was lower in the psychotherapy group than the pharmacotherapy and combination therapy groups. By definition, patients in the psychotherapy only group did not have any medication use; however, the proportion of long-acting medication users was relatively high in the pharmacotherapy (83.9%) and combination therapy (86.0%) groups. Similarly, the

proportion of patients receiving stimulants was also relatively high in the pharmacotherapy (94.4%) and combination therapy (94.4%) groups. Analysis of age based on ANOVA revealed that the age at index was significantly different between the treatment groups. Age at index was lowest in the psychotherapy group (4.7 vs. 4.2 vs. 4.7; $p < 0.0001$) as compared to the pharmacotherapy and combination therapy groups. Kruskal-Wallis tests for continuous variables that did not satisfy the normality assumption revealed that pre-index office-based psychiatric, non-psychiatric visits, and total pre-index costs were significantly different between the three treatment groups. Pre-index psychiatric visits were slightly higher in the pharmacotherapy group as compared to the other groups (means = 1.5 visits vs. 1.4 visits vs. 1.3 visits; $p < 0.01$). Conversely, pre-index non-psychiatric visits were slightly higher in the in the psychotherapy group as compared to other groups (means = 3.2 visits vs. 4.5 visits vs. 3.2 visits; $p < 0.0001$). Average ($\pm$SD) total pre-index costs were higher in the psychotherapy group as compared to the other groups [\$2,452.49 ($\pm$ 5,186.51) vs. \$2,632.26 ($\pm$ \$4,829.05) vs. \$2,225.97 ($\pm$ \$4,756.58); $p < 0.0001$].

Table 4.4: Descriptive. Comparison of patient demographics, clinical, and prior utilization characteristics – stratified by treatment groups

Characteristics	RX (n = 5,904)		PSY (n = 622)		RX+PSY (n = 4,351)		Value	p-value*
Age[a] (Mean +/- SD)	4.7	0.9	4.2	0.9	4.7	0.9	**185.1**	**<.0001**
Gender[b]							0.5	0.79
Female	1,603	27.1%	161	25.9%	1,180	27.1%		
Male	4,301	72.9%	461	74.1%	3,171	72.9%		
Race/Ethnicity[b]							**71.0**	**<.0001**
White	1,517	25.7%	119	19.1%	948	21.8%		
African American	813	13.8%	73	11.7%	771	17.7%		
Hispanic	3,002	50.8%	377	60.6%	2,177	50.0%		
Other/unknown	572	9.7%	53	8.6%	455	10.4%		
Urban/rural status[b]							**8.6**	**0.01**
Urban	4,034	68.3%	455	73.1%	2,930	67.3%		
Rural	1,870	31.7%	167	26.9%	1,421	32.7%		
Pre-index psychotropic medications[b]							3.3	0.19
Yes	274	4.6%	24	3.9%	228	5.2%		
No	5,630	95.4%	598	96.1%	4,123	94.8%		
Other mental health diagnosis[b]							**15.2**	**<.01**
Yes	1,783	30.2%	235	37.8%	1,352	31.1%		
No	4,121	69.8%	387	62.2%	2,999	68.9%		
Long-acting medications[b]							**2640.4**	**<.0001**
Yes	4,955	83.9%	-	0.0%	3,743	86.0%		
No	949	16.1%	622	100.0%	608	14.0%		
Short-acting medications[b]							**449.3**	**<.0001**
Yes	2,488	42.1%	-	0.0%	1,903	43.7%		
No	3,416	57.9%	622	100.0%	2,448	56.3%		
Stimulants[b]							**5340.1**	**<.0001**
Yes	5,574	94.4%	-	0.0%	4,107	94.4%		
No	330	5.6%	622	100.0%	244	5.6%		
Pre-index psychiatric visits[c] (Mean +/- SD)	1.5	7.3	1.4	5.6	1.3	6.1	**10.8**	**<.01**
Pre-index non-psychiatric visits[c] (Mean +/- SD)	3.2	4.3	4.5	5.2	3.2	4.3	**79.6**	**<.0001**

Table 4.4: Descriptive. Comparison of patient demographics, clinical, and prior utilization characteristics – stratified by treatment groups (continued)

Characteristics	**RX (n = 5,904)**		**PSY (n = 622)**		**RX+PSY (n = 4,351)**		**Value**	**p-value***
Total pre-index costs[c] (Mean +/- SD)	$2,452.49	$5,186.51	$2,632.26	$4,829.05	$2,225.97	$4,756.58	**24.4**	**<.0001**

*p < 0.05 (in bold); SD = Standard Deviation; RX = Pharmacotherapy only, PSY = Psychotherapy only; RX+PSY = Combination therapy;
[a] Age was tested using ANOVA;
[b] Chi-square tests were used for categorical variables;
[c] Kruskal-Wallis tests were used for continuous variables;
Cost adjusted to 2013 dollars

4.4.2 Treatment pattern cohort

Table 4.5 provides a detailed description and comparison of patient demographic, clinical, and prior utilization characteristics between the pharmacotherapy and combination therapy groups. Comparison of the pharmacotherapy and combination therapy groups revealed similar trends across all categories. Chi-square tests revealed statistically significant differences in race/ethnicity, pre-index psychotropic medication use, and other mental health diagnosis between the pharmacotherapy and combination therapy groups. In both treatment groups, the proportion of patients were relatively high and similar for male gender (72.8% vs. 73.1%; $p = 0.77$), Hispanic ethnicity (50.2% vs. 50.5%; $p < 0.0001$), urban residents (67.7% vs. 69.3%; $p = 0.11$), without pre-index psychotropic medication use (89.0% vs. 86.8%; $p < 0.01$), and without other mental health diagnosis (66.3% vs. 62.5%; $p < 0.01$). Within race/ethnicity, although Hispanics formed the largest group, the proportion of African Americans (13.9% vs. 18.2%; $p < 0.0001$) was higher in the combination therapy group as compared to the pharmacotherapy group. The proportion of long-acting medication initiators was relatively high in the pharmacotherapy (69.0%) and combination therapy (68.0%) groups. Short-acting medications were not included as a separate category in the treatment pattern cohort since by default, patients not receiving long-acting medications were taking short-acting medications. The proportion of patients receiving stimulants was also relatively high in the pharmacotherapy (90.0%) and the combination therapy (89.5%) groups. Age was tested using ANOVA and other continuous variables were tested using Kruskal-Wallis tests due to violation of the normality assumption. The mean age did not differ significantly between the pharmacotherapy and combination therapy groups. However, the average (±SD) pre-index psychiatric visits was higher in the pharmacotherapy group as compared to the combination therapy group (2.0 visits vs. 1.6 visits; p

< 0.01). Conversely, the average (±SD) pre-index non-psychiatric visits was higher in the combination therapy group as compared to the pharmacotherapy group (5.3 visits vs. 4.1 visits; p< 0.0001). Average (±SD) total pre-index costs was higher in the pharmacotherapy group as compared to the combination therapy group ($2,577.52 [±$4,532.10] vs. $2,444.17 [±$3,412.86]; p < 0.0001).

Table 4.5: Descriptive. Comparison of patient demographics, clinical, and prior utilization characteristics – stratified by treatment groups (treatment pattern cohort)

Characteristics	RX (n = 5,382)		RX+PSY (n = 3,451)		Value	p-value*
Age[a] (Mean +/- SD)	4.7	0.9	4.7	0.9	0.0	0.83
Gender[b]					0.1	0.77
Female	1,464	27.2%	929	26.9%		
Male	3,918	72.8%	2,522	73.1%		
Race/Ethnicity[b]					**50.9**	**<.0001**
White	1,383	25.7%	705	20.4%		
African American	746	13.9%	628	18.2%		
Hispanic	2,703	50.2%	1,744	50.5%		
Unknown/Other	550	10.2%	374	10.8%		
Urban/rural status[b]					2.6	0.11
Urban	3,643	67.7%	2,392	69.3%		
Rural	1,739	32.3%	1,059	30.7%		
Pre-index psychotropic medications[b]					**9.7**	**<.01**
Yes	593	11.0%	456	13.2%		
No	4,789	89.0%	2,995	86.8%		
Other mental health diagnosis[b]					**13.6**	**<.01**
Yes	1,813	33.7%	1,295	37.5%		
No	3,569	66.3%	2,156	62.5%		
Long-acting medications[b]					0.8	0.37
Yes	3,711	69.0%	2,348	68.0%		
No	1,671	31.0%	1,103	32.0%		
Stimulants[b]					1.0	0.31
Yes	4,844	90.0%	3,087	89.5%		
No	538	10.0%	364	10.5%		
Pre-index psychiatric visits[c] (Mean +/- SD)	2.0	8.2	1.6	6.5	**13.6**	**<.01**
Pre-index non-psychiatric visits[c] (Mean +/- SD)	4.1	5.0	5.3	5.6	**170.8**	**<.0001**
Total pre-index costs[c] (Mean +/- SD)	$2,577.52	$4,532.10	$2,444.17	$3,412.86	**32.2**	**<.0001**

*p < 0.05 (in bold); SD = Standard Deviation; RX = Pharmacotherapy only, PSY = Psychotherapy only; RX+PSY = Combination therapy;
[a] Age was tested using ANOVA;
[b] Chi-square tests were used for categorical variables;
[c] Wilcoxon-Mann-Whitney tests were used for continuous variables;
Cost adjusted to 2013 dollars

4.5 Objective 3: Treatment patterns in preschoolers with ADHD

Objective 3 was to assess the treatment patterns including time-to-initiation, medication adherence, persistence, augmentation, and switching.

4.5.1 Time-to-initiation of first pharmacotherapy, psychotherapy, and combination therapy

Objective 3a: *To determine the time to "first pharmacotherapy," "first psychotherapy," or "first combination therapy"*

Time-to-initiation of RX, PSY, or RX+PSY was measured as the number of days between the first ADHD diagnosis and the date of receiving the first ADHD-related treatment (i.e., "first RX," "first PSY," or "first RX+PSY"). The definitions used for first RX (pharmacotherapy initiators), first PSY (psychotherapy initiators), and first RX+PSY (combination therapy initiators) for this analysis vary from the definitions used for RX, PSY, and RX+PSY in the rest of the study. For this objective, patients were categorized into one of the three groups based on the initial therapy received. Patients initiating both psychotherapy and pharmacotherapy on the same day were categorized in the combination therapy group.

Table 4.6 shows the descriptive statistics for time-to-initiation of first therapy (i.e., pharmacotherapy initiators, psychotherapy initiators, or combination therapy initiators). Of the patients diagnosed with ADHD, a higher proportion of patients initiated pharmacotherapy (n = 7,184; 66.0%), followed by psychotherapy (n = 3,513; 32.3%), and combination therapy (n = 180; 1.7%). The mean time-to-therapy was smallest for the psychotherapy initiators (43.0 $\pm$ 89.7 days) followed by combination therapy initiators (68.9 $\pm$ 92.7 days), and pharmacotherapy initiators (107.4 $\pm$ 112.1 days).

Table 4.6: Descriptive. Time-to-initiation of pharmacotherapy, psychotherapy, or combination therapy after ADHD diagnosis

Treatment initiators (N = 10,877)	N	%	Mean (days)	SD	Median (days)
Pharmacotherapy initiators[a]	7,184	66.0%	107.4	112.1	67.0
Psychotherapy initiators[b]	3,513	32.3%	43.0	89.7	15.0
Combination therapy initiators[c]	180	1.7%	68.9	92.7	28.0

SD = Standard deviation;

[a] Pharmacotherapy initiators include patients who were started on pharmacotherapy irrespective of the type of therapy they received later;

[b] Psychotherapy initiators include patients who were started on psychotherapy irrespective of the type of therapy they received later;

[c] Combination therapy initiators include patients who were started on pharmacotherapy and psychotherapy on the same day irrespective of the type of therapy they received later

Objective 3b: *To compare the time to first pharmacotherapy, time to first psychotherapy, and time to first combination therapy in preschoolers with ADHD and to compare time-to-pharmacotherapy with respect to gender, race, and medication duration of action*

$H_0 3b_1$: *There is no difference in time-to-initiation of first pharmacotherapy ("first RX"), first psychotherapy ("first PSY"), and "first combination therapy"* **- Rejected**

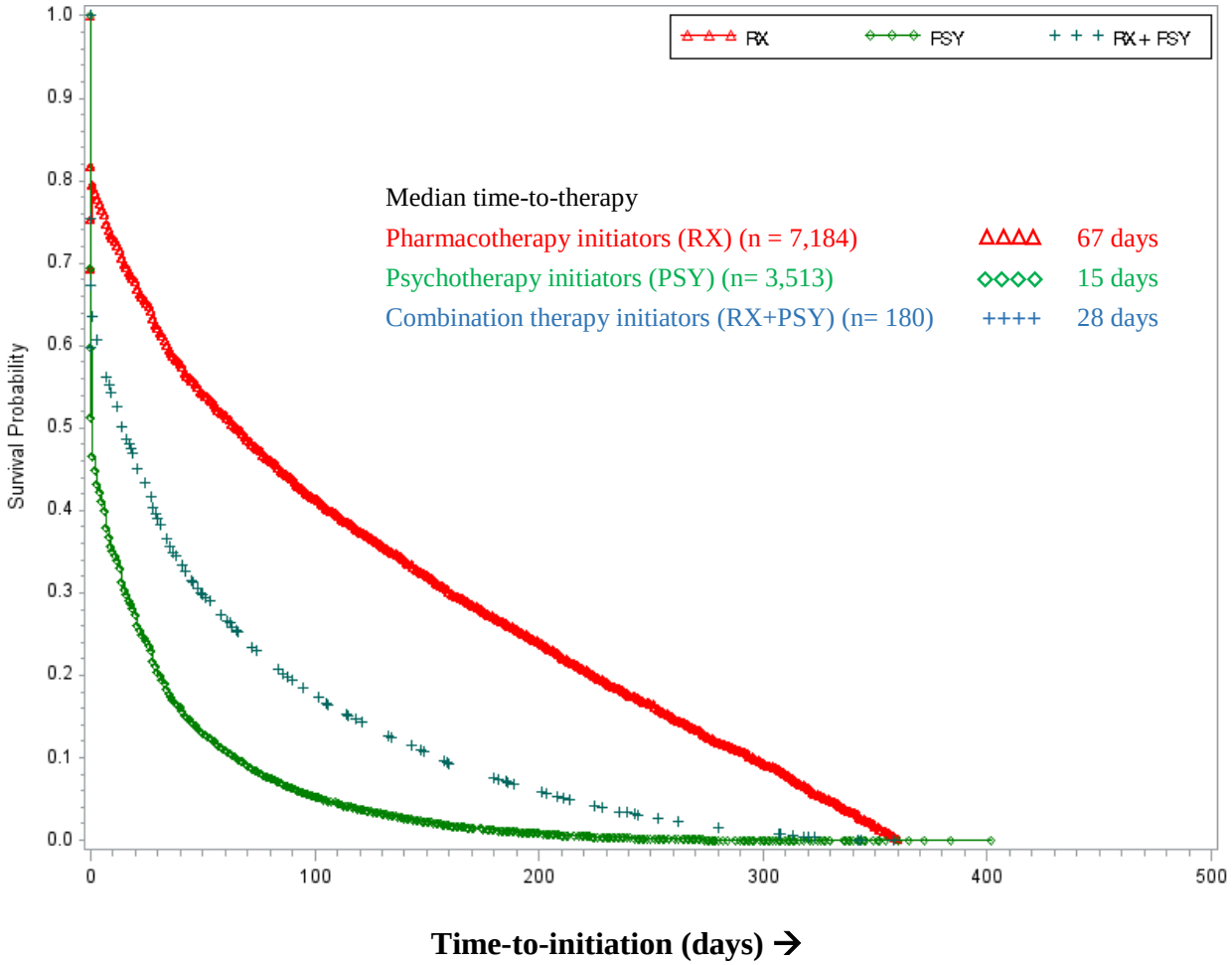
Table 4.7 presents the unadjusted Cox proportional hazards regression estimates for comparison of time-to-initiation of first pharmacotherapy, first psychotherapy, and first combination therapy in preschoolers with ADHD. Time-to-initiation was significantly different between the pharmacotherapy initiators, psychotherapy initiators, and combination therapy initiators. The hazard rate of psychotherapy initiators was 82.7% higher as compared to pharmacotherapy initiators (β = 0.602; HR = 1.827; x^2= 800.7; p = <0.0001). Similarly, the hazard rate of combination therapy initiators was 40.8% higher as compared to pharmacotherapy initiators (β = 0.342; HR = 1.408; x^2= 20.5; p = <0.0001). **Figure 4.2** represents the time-to-initiation curves for pharmacotherapy initiators, psychotherapy initiators, and combination therapy initiators. The median time-to-initiation for psychotherapy was 15 days, followed by combination therapy (28 days) and psychotherapy initiators (67 days).

Table 4.7: Cox proportional hazards regression. Comparison of time-to-initiation of pharmacotherapy initiators, psychotherapy initiators, and combination therapy initiators

Treatment initiators (N = 10,877)	β	HR	x^2	p-value
Pharmacotherapy initiators[a]	**Reference**			
Psychotherapy initiators[b]	0.602	1.827	**800.7**	**<.0001**
Combination therapy initiators[c]	0.342	1.408	**20.5**	**<.0001**

*p < 0.05 (in bold); β= Log Hazard Rate (parameter estimate); HR = Hazard Ratio; x^2 = Chi-square;
[a] Pharmacotherapy initiators include patients who were started on pharmacotherapy irrespective of the type of therapy they received later;
[b] Psychotherapy initiators include patients who were started on psychotherapy irrespective of the type of therapy they received later;
[a] Combination therapy initiators include patients who were started on pharmacotherapy and psychotherapy on the same day irrespective of the type of therapy they received later

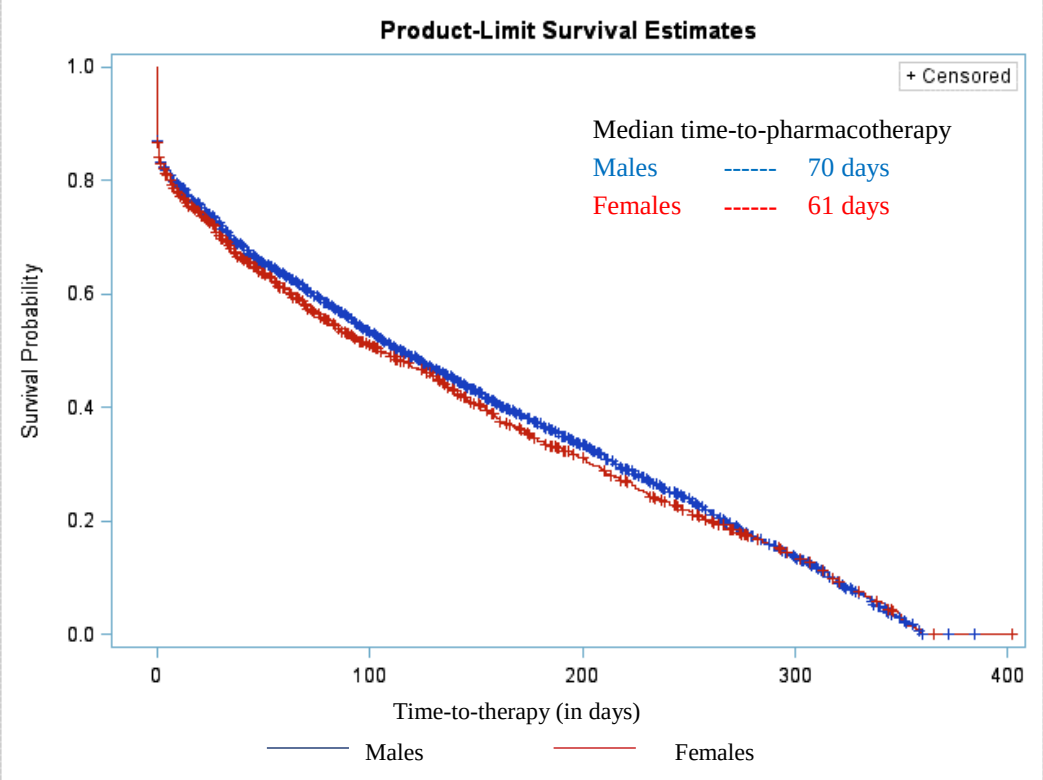
Figure 4.2: Kaplan-Meier estimate of time-to-therapy for pharmacotherapy, psychotherapy, and combination therapy initiators (N = 10,877)



4.5.2 Time-to-pharmacotherapy with respect to gender, race/ethnicity, and medication duration of action

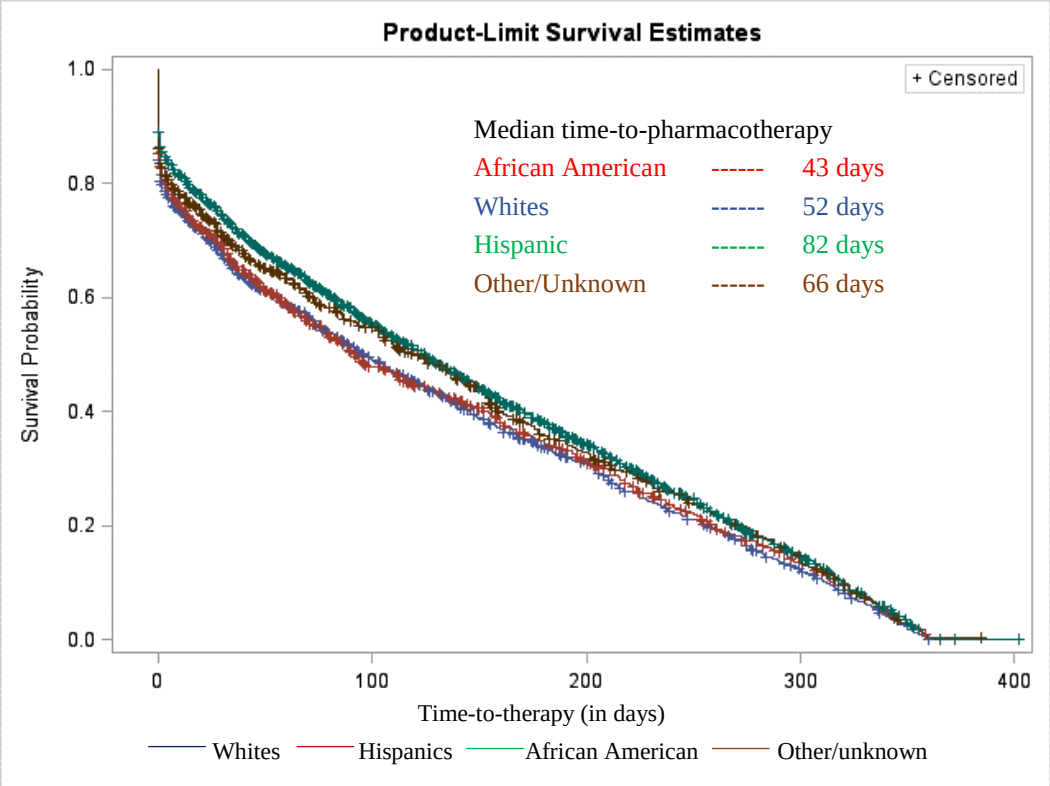
Figures 4.3, 4.4, and 4.5 show time-to-pharmacotherapy according to gender, race/ethnicity, and medication duration of action. As shown in Table 4.8, time-to-pharmacotherapy did not differ significantly with respect to gender. Time-to-pharmacotherapy was significantly different among certain race/ethnicity groups, and medication duration of action.

Figure 4.3: Time-to-pharmacotherapy stratified by gender (N = 7,184)



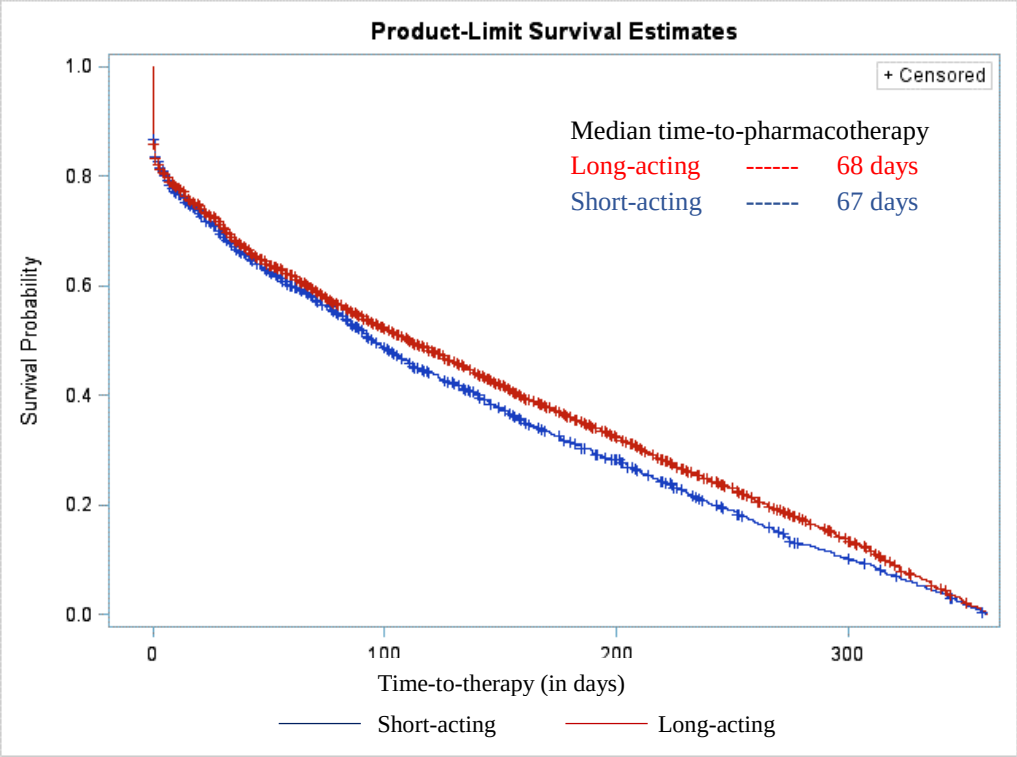
Y = Survival probability (proportion of patients); X = Time-to-therapy (in days);
Estimated using Log-Rank test; + censored observations include patients receiving psychotherapy or combination therapy;

Figure 4.4: Time-to-pharmacotherapy stratified by race/ethnicity (N = 7,184)



Y = Survival probability (proportion of patients); X = Time-to-therapy (in days);
Estimated using Cox proportional hazard regression; + censored observations include patients receiving psychotherapy or combination therapy;

Figure 4.5: Time-to-pharmacotherapy stratified by medication duration of action (N = 7,184)



Y = Survival probability (proportion of patients); X = Time-to-therapy (in days);
Estimated using Log-Rank test; + censored observations include patients receiving psychotherapy or combination therapy;

$H_0 3b_2$: *There is no significant difference in the time-to-initiation of RX in male vs. female ADHD patients* – **Failed to reject**

$H_0 3b_3$: *There is no significant difference in the time-to-initiation of RX in different race/ethnicity groups diagnosed with ADHD* – **Rejected for Hispanic vs. White and for Others/unknown vs. White**

$H_0 3b_4$: *There is no significant difference in the time-to-initiation of RX with respect to long-acting (LA) vs. short-acting (SA) medications in ADHD patients* – **Rejected**

$H_0 3b_5$: *There is no significant difference in the time-to-initiation of RX by physician specialty* – **Could not test**

Table 4.8 represents results for time-to-pharmacotherapy according to gender, race/ethnicity, and medication duration of action. Compared to Whites (100.0 ± 111.6 days), the mean time-to-pharmacotherapy was significantly higher in Hispanics (115.1 ± 112.6 days; $p < 0.0001$) and other/unknown races (106.2 ± 112.1 days; $p = 0.03$). Similarly, compared to short-acting medication users (103.0 ± 108.0 days), the mean time-to-pharmacotherapy was significantly higher in the long-acting (109.3 ± 113.8 days; $p<0.01$) medication users. We could not test time-to-initiation of RX with respect to physician specialty due to issues surrounding the validity of physician specialty information.

Table 4.8: Cox proportional hazards regression/Log-rank test. Time-to-pharmacotherapy stratified according to gender, race/ethnicity, and medication duration of action (N = 7,184)

Characteristics	N	%	Mean (days)	SD	Median (days)	x^2	p-value*
Gender[a]							
Male	5,233	72.8%	108.6	107.6	70.0	1.8	0.17
Female	1,951	27.2%	104.1	107.1	61.0		
Race/Ethnicity[b]							
White	1,765	24.6%	100.0	111.6	52.0		
African American	1,028	14.3%	93.4	109.2	43.0	0.8	0.37
Hispanic	3,680	51.2%	115.1	112.6	82.0	**25.3**	**<.0001**
Others/unknown	711	9.9%	106.2	112.1	66.0	**4.9**	**0.03**
Medication duration of action[a,c]							
Long-acting medication	5,041	70.2%	109.3	113.8	68.0	**7.9**	**<.01**
Short-acting medication	2,143	29.8%	103.0	108.0	67.0		

*$p < 0.05$ (in bold); SD = Standard deviation; x^2 = Chi Square;

[a] Log-rank test was used to test gender and medication duration of action;

[b] Cox proportional hazards regression (unadjusted) was used to test race/ethnicity;

[c] Long-acting medications and short-acting medications are defined based on the type of medications the patients were initiated on and differs from the definition used in the rest of the study

4.5.3 Multinomial logistic regression – predictors of treatment group membership

Objective 3c: *To assess the factors associated with receiving RX, PSY, or RX+PSY treatments*

Table 4.9 presents the results for multinomial logistic regression comparing the factors associated with receiving pharmacotherapy, psychotherapy, or combination therapy treatments, after controlling for covariates. The results for the multinomial logistic regression reveal that a one-year increase in age was significantly associated with 44.0% lower odds of receiving psychotherapy as compared to pharmacotherapy (Odds ratio [OR] = 0.560; Confidence Interval [CI] = 0.510 – 0.615; p <0.0001) while controlling for covariates. Patients with one additional pre-index non-psychiatric visit (OR= 1.050; CI = 1.033 – 1.068; p < 0.0001) had a 5% higher odds of receiving psychotherapy as compared to pharmacotherapy, while controlling for covariates. Compared to Whites, Hispanic patients had a 30.5% higher odds of receiving psychotherapy (OR= 1.305; CI = 1.022 – 1.666; p = 0.03) as compared to pharmacotherapy, while controlling for covariates. Similarly, compared to patients with no other psychotropic use, patients receiving other psychotropics (OR= 1.687; CI = 1.082 – 2.628; p = 0.02) had a 68.7% higher odds of receiving psychotherapy as compared to pharmacotherapy, while controlling for covariates. Compared to patients with no other mental disorders, the patients diagnosed with other mental disorders (OR= 1.294; CI = 1.073 – 1.560; p = 0.01) had a 29.4% higher odds of receiving psychotherapy as compared to pharmacotherapy, while controlling for covariates.

Comparison of combination therapy group with pharmacotherapy revealed that compared to Whites, African Americans (OR= 1.554; CI = 1.366 – 1.768; p < 0.0001), Hispanics (OR = 1.181; CI = 1.059 – 1.317; p < 0.01), other/unknown race/ethnicity (OR= 1.291; CI = 1.111 – 1.500; p <0.01), had a 55.4%, 18.1%, 29.1% higher odds, respectively, of receiving combination therapy as compared to pharmacotherapy, while controlling for covariates.

Compared to patients with no other mental disorders, the patients diagnosed with other mental diagnosis (OR= 1.201; CI = 1.101 – 1.311; $p < 0.0001$) were associated with a 20.1% higher odds, of receiving combination therapy as compared to pharmacotherapy, while controlling for covariates. Although, total pre-index costs were significant according to the p-value, the confidence interval crosses 1 and was considered non-significant for the psychotherapy and combination therapy groups.

Table 4.9: Multinomial logistic regression. Factors associated with receiving pharmacotherapy (RX), psychotherapy (PSY), or combination therapy (RX+PSY)

	PSY (N = 622)				RX+PSY (N = 3,451)			
Characteristics	**OR**	**95% CI**	**x^2**	**p-value**	**OR**	**95% CI**	**x^2**	**p-value***
Age[a]	0.560	0.510 – 0.615	**146.2**	**<.0001**	1.012	0.965 – 1.061	0.2	0.63
Total pre-index costs[a]	1.000	1.000 – 1.000	**6.7**	**0.01**	1.000	1.000 – 1.000	**7.6**	**0.01**
Pre-index psychiatric visits[a]	0.989	0.974 – 1.004	2.2	0.14	0.994	0.987 – 1.000	3.9	0.05
Pre-index non-psychiatric visits[a]	1.050	1.033 – 1.068	**32.4**	**<.0001**	1.009	0.999 – 1.019	2.9	0.09
Gender								
Male	**Reference**				**Reference**			
Female	0.945	0.781 – 1.144	0.3	0.56	1.005	0.920 – 1.098	0.0	0.91
Race/Ethnicity								
Whites	**Reference**				**Reference**			
African American	1.224	0.899 – 1.667	1.7	0.20	1.554	1.366 – 1.768	**44.7**	**<.0001**
Hispanics	1.305	1.022 – 1.666	**4.6**	**0.03**	1.181	1.059 – 1.317	**8.9**	**<.01**
Other/unknown	1.044	0.738 – 1.476	0.1	0.81	1.291	1.111 – 1.500	**11.1**	**<.01**
Urban/Rural status								
Urban	**Reference**				**Reference**			
Rural	1.090	0.880 – 1.350	0.6	0.43	1.091	0.994 – 1.199	3.3	0.07
Other pre-index psychotropics								
No	**Reference**				**Reference**			
Yes	1.687	1.082 – 2.628	**5.3**	**0.02**	1.150	0.955 – 1.384	2.2	0.14
Other mental health diagnosis								
No	**Reference**				**Reference**			
Yes	1.294	1.073 – 1.560	**7.3**	**0.01**	1.201	1.101 – 1.311	**16.8**	**<.0001**

*p < 0.05 (in bold); Reference class= Pharmacotherapy (N = 5,382); OR = Odds Ratio; x^2 = Chi-square; CI = Confidence Interval; PSY = Psychotherapy only group (N = 622); RX+PSY = Combination therapy group (N = 3,451);

[a] Recorded as a continuous variable in the model;

Long-, short-acting medications, and stimulants were not included as covariates since psychotherapy group did not report any medication use during that period

4.5.4 Medication adherence, persistence, augmentation and switching

Objective 3d: *To compare adherence, discontinuation (medication persistence), switching, and augmentation of pharmacotherapy between the RX and the RX+PSY groups*

4.5.4.1 Medication adherence

Table 4.10 presents the mean adherence rates to index medications for the pharmacotherapy and combination therapy groups for the treatment pattern cohort. The mean (±SD) adherence rate (proportion of days covered) was 0.48 (± 0.3) in the pharmacotherapy group and 0.50 (±0.3) in the combination therapy group.

Table 4.10: Descriptive statistics. Medication adherence rate stratified by treatment groups

Treatment group	N	%	Mean	SD	Median
RX	5,382	60.9%	0.48	0.3	0.44
RX+PSY	3,451	39.1%	0.50	0.3	0.49
Overall	8,833	100.0%	0.48	0.3	0.46

SD = Standard Deviation; RX = Pharmacotherapy; PSY = Psychotherapy; RX+PSY = Combination therapy; Adherence to index medications was measured using proportion of days covered methodology

Table 4.11 provides a chi-square comparison of the proportion of patients between the pharmacotherapy and the combination therapy groups according to adherence status. Patients with a PDC ≥ 80% were defined as adherent and those with a PDC < 80% were defined as non-adherent. A majority of the patients were non-adherent in the pharmacotherapy (n = 4,244; 78.9%) and the combination therapy groups (n = 2,674; 77.5%).

Table 4.11: Chi-square test. Adherence (dichotomous) stratified by treatment groups

Treatment group (N = 8,833)	**RX (n = 5,382)**		**RX+PSY (n = 3,451)**		x^2	**p-value**
					2.3	0.13
Adherence status	**n**	**%**	**n**	**%**		
Adherent[a,b]	1,138	21.1%	777	22.5%		
Non-adherent[a,b]	4,244	78.9%	2,674	77.5%		
Total	5,382	100.0%	3,451	100.0%		

RX = Pharmacotherapy; PSY = Psychotherapy; RX+PSY = Combination therapy; x^2 = Chi-square;
[a] Adherence to index medications was measured using proportion of days covered (PDC) methodology;
[b] PDC ≥ 80% was defined as adherent and < 80% was defined as non-adherent

Table 4.12 presents results for a t-test comparison of adherence as a continuous measure between the pharmacotherapy and combination therapy groups. The mean (±SD) adherence rate was significantly higher (t = 2.9, p < 0.01) in the combination therapy group (0.50 [±0.3]) as compared to the pharmacotherapy group (0.48 [±0.3]); however, this difference was very small.

Table 4.12: T-test. Adherence (continuous) stratified by treatment groups

Treatment group (N = 8,883)	**N**	**%**	**Mean[a]**	**SD**	**95% CI**	**t-value**	**p-value***
						2.9	**<.01**
RX	5,382	60.9%	0.48	0.30	0.47 - 0.48		
RX+PSY	3,451	39.1%	0.50	0.31	0.49 - 0.51		

*p < 0.05 (in bold); SD = Standard Deviation; CI = Confidence Interval; RX = Pharmacotherapy; PSY = Psychotherapy; RX+PSY = Combination therapy;
[a]Adherence to index medications was measured using proportion of days covered (PDC) methodology

Table 4.13 shows the result for linear regression analysis of adherence as a continuous measure between the pharmacotherapy and combination therapy groups, after controlling for covariates. The adherence rate for the index medication was significantly lower in the pharmacotherapy group (β = -0.021; t = -3.10; p < 0.01) as compared to the combination therapy group. Adherence in the pharmacotherapy group was lower by a factor of -0.021 as compared to the combination therapy group, while controlling for covariates. Although significant, difference in adherence between the pharmacotherapy and combination therapy group was small. Tolerance

and variance inflation factors for the main independent variable as well as the covariates did not reveal multi-collinearity among the selected variables.

Table 4.13: Linear regression. Medication adherence (continuous) by treatment group (N = 8,883) – after controlling for covariates

Characteristics	Estimate	t value	p-value*	Tolerance	VIF
Pharmacotherapy[a]	**-0.021**	**-3.10**	**<.01**	**0.980**	**1.021**
Covariates					
Age	0.026	**6.55**	**<.0001**	0.874	1.144
Pre-index psychiatric visits	0.000	0.23	0.81	0.886	1.128
Pre-index non-psychiatric visits	-0.001	-0.78	0.43	0.849	1.178
Total pre-index costs	0.000	0.25	0.80	0.723	1.382
Female	-0.020	**-2.79**	**0.01**	0.994	1.006
Non-whites	-0.022	**-6.20**	**<.0001**	0.862	1.160
Rural	0.020	**2.72**	**0.01**	0.869	1.151
Other psychotropics	-0.001	-0.11	0.91	0.951	1.052
Other mental health diagnosis	0.011	1.51	0.13	0.796	1.256
Long-acting medications	0.023	**2.44**	**0.01**	0.941	1.063
Stimulants	-0.031	**-2.10**	**0.04**	0.981	1.019

*p < 0.05 (in bold); VIF = Variance Inflation Factor; [a] Combination therapy group was the primary reference group

$H_0 3d_1$: *There is no significant difference in the medication adherence status between the RX and the RX+PSY groups, after controlling for covariates* **– Rejected**

Table 4.14 presents the results for a logistic regression analysis of adherence status between the pharmacotherapy and combination therapy group, after controlling for covariates. After controlling for covariates, the odds of adherence were 11.1% lower in the pharmacotherapy group as compared to the combination therapy group (OR = 0.889; CI = 0.799 – 0.988; p = 0.03). Model fit was assessed using deviance and Pearson goodness-of-fit statistic and the Hosmer-Lemeshow test. Deviance and Pearson goodness-of-fit statistics were non-significant indicating that the model-fit was appropriate. However, since the number of unique values was too high (n = 8,831) this test result was considered invalid. Another model fit test, the Hosmer-Lemeshow

test, did not detect significant differences between the observed and predicted values thus validating adequate model fit.

Covariates that were significantly associated with higher odds of being adherent included increasing age and long-acting medication use. Conversely, the covariates significantly associated with lower odds of being adherent included females, Hispanics, African Americans, Other/unknown race/ethnicity, and stimulant medication users.

Table 4.14: Logistic regression. Adherence status by pharmacotherapy and combination therapy treatment groups (N = 8,883) – after controlling for covariates

Characteristics	OR	95% CI	x^2	p-value*
Pharmacotherapy	**0.889**	**0.799 – 0.988**	**4.8**	**0.03**
Covariates				
Age[a]	1.123	1.053 – 1.197	**12.5**	**<.01**
Pre-index psychiatric visits[a]	1.003	0.996 – 1.010	0.6	0.46
Pre-index non-psychiatric visits[a]	0.994	0.983 – 1.005	1.2	0.28
Total pre-index costs[a]	1.000	1.000 – 1.000	0.4	0.52
Gender				
Males	**Reference**			
Females	0.865	0.768 – 0.973	**5.9**	**0.02**
Race/Ethnicity				
Whites	**Reference**			
African Americans	0.508	0.430 – 0.599	**63.9**	**<.0001**
Hispanics	0.513	0.449 – 0.587	**94.2**	**<.0001**
Others/unknown	0.585	0.485 – 0.706	**31.1**	**<.0001**
Urban/rural status				
Urban	**Reference**			
Rural	1.071	0.951 – 1.207	1.3	0.26
Other psychotropics				
No	**Reference**			
Yes	1.057	0.897 – 1.245	0.4	0.51
Other mental health diagnosis				
No	**Reference**			
Yes	1.073	0.955 – 1.205	1.4	0.24
Medication duration of action				
Short-acting medications	**Reference**			
Long-acting medications	1.591	1.346 – 1.882	**29.5**	**<.0001**
Medication type				
Non-stimulants	**Reference**			
Stimulants	0.737	0.594 – 0.913	**7.8**	**0.01**

*p < 0.05 (in bold); OR = Odds Ratio; CI = Confidence Interval; x^2= Chi-square;

[a] Recorded as a continuous variable in the model;

Adherence to index medications was measured using proportion of days covered (PDC) methodology;

PDC ≥ 80% was defined as adherent and < 80% was defined as non-adherent

4.5.4.2 Medication persistence

Table 4.15 presents the mean medication persistence of the index medication for the pharmacotherapy and combination therapy groups. The mean (±SD) medication persistence was 141.8 (±127.2) days in the combination therapy group and 137.1 (±127.3) days in the pharmacotherapy group.

Table 4.15: Descriptive. Medication persistence (continuous) stratified by treatment groups

Treatment group (N = 8,883)	N	%	Mean (days)	SD	Median (days)
RX	5,382	60.9%	137.1	127.3	79.0
RX+PSY	3,451	39.1%	141.8	127.2	87.0
Overall	8,833	100.0%	139.0	127.3	82.0

SD = Standard Deviation; RX = Pharmacotherapy; RX+PSY = Combination therapy; Persistence measured over a 365-day follow-up period with a 30-day allowable gap

Table 4.16 shows the results of a t-test comparison of mean medication persistence between the pharmacotherapy and combination therapy groups. There was no statistically significant difference (t = 1.7, p = 0.09) in the mean persistence between the pharmacotherapy and combination therapy groups.

Table 4.16: T-test. Medication persistence (continuous) stratified by treatment groups

Treatment group (N = 8,883)	N	Mean (days)[a]	SD	95% CI	t-value	p-value
					1.7	0.09
RX	5,382	137.1	127.3	133.7 – 140.5		
RX+PSY	3,451	141.8	127.2	137.6 – 146.1		

SD = Standard Deviation; CI = Confidence Interval; RX = Pharmacotherapy; PSY = Psychotherapy; RX+PSY = Combination therapy;
[a] Persistence was calculated over a 365-day period with a 30-day allowable gap

Table 4.17 shows the result for linear regression analysis of medication persistence as a continuous measure between the pharmacotherapy and combination therapy groups, after controlling for patient demographics, clinical, and prior utilization characteristics. Medication

persistence for the index medication was significantly lower in the pharmacotherapy group (β = -5.617; t-value = -2.02; p = 0.04) as compared to the combination therapy group. Persistence in the combination therapy group was lower by approximately 6 days as compared to the combination therapy group, after controlling for covariates. Tolerance and variance inflation factors for the main independent variable as well as the covariates did not indicate multi-collinearity among the selected variables.

Table 4.17: Linear regression. Persistence (continuous) by treatment groups (N = 8,883) – after controlling for covariates

Characteristics	Estimate	t-value	p-value	Tolerance	VIF
Pharmacotherapy	**-5.617**	**-2.02**	**0.04**	**0.980**	**1.021**
Covariates					
Age	9.913	**6.07**	**<.0001**	0.876	1.142
Pre-index psychiatric visits	0.052	0.28	0.78	0.886	1.129
Pre-index non-psychiatric visits	-0.366	-1.32	0.19	0.848	1.179
Total pre-index costs	0.000	0.24	0.81	0.727	1.376
Females	-10.847	**-3.59**	**<.01**	0.995	1.005
Non-whites	-12.517	**-8.69**	**<.0001**	0.930	1.076
Rural	2.919	1.93	0.05	0.983	1.017
Other psychotropic	1.541	0.36	0.72	0.952	1.050
Other mental health diagnosis	2.262	0.75	0.46	0.802	1.247
Long acting medications	14.765	**3.81**	**<.01**	0.940	1.064
Stimulants	-18.635	**-3.05**	**<.01**	0.981	1.020

*p < 0.05 (in bold); VIF = Variance Inflation Factor; Combination therapy group was the primary reference group

***$H_0 3d_2$**: *There is no significant difference in time to discontinuation of index therapy between the RX and the RX+PSY groups, after controlling for covariates* – **Failed to reject**

Table 4.18 shows the Cox proportional hazards regression of persistence as a continuous measure between the pharmacotherapy and combination therapy groups, after controlling for covariates. The hazard rate of discontinuation of medication therapy did not differ significantly between the pharmacotherapy and combination therapy treatment groups (HR = 1.044; CI = 0.997 – 1.093; p = 0.07.) Proportional hazards assumptions were tested using the Schoenfeld

residuals test (Appendix III). The results show that the curves for all the covariates were close to zero, indicating that the proportional hazards assumption was not violated.

Covariates that were significantly associated with higher hazard rates of discontinuation included females, African American, Hispanics, Other/unknown race/ethnicity, and stimulant medication use. Conversely, covariates significantly associated with lower hazard rates of discontinuation included age, rural residence status, and long-acting medication use. **Figure 4.6** presents the survival curve of time to discontinuation of the index medication.

Table 4.18: Cox proportional hazards regression. Determinants of time to discontinuation between pharmacotherapy and combination therapy groups (N = 8,883) – after controlling for covariates

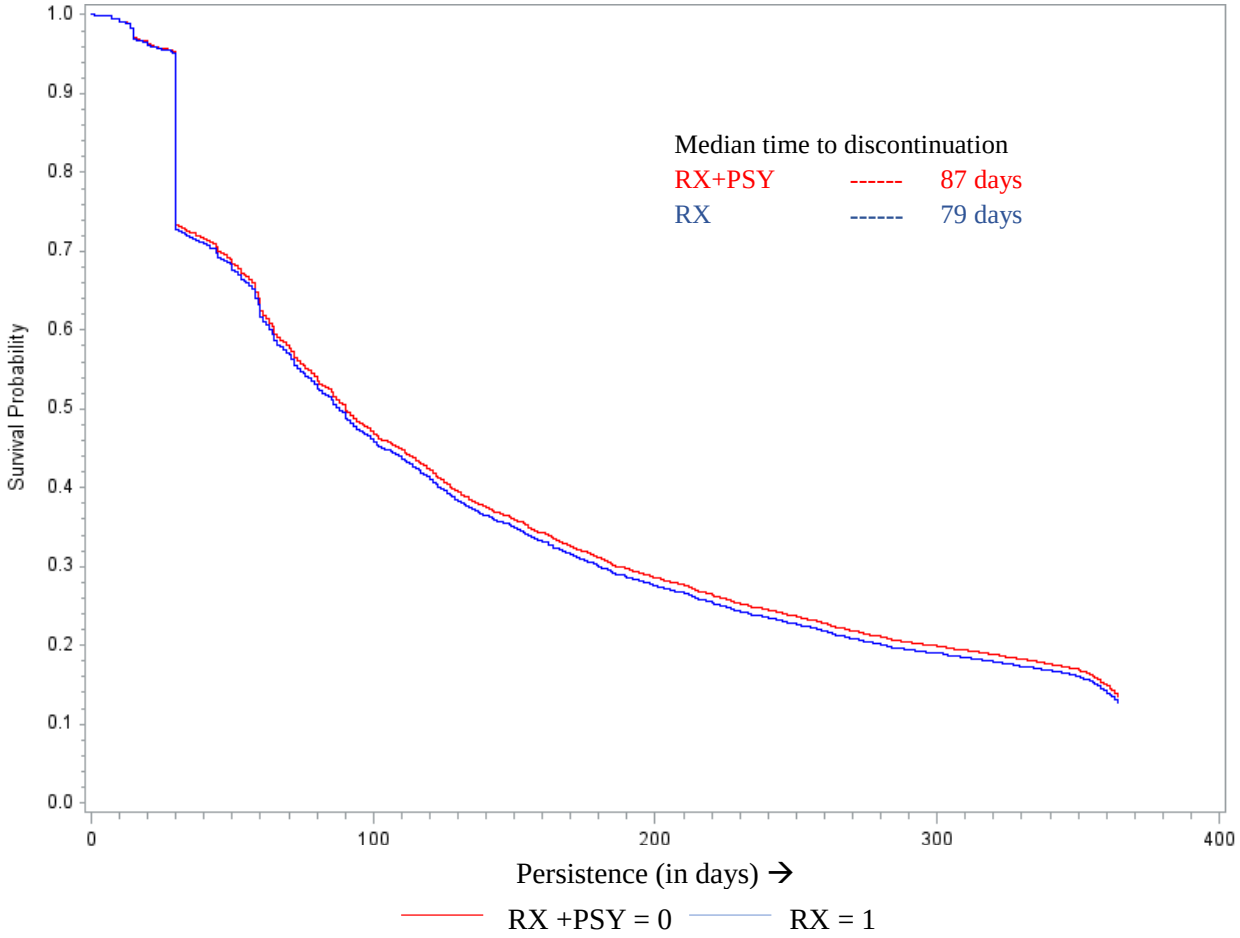
Characteristics	HR	95% CI	x^2	p-value*
Pharmacotherapy	1.044	0.997 – 1.093	3.3	0.07
Covariates				
Age[a]	0.920	0.895 – 0.945	**36.1**	**<.0001**
Pre-index psychiatric visits[a]	1.000	0.997 – 1.003	0.0	0.87
Pre-index non-psychiatric visits[a]	1.005	1.000 – 1.009	3.8	0.05
Total pre-index costs[a]	1.000	1.000 – 1.000	0.5	0.46
Gender				
Males	**Reference**			
Females	1.099	1.045 – 1.155	**13.6**	**<.01**
Race/Ethnicity				
Whites	**Reference**			
African Americans	1.355	1.257 – 1.460	**63.5**	**<.0001**
Hispanics	1.319	1.239 – 1.405	**74.1**	**<.0001**
Others/unknown	1.257	1.154 – 1.370	**27.3**	**<.0001**
Urban/rural status				
Urban	**Reference**			
Rural	0.938	0.889 – 0.990	**5.4**	**0.02**
Other psychotropics				
No	**Reference**			
Yes	0.987	0.920 – 1.060	0.1	0.72
Other mental health diagnosis				
No	**Reference**			
Yes	0.983	0.934 – 1.035	0.4	0.52
Medication duration of action				
Short-acting medications	**Reference**			
Long-acting medications	0.876	0.822 – 0.933	**16.8**	**<.0001**
Medication type				
Non-stimulants	**Reference**			
Stimulants	1.151	1.037 – 1.278	**6.9**	**0.01**

*p < 0.05 (in bold); HR = Hazard Ratio; CI = Confidence Interval; x^2 = Chi-square;

[a] Recorded as a continuous variable in the model;

Persistence was calculated over a 365-day period with a 30-day allowable gap

Figure 4.6: Survival curve of time to discontinuation (N = 8,883)



Y = Survival probability (proportion of patients); X = Persistence [time to discontinuation (in days)];
Estimated using Cox proportional hazard regression while adjusting for age, race/ethnicity, gender, pre-index psychiatric visits, pre-index non-psychiatric visits, pre-index total costs, other psychotropics, other mental health diagnosis, long-acting medications, short-acting medications, and stimulants;
Censored observations include patients still persistent at the end of the 365-day period

4.5.4.3 Augmentation

Medication augmentation was defined as starting an alternative ADHD medication (different chemical entity) along with the index medication with an overlap of at least 30 days.

Table 4.19 shows the proportion of patients by augmentation status. A majority of the patients did not augment (n = 7,904; 89.5%) their index medication therapy with another ADHD medication. Overall, 10.5% of the patients from the treatment pattern cohort augmented therapy with an alternative ADHD medication with an overlap of at least 30 days.

Table 4.19: Descriptive statistics. Proportion of patients augmenting medications with their index medication

Augmentation[a]	Frequency	%
Yes	929	10.5%
No	7,904	89.5%

Yes = Augmented; No = Did not augment;
[a] Augmentation was defined as initiation of a new ADHD medication (chemical entity) with a continuous overlap of at least 30 days with the index medication

Table 4.20 reports the chi-square results for the proportion of patients augmenting medications in the pharmacotherapy and combination therapy groups. Nearly 9.2% (n = 495) patients augmented medication in the pharmacotherapy group as compared to 12.6% (n = 434) patients in the combination therapy group. The difference in proportions of patients augmenting medications was statistically significant ($x^2 = 25.5$; $p < 0.0001$) between the pharmacotherapy and combination therapy groups; however, this difference is relatively small.

Table 4.20: Chi-square test. Proportion of patients augmenting medications in the pharmacotherapy and combination therapy groups

Treatment group (N = 8,883)	**RX**		**RX+PSY**		**x^2**	**p-value***
					25.5	**<.0001**
Augmentation[a]	**n**	**%**	**n**	**%**		
Yes	495	9.2%	434	12.6%		
No	4,887	90.8%	3,017	87.4%		

*p < 0.05 (in bold); RX = Pharmacotherapy; PSY = Psychotherapy; RX+PSY = Combination therapy; x^2 = Chi-square; Yes = Augmented; No = Did not augment;
[a]Augmentation was defined as initiation of a new ADHD medication (chemical entity) with a continuous overlap of at least 30 days with the index medication

$H_0 3 d_3$: *There is no significant difference in the augmentation status between the RX and the RX+PSY groups, after controlling for covariates* **- Rejected**

Table 4.21 reports the logistic regression results of augmentation status in the pharmacotherapy group as compared to the combination therapy group while controlling for covariates. Deviance and Pearson goodness-of-fit statistics were non-significant indicating that the model-fit was appropriate. However, since the number of unique values was too high (n = 8,831) this test result was considered invalid. Model fit assessed using the Hosmer-Lemeshow test did not indicate a significant difference between the observed and predicted values thus validating adequate model fit. Patients in the pharmacotherapy group had a 26.2% lower odds of augmentation (OR = 0.738; CI = 0.642 – 0.850; p < 0.0001) with an alternative medication therapy as compared to patients in the combination therapy group while controlling for covariates.

As for covariates, patients with other psychotropic drug use, other mental health diagnosis, long-acting, and stimulant medication use had significantly higher odds of augmenting their index therapy. Conversely, females, Hispanics, other/unknown race/ethnicity, and rural area residents had lower odds of augmenting their index therapy.

Table 4.21: Logistic regression. Augmentation status by pharmacotherapy and combination therapy treatment groups (N = 8,883) – after controlling for covariates

Characteristics	OR	95% CI	x^2	p-value
Pharmacotherapy	**0.738**	**0.642 – 0.850**	**17.9**	**<.0001**
Covariates				
Age[a]	0.995	0.913 – 1.083	0.0	0.90
Pre-index psychiatric visits[a]	1.002	0.992 – 1.013	0.2	0.64
Pre-index non-psychiatric visits[a]	1.001	0.986 – 1.016	0.0	0.86
Total pre-index costs[a]	1.000	1.000 – 1.000	**9.5**	**<.01**
Gender				
Males	**Reference**			
Females	0.786	0.667 – 0.924	**8.4**	**<.01**
Race/Ethnicity				
Whites	**Reference**			
African Americans	1.009	0.816 – 1.246	0.0	0.94
Hispanics	0.737	0.612 – 0.888	**10.3**	**<.01**
Others/unknown	0.670	0.512 – 0.877	**8.5**	**<.01**
Urban/rural status				
Urban	**Reference**			
Rural	0.789	0.669 – 0.930	**8.0**	**<.01**
Other psychotropics				
No	**Reference**			
Yes	1.551	1.268 – 1.897	**18.2**	**<.0001**
Other mental health diagnosis				
No	**Reference**			
Yes	1.235	1.059 – 1.441	**7.3**	**0.01**
Medication duration of action				
Short-acting medications	**Reference**			
Long-acting medications	8.155	5.304 – 12.540	**91.4**	**<.0001**
Medication type				
Non-stimulants	**Reference**			
Stimulants	1.972	1.363 – 2.854	**13.0**	**<.01**

*p < 0.05 (in bold); OR = Odds Ratio; CI = Confidence Interval; x^2= Chi-square;

[a] Recorded as a continuous variable in the model;

Augmentation was defined as initiation of a new ADHD medication (chemical entity) with a continuous overlap of at least 30 days with the index medication

4.5.4.4 Switching

Switching was defined as a prescription claim for an ADHD medication (i.e., long-acting or short-acting medication that differed from the initial medication in terms of chemical entity) other than the index medication, within 30 days of discontinuation of the index medication (i.e., no subsequent dispensing of the index medication for ≥ 60 days). The "switched-to" medication must have been prescribed for at least 30 days to be considered as switching.

Table 4.22 shows the proportion of patients by switch status. A majority of the patients did not switch (n = 6,024; 68.2%) their index medication. Overall, 31.8% (n = 2,809) of the patients in the treatment pattern cohort switched to an alternative ADHD medication.

Table 4.22: Descriptive statistics. Proportion of patients switching to alternative ADHD medications

Switching[a]	Frequency	%
Yes	2,809	31.8%
No	6,024	68.2%

Yes = Switched; No = Did not switch;

[a] Switching was defined as a prescription claim for an alternative ADHD medication (i.e., long-acting or short-acting medications that differed from the initial medication in terms of chemical entity) other than the index medication, before or within 30 days of discontinuation of the index medication (i.e., no subsequent dispensing of the index medication for ≥ 60 days). The "switched-to" medication must have been prescribed for at least 30 days to be considered as switching.

Table 4.23 reports the chi-square results for the proportion of patients switching medications in each treatment group. A total of 29.6% (n = 1,594) patients switched in the pharmacotherapy group as compared to 35.2% (n = 1,215) patients in the combination therapy group. This difference in proportions of patients switching between the pharmacotherapy and combination therapy groups medications was statistically significant (x^2 = 30.3; p = <0.0001).

Table 4.23: Chi-square test. Proportion of patients switching medications in the pharmacotherapy and combination therapy treatment groups

Treatment group (N = 8,883)	**RX**		**RX+PSY**		**x^2**	**p-value***
					30.3	**<.0001**
Switching[a]	**n**	**%**	**n**	**%**		
Yes	1,594	29.6%	1,215	35.2%		
No	3,788	70.4%	2,236	64.8%		

*p < 0.05 (in bold); RX = Pharmacotherapy; PSY = Psychotherapy; RX+PSY = Combination therapy; x^2 = Chi-square; Yes = Switched; No = Did not switch;

[a] Switching was defined as a prescription claim for an alternative ADHD medication (i.e., long-acting or short-acting medications that differed from the initial medication in terms of chemical entity) other than the index medication, before or within 30 days of discontinuation of the index medication (i.e., no subsequent dispensing of the index medication for ≥ 60 days). The "switched-to" medication should have been prescribed for at least 30 days to be considered as switching.

$H_0 3 d_4$: *There is no significant difference in the switch status between the RX and the RX+PSY groups, after controlling for covariates* – **Rejected**

Table 4.24 reports the logistic regression results by switching status in the pharmacotherapy group as compared to the combination therapy group while controlling for covariates. Deviance and Pearson goodness-of-fit statistics were significant indicating that the model-fit was not appropriate. However, since the number of unique values was too high (n = 8,831) this test result was considered invalid. Model fit assessed using a Hosmer-Lemeshow test did not indicate a significant difference between the observed and predicted values thus validating adequate model fit. Patients in the pharmacotherapy group had a 20.2% (OR = 0.798; CI = 0.725 – 0.878; p < 0.0001) lower odds of switching as compared to patients in the combination therapy group while controlling for covariates. As for covariates, patients with other psychotropic drug use, with other mental health diagnosis, long-acting, and stimulant medication use had significantly higher odds of switching medications. Conversely, females, Hispanics, African Americans, and other/unknown race/ethnicity had a lower likelihood of switching to alternative ADHD therapy.

Table 4.24: Logistic regression. Switching status by pharmacotherapy and combination therapy treatment groups (N = 8,883) – after controlling for covariates

Characteristics	OR	95% CI	x^2	p-value*
Pharmacotherapy	**0.798**	**0.725-0.878**	**21.4**	**<.0001**
Covariates				
Age[a]	0.978	0.924 – 1.036	0.6	0.45
Pre-index psychiatric visits[a]	1.002	0.995 – 1.008	0.2	0.64
Pre-index non-psychiatric visits[a]	1.007	0.997 – 1.017	2.1	0.15
Total pre-index costs[a]	1.000	1.000 – 1.000	**15.1**	**<.01**
Gender				
Males	**Reference**			
Females	0.882	0.793 – 0.980	**5.4**	**0.02**
Race/Ethnicity				
Whites	**Reference**			
African Americans	0.733	0.631 – 0.852	**16.4**	**<.0001**
Hispanics	0.670	0.590 – 0.760	**38.8**	**<.0001**
Others/Unknown	0.814	0.685 – 0.966	**5.5**	**0.02**
Urban/rural status				
Urban	**Reference**			
Rural	0.971	0.870 – 1.084	0.3	0.60
Other psychotropics				
No	**Reference**			
Yes	1.282	1.105 – 1.486	**10.8**	**<.01**
Other mental health diagnosis				
No	**Reference**			
Yes	1.218	1.096 – 1.353	**13.4**	**<.01**
Medication duration of action				
Short-acting medications	**Reference**			
Long-acting medications	7.177	5.810 – 8.866	**334.1**	**<.0001**
Medication type				
Non-stimulants	**Reference**			
Stimulants	3.317	2.561 – 4.296	**82.5**	**<.0001**

*p < 0.05 (in bold); OR = Odds Ratio; CI = Confidence Interval; x^2= Chi-square;

[a] Recorded as a continuous variable in the model;

Switching was defined as a prescription claim for an alternative ADHD medication (i.e., long-acting or short-acting medications that differed from the initial medication in terms of chemical entity) other than the index medication, before or within 30 days of discontinuation of the index medication (i.e., no subsequent dispensing of the index medication for ≥ 60 days). The "switched-to" medication must have been prescribed for at least 30 days to be considered as switching.

4.6 Objective 4: Healthcare utilization between pharmacotherapy and combination therapy groups

Objectives 4a-4c were to determine and compare all-cause, ADHD-related, and other mental health-related healthcare utilization between the pharmacotherapy and combination therapy groups after controlling for covariates. A Modified Park test was conducted to identify the distribution and functional form for each resource utilization category (Appendix VI). Based on the results of the Vuong test, in adjusted analysis, resource utilization in pharmacotherapy group was compared to combination therapy using separate zero-inflated Poisson regression models for each resource utilization category (i.e., office-based, inpatient, outpatient hospital, ED visits, and prescriptions) except for all-cause and ADHD-related prescriptions (Appendix VII.) The Vuong test indicated that the Poisson model is a better fit for all-cause and ADHD-related prescriptions and thus, these variables were modelled using a Poisson regression.

4.6.1 All-cause healthcare utilization

Objective 4a: *To determine and compare the healthcare utilization for all-cause office-based, inpatient, outpatient hospital, ED visits, and prescriptions between the RX and the RX+PSY groups*

4.6.1.1 All-cause office-based visits

$H4a_1$: *The number of all-cause office-based visits are significantly higher in the RX+PSY group as compared to the RX group* – **Failed to reject**

Table 4.25 presents a zero-inflated Poisson regression comparison of all-cause office-based visits between the pharmacotherapy and combination therapy groups in the overall cohort. After controlling for covariates, for patients with visits, the expected number of all-cause office-based visits in the pharmacotherapy group was 0.782 times [exp (-0.246)] the expected number

of all-cause office-based visits in the combination therapy group (β = -0.246; x^2= 2,414.3; p < 0.0001). Thus, among those who have all-cause office-based visits, being in the pharmacotherapy group decreases the expected number of all-cause office-based visits by 21.8%, holding other covariates constant, and this is statistically significant (p < 0.0001).

As for the covariates, patients with higher age, females, and rural area status had significantly lower all-cause office-based visits. Conversely, patients with higher pre-index psychiatric visits, pre-index non-psychiatric visits, total pre-index costs, Hispanic, other/unknown race/ethnicity, other psychotropic use, other mental health disorders, long- or short-acting medication use, and stimulant use were associated with significantly higher all-cause office-based visits. The unit increments on the scale for total pre-index costs ($1) were relatively small; therefore, a one unit change in pre-index costs may result in a very small change in post-index utilization.

4.6.1.2 All-cause inpatient visits

H4a$_2$: *The number of all-cause inpatient visits are significantly higher in the RX+PSY group as compared to the RX group* **– Failed to reject**

Table 4.26 presents a zero-inflated Poisson regression comparison of all-cause inpatient visits between the pharmacotherapy and combination therapy groups in the overall cohort. After controlling for covariates, for patients with visits, the expected number of all-cause inpatient visits in the pharmacotherapy group was 0.827 times [exp (-0.190)] the expected number of all-cause inpatient visits in the combination therapy group (β = -0.190; x^2= 21.5; p < 0.0001). Thus, among those who have all-cause inpatient visits, being in the pharmacotherapy group decreases

the expected number of all-cause inpatient visits by 17.3%, holding other covariates constant, and this is statistically significant ($p < 0.0001$).

As for the covariates, rural area status had significantly lower all-cause inpatient visits. Conversely, African American, Hispanic, other/unknown race/ethnicity, other mental health disorders, and long-acting medication use were associated with significantly higher all-cause inpatient visits. The unit increments on the scale for total pre-index costs were relatively small; therefore, a one unit change in pre-index costs may result in a very small change in post-index utilization.

4.6.1.3 All-cause outpatient hospital visits

H4a$_3$: *The number of all-cause outpatient hospital visits are significantly higher in the RX+PSY group as compared to the RX group* **– Failed to reject**

Table 4.27 presents a zero-inflated Poisson regression comparison of all-cause outpatient hospital visits between the pharmacotherapy and combination therapy groups in the overall cohort. After controlling for covariates, for patients with visits, the expected number of all-cause outpatient hospital visits in the pharmacotherapy group was 0.945 times [exp (-0.057)] the expected number of all-cause outpatient hospital visits in the combination therapy group (β = -0.057; x^2= 70.3; $p < 0.0001$). Thus, among those who have all-cause outpatient hospital visits, being in the pharmacotherapy group decreases the expected number of all-cause outpatient hospital visits by 5.5%, holding other covariates constant, and this is statistically significant ($p < 0.0001$).

As for the covariates, patients with higher age, higher pre-index psychiatric visits, female, African American, rural area residents, and long-acting medication users had significantly lower

all-cause outpatient hospital visits. Conversely, higher pre-index non-psychiatric visits, higher total pre-index costs, Hispanic, other/unknown race/ethnicity, other psychotropic use, other mental health disorders, and stimulant medication use were associated with significantly higher all-cause outpatient hospital visits. The unit increments on the scale for total pre-index costs were relatively small; therefore, a one unit change in pre-index costs may result in a very small change in post-index utilization.

4.6.1.4 All-cause ED visits

H4a$_4$: *The number of all-cause ED visits are significantly higher in the RX+PSY group as compared to the RX group* **– Failed to reject**

Table 4.28 presents a zero-inflated Poisson regression comparison of all-cause ED visits between the pharmacotherapy and combination therapy groups in the overall cohort. After controlling for covariates, for patients with ED visits, the expected number of all-cause ED visits in the pharmacotherapy group was 0.774 times [exp (-0.256)] the expected number of all-cause ED visits in the combination therapy group (β = -0.256; x^2= 18.0; p < 0.0001). Thus, among those who have all-cause ED visits, being in the pharmacotherapy group decreases the expected number of all-cause ED visits by 22.6%, holding other covariates constant, and this is statistically significant (p < 0.0001).

As for the covariates, patients with higher age and Hispanic race/ethnicity were associated with significantly lower all-cause ED visits. Conversely, patients with higher pre-index non-psychiatric visits, total pre-index costs, other/unknown race, and residing in the rural area were associated with a higher number of all-cause ED visits. The unit increments on the

scale for total pre-index costs were relatively small; therefore, a one unit change in pre-index costs may result in a very small change in post-index utilization.

4.6.1.5 All-cause prescriptions

H4a$_5$: *The number of all-cause prescriptions are significantly higher in the RX+PSY group as compared to the RX group* **– Failed to reject**

Table 4.29 represents a Poisson regression comparison of all-cause prescription medications between the pharmacotherapy and combination therapy groups in the overall cohort. After controlling for covariates, the difference in the expected number of all-cause prescriptions in the pharmacotherapy group is 0.962 times (exp[-0.039]) that in the combination therapy group (β = -0.039; x^2= 81.2; p < 0.0001). Thus, being in the pharmacotherapy group decreases the expected number of all-cause prescriptions counts by 3.8%, holding other covariates constant, and this is statistically significant (p < 0.0001).

As for the covariates, patients with higher age, higher pre-index psychiatric visits, African American race, Hispanic, other/unknown race/ethnicity, residency in rural area, and using other psychotropic medications were associated with a significantly lower number of all-cause prescriptions. Conversely, higher pre-index non-psychiatric visits, total pre-index costs, female, having other mental health diagnosis, and using long-acting or short-acting medications were associated with a significantly higher number of all-cause prescriptions. The unit increments on the scale for total pre-index costs were relatively small; therefore, a one unit change in pre-index costs may result in a very small change in post-index utilization.

Table 4.25: Zero-Inflated Poisson Regression: Comparison of all-cause office-based visits between the pharmacotherapy (RX) and combination (RX+PSY) groups (N = 10,255) – after controlling for covariates

Characteristics	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**-0.246**	**-0.256- -0.236**	**2,414.3**	**<.0001**
Covariates				
Age[b]	-0.079	-0.085- -0.073	**722.4**	**<.0001**
Pre-index psychiatric visits[b]	0.023	0.023- 0.024	**20,751.8**	**<.0001**
Pre-index non-psychiatric visits[b]	0.048	0.047- 0.049	**15,912.1**	**<.0001**
Total pre-index costs[b]	0.000	0.000- 0.000	**97.8**	**<.0001**
Female[a]	-0.062	-0.074- -0.051	**117.9**	**<.0001**
African American[a]	-0.002	-0.022- 0.017	0.1	0.83
Hispanic[a]	0.172	0.157- 0.187	**489.4**	**<.0001**
Other/unknown[a] race/ethnicity	0.248	0.229- 0.267	**666.6**	**<.0001**
Rural[a]	-0.059	-0.071- -0.046	**78.8**	**<.0001**
Other psychotropics[a]	0.114	0.089- 0.139	**79.4**	**<.0001**
Other mental health diagnosis[a]	0.581	0.570- 0.593	**10,027.2**	**<.0001**
Long-acting medications[a]	0.049	0.034- 0.064	**40.6**	**<.0001**
Short-acting medications[a]	0.019	0.007- 0.030	**10.4**	**<.01**
Stimulants[a]	0.102	0.079- 0.126	**71.7**	**<.0001**

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no other mental health diagnosis, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as a continuous variable in the model

Table 4.26: Zero-Inflated Poisson Regression: Comparison of all-cause inpatient visits between the pharmacotherapy (RX) and combination (RX+PSY) groups (N = 10,255) – after controlling for covariates

Characteristics	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**-0.190**	**-0.270- -0.110**	**21.5**	**<.0001**
Covariates				
Age[b]	0.042	-0.005- 0.090	3.1	0.08
Pre-index psychiatric visits[b]	-0.005	-0.010- 0.000	3.3	0.07
Pre-index non-psychiatric visits[b]	0.008	0.000- 0.016	3.9	0.05
Total pre-index costs[b]	0.000	0.000- 0.000	1.5	0.22
Female[a]	-0.065	-0.161- 0.032	1.7	0.19
African American[a]	0.268	0.101- 0.435	**9.9**	**<.01**
Hispanic[a]	0.250	0.116- 0.383	**13.4**	**<.01**
Other/unknown[a] race/ethnicity	0.380	0.230- 0.529	**24.8**	**<.0001**
Rural[a]	-0.206	-0.320- -0.092	**12.5**	**<.01**
Other psychotropics[a]	0.148	-0.029- 0.325	2.7	0.10
Other mental health diagnosis[a]	0.410	0.316- 0.505	**72.3**	**<.0001**
Long-acting medications[a]	0.131	0.006- 0.255	**4.2**	**0.04**
Short-acting medications[a]	0.052	-0.037- 0.140	1.3	0.25
Stimulants[a]	0.124	-0.064- 0.312	1.7	0.20

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no other mental health diagnosis, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as a continuous variable in the model

Table 4.27: Zero-Inflated Poisson Regression: Comparison of all-cause outpatient hospital visits between the pharmacotherapy (RX) and combination (RX+PSY) groups (N = 10,255) – after controlling for covariates

Characteristics	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**-0.057**	**-0.070- -0.044**	**70.3**	**<.0001**
Covariates				
Age[b]	-0.114	-0.122- -0.107	**886.7**	**<.0001**
Pre-index psychiatric visits[b]	-0.016	-0.017- -0.015	**953.7**	**<.0001**
Pre-index non-psychiatric visits[b]	0.012	0.011- 0.013	**370.3**	**<.0001**
Total pre-index costs[b]	0.000	0.000- 0.000	**8,136.0**	**<.0001**
Female[a]	-0.066	-0.082- -0.051	**69.9**	**<.0001**
African American[a]	-0.359	-0.401- -0.317	**281.6**	**<.0001**
Hispanic[a]	0.643	0.618- 0.668	**2,468.4**	**<.0001**
Other/ unknown[a] race/ethnicity	0.305	0.275- 0.336	**379.1**	**<.0001**
Rural[a]	-0.357	-0.378- -0.336	**1,082.8**	**<.0001**
Other psychotropics[a]	0.177	0.143- 0.212	**101.8**	**<.0001**
Other mental health diagnosis[a]	1.224	1.205- 1.244	**14,948.4**	**<.0001**
Long-acting medications[a]	-0.022	-0.041- -0.003	**4.9**	**0.03**
Short-acting medications[a]	0.004	-0.012- 0.020	0.3	0.61
Stimulants[a]	0.065	0.034- 0.096	**16.5**	**<.0001**

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no other mental health diagnosis, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as a continuous variable in the model

Table 4.28: Zero-Inflated Poisson Regression: Comparison of all-cause emergency department visits between the pharmacotherapy (RX) and combination (RX+PSY) groups (N = 10,255) – after controlling for covariates

Characteristics	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**-0.256**	**-0.375- -0.138**	**18.0**	**<.0001**
Covariates				
Age[b]	-0.183	-0.232- -0.135	**55.1**	**<.0001**
Pre-index psychiatric visits[b]	-0.004	-0.011- 0.003	1.4	0.23
Pre-index non-psychiatric visits[b]	0.019	0.010- 0.028	**16.4**	**<.0001**
Total pre-index costs[b]	0.000	0.000- 0.000	**7.6**	**0.01**
Female[a]	-0.027	-0.120- 0.065	0.3	0.56
African American[a]	-0.013	-0.136- 0.110	0.0	0.84
Hispanic[a]	-0.376	-0.487- -0.265	**44.1**	**<.0001**
Other/ unknown[a] race/ethnicity	0.207	0.078- 0.336	**9.9**	**<.01**
Rural[a]	0.478	0.387- 0.570	**105.2**	**<.0001**
Other psychotropics[a]	0.055	-0.144- 0.254	0.3	0.59
Other mental health diagnosis[a]	0.008	-0.080- 0.096	0.0	0.86
Long-acting medications[a]	-0.075	-0.200- 0.050	1.4	0.24
Short-acting medications[a]	0.063	-0.031- 0.158	1.7	0.19
Stimulants[a]	-0.007	-0.181- 0.167	0.0	0.94

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no other mental health diagnosis, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as a continuous variable in the model

Table 4.29: Poisson Regression: Comparison of all-cause prescriptions between the pharmacotherapy (RX) and combination (RX+PSY) groups (N = 10,255) – after controlling for covariates

Characteristics	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**-0.039**	**-0.047- -0.030**	**81.2**	**<.0001**
Covariates				
Age[b]	-0.091	-0.096- -0.086	**1,292.7**	**<.0001**
Pre-index psychiatric visits[b]	-0.003	-0.003- -0.002	**87.7**	**<.0001**
Pre-index non-psychiatric visits[b]	0.029	0.028- 0.030	**5,244.5**	**<.0001**
Total pre-index costs[b]	0.000	0.000- 0.000	**2,037.8**	**<.0001**
Female[a]	0.043	0.034- 0.053	**84.7**	**<.0001**
African American[a]	-0.143	-0.158- -0.128	**350.0**	**<.0001**
Hispanic[a]	-0.026	-0.037- -0.014	**18.4**	**<.0001**
Other/ unknown[a] race/ethnicity	-0.025	-0.041- -0.009	**9.4**	**<.01**
Rural[a]	-0.222	-0.233- -0.211	**1,691.7**	**<.0001**
Other psychotropics[a]	-0.046	-0.067- -0.025	**17.9**	**<.0001**
Other mental health diagnosis[a]	0.142	0.133- 0.151	**922.7**	**<.0001**
Long-acting medications[a]	0.192	0.179- 0.205	**820.9**	**<.0001**
Short-acting medications[a]	0.126	0.117- 0.136	**660.3**	**<.0001**
Stimulants[a]	0.003	-0.016- 0.021	0.1	0.79

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no other mental health diagnosis, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as continuous variable in the model

4.6.2 ADHD-related healthcare utilization

Objective 4b*: To determine and compare the healthcare utilization frequencies for ADHD-related office-based, inpatient, outpatient hospital, ED visits, and prescription medications between the RX and the RX+PSY groups*

4.6.2.1 ADHD-related office-based visits

H4b₁: *The number of ADHD-related office-based visits are significantly higher in the RX+PSY group as compared to the RX group* – **Failed to reject**

Table 4.30 presents a zero-inflated Poisson regression comparison of ADHD-related office-based visits between pharmacotherapy and combination therapy groups in the overall cohort. After controlling for covariates, for patients with ADHD-related office-based visits, the expected number of ADHD-related office-based visits in the pharmacotherapy group was 0.472 times [exp (-0.750)] the expected number of ADHD-related office-based visits in the combination therapy group (β = -0.750; x^2= 6464.3; p < 0.0001). Thus, among those who have ADHD-related office-based visits, being in the pharmacotherapy group decreases the expected number of ADHD-related office-based visits by 52.8%, holding other covariates constant, and this is statistically significant (p < 0.0001).

As for the covariates, patients with higher age, higher pre-index psychiatric visits, and females had a significantly lower ADHD-related office-based visits. Conversely, higher pre-index non-psychiatric visits, Hispanic, other/unknown race/ethnicity, other psychotropic use, other mental health diagnosis, long- or short-acting medication use, and stimulant medication use were associated with a significantly higher number of ADHD-related office-based visits.

4.6.2.2 ADHD-related inpatient visits

H4b$_2$: *The number of ADHD-related inpatient visits are significantly higher in the RX+PSY group as compared to the RX group* – **Failed to reject**

Table 4.31 presents a zero-inflated Poisson regression comparison of ADHD-related inpatient visits between the pharmacotherapy and combination therapy groups in the overall cohort. After controlling for covariates, for patients with ADHD-related inpatient visits, the expected number of ADHD-related inpatient visits in the pharmacotherapy group was 0.725 times [exp (-0.322)] the expected number of ADHD-related inpatient visits in the combination therapy group (β = -0.322; x^2= 11.8; p <0.01). Thus, among those who have ADHD-related inpatient visits, being in the pharmacotherapy group decreases the expected number of ADHD-related inpatient visits by 27.5%, holding other covariates constant, and this is statistically significant (p < 0.01).

As for the covariates, patients with higher age, higher pre-index psychiatric visits, females, rural area residents, and short-acting medication users were significantly associated with lower ADHD-related inpatient visits. Conversely, higher pre-index non-psychiatric visits, Hispanic, other/unknown race/ethnicity, other mental health diagnosis, long-acting medication use, and stimulant medication use were associated with significantly higher ADHD-related inpatient visits.

4.6.2.3 ADHD-related outpatient hospital visits

H4b$_3$: *The number of ADHD-related outpatient hospital visits are significantly higher in the RX+PSY group as compared to the RX group* – **Failed to reject**

Table 4.32 presents a zero-inflated Poisson regression comparison of ADHD-related outpatient hospital visits between the pharmacotherapy and combination therapy groups in the overall cohort. After controlling for covariates, for patients with ADHD-related outpatient hospital visits, the expected number of ADHD-related outpatient hospital visits in the pharmacotherapy group was 0.705 times [exp (-0.350)] the expected number of ADHD-related outpatient hospital visits in the combination therapy group (β = -0.350, x^2= 294.0, p < 0.0001). Thus, among those who have ADHD-related outpatient hospital visits, being in the pharmacotherapy group decreases the expected number of ADHD-related outpatient hospital visits by 29.5%, holding other covariates constant, and this is statistically significant (p < 0.0001).

As for the covariates, patient with higher age, higher pre-index psychiatric visits, African American, rural residence status, and stimulant medication use were associated with a significantly lower number of ADHD-related outpatient hospital visits. Conversely, higher pre-index non-psychiatric visits, total pre-index costs, Hispanics, other/unknown race/ethnicity, other mental health diagnosis, and long-acting medication use were associated with a significantly higher number of ADHD-related outpatient hospital visits. The unit increments on the scale for total pre-index costs were relatively small; therefore, a one unit change in pre-index costs may result in a very small change in post-index utilization.

4.6.2.4 ADHD-related ED visits

H4b$_4$: *The number of ADHD-related ED visits are significantly higher in the RX+PSY group as compared to the RX group* – **Could not test**

Since the number of events in both treatment groups was mostly zero, this hypothesis could not be tested.

4.6.2.5 ADHD-related prescriptions

H4b$_5$: *The number of ADHD-related prescriptions are significantly higher in the RX+PSY group as compared to the RX group* **- Rejected**

Table 4.33 presents a Poisson regression comparison of ADHD-related prescriptions between pharmacotherapy and combination therapy groups in the overall population. After controlling for covariates, there was no significant difference in ADHD-related prescription counts in the pharmacotherapy group as compared to the combination therapy group.

Table 4.30: Zero-Inflated Poisson Regression: Comparison of ADHD-related office-based visits between the pharmacotherapy (RX) and combination (RX+PSY) groups (N = 10,255) – after controlling for covariates

Characteristics	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**-0.750**	**-0.769- -0.732**	**6464.3**	**<.0001**
Covariates				
Age[b]	-0.017	-0.028- -0.070	**10.6**	**<.01**
Pre-index psychiatric visits[b]	-0.003	-0.004- -0.001	**14.0**	**<.01**
Pre-index non-psychiatric visits[b]	0.016	0.015- 0.018	**293.2**	**<.0001**
Total pre-index costs[b]	0.000	0.000- 0.000	0.7	0.42
Female[a]	-0.031	-0.051- -0.012	**10.2**	**<.01**
African American[a]	0.006	-0.024- 0.036	0.2	0.68
Hispanic[a]	0.131	0.106- 0.156	**106.9**	**<.0001**
Other/unknown[a] race/ethnicity	0.048	0.014- 0.082	**7.8**	**0.01**
Rural[a]	-0.020	-0.042- 0.001	3.6	0.06
Other psychotropics[a]	0.064	0.024- 0.103	**9.9**	**<.01**
Other mental health diagnosis[a]	0.101	0.082- 0.120	**110.1**	**<.0001**
Long-acting medications[a]	0.234	0.206- 0.262	**268.8**	**<.0001**
Short-acting medications[a]	0.125	0.106- 0.145	**158.7**	**<.0001**
Stimulants[a]	0.202	0.159- 0.245	**85.4**	**<.0001**

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no other mental health diagnosis, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as a continuous variable in the model

Table 4.31: Zero-Inflated Poisson Regression: Comparison of ADHD-related inpatient visits between the pharmacotherapy (RX) and combination (RX+PSY) groups (N = 10,255) – after controlling for covariates

Characteristics	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**-0.322**	**-0.506- -0.138**	**11.8**	**<.01**
Covariates				
Age[b]	-0.165	-0.271- -0.060	**9.5**	**<.01**
Pre-index psychiatric visits[b]	-0.016	-0.030- -0.002	**5.1**	**0.02**
Pre-index non-psychiatric visits[b]	0.023	0.002- 0.043	**4.6**	**0.03**
Total pre-index costs[b]	0.000	0.000- 0.000	2.0	0.16
Female[a]	-0.365	-0.596- -0.135	**9.7**	**<.01**
African American[a]	0.474	-0.080- 1.028	2.8	0.09
Hispanic[a]	1.009	0.544- 1.473	**18.1**	**<.0001**
Other/unknown[a] race/ethnicity	0.638	0.114- 1.161	**5.7**	**0.02**
Rural[a]	-1.179	-1.621- -0.736	**27.2**	**<.0001**
Other psychotropics[a]	-0.173	-0.574- 0.227	0.7	0.40
Other mental health diagnosis[a]	0.592	0.348- 0.837	**22.5**	**<.0001**
Long-acting medications[a]	0.514	0.194- 0.833	**10.0**	**<.01**
Short-acting medications[a]	-0.258	-0.445- -0.071	**7.3**	**0.01**
Stimulants[a]	0.815	0.320- 1.310	**10.4**	**<.01**

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no other mental health diagnosis, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as a continuous variable in the model

Table 4.32: Zero-Inflated Poisson Regression: Comparison of ADHD-related outpatient hospital visits between the pharmacotherapy (RX) and combination (RX+PSY) groups (N = 10,255) – after controlling for covariates

Characteristics	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**-0.350**	**-0.390- -0.310**	**294.0**	**<.0001**
Covariates				
Age[b]	-0.053	-0.077- -0.028	**18.0**	**<.0001**
Pre-index psychiatric visits[b]	-0.005	-0.009- -0.001	**7.3**	**0.01**
Pre-index non-psychiatric visits[b]	0.015	0.011- 0.019	**47.1**	**<.0001**
Total pre-index costs[b]	0.000	0.000- 0.000	**50.1**	**<.0001**
Female[a]	0.018	-0.028- 0.063	0.6	0.45
African American[a]	-0.183	-0.267- -0.098	**18.0**	**<.0001**
Hispanic[a]	0.461	0.404- 0.518	**250.8**	**<.0001**
Other/unknown[a] race/ethnicity	0.199	0.124- 0.275	**26.8**	**<.0001**
Rural[a]	-0.311	-0.360- -0.263	**157.6**	**<.0001**
Other psychotropics[a]	0.050	-0.041- 0.140	1.2	0.28
Other mental health diagnosis[a]	0.362	0.318- 0.407	**252.5**	**<.0001**
Long-acting medications[a]	0.088	0.027- 0.149	**8.0**	**<.01**
Short-acting medications[a]	0.019	-0.028- 0.065	0.6	0.43
Stimulants[a]	-0.110	-0.195- -0.026	**6.5**	**0.01**

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no other mental health diagnosis, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as a continuous variable in the model

Table 4.33: Poisson Regression: Comparison of ADHD-related prescriptions between the pharmacotherapy (RX) and combination (RX+PSY) groups (N = 10,255) – after controlling for covariates

Characteristics	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	0.011	-0.004- 0.026	2.1	0.15
Covariates				
Age[b]	0.124	0.114- 0.133	**643.1**	**<.0001**
Pre-index psychiatric visits[b]	0.000	-0.001- 0.001	0.1	0.82
Pre-index non-psychiatric visits[b]	-0.003	-0.005- -0.001	**10.1**	**<.01**
Total pre-index costs[b]	0.000	0.000- 0.000	**16.5**	**<.0001**
Female[a]	-0.056	-0.073- -0.039	**42.0**	**<.0001**
African American[a]	-0.192	-0.215- -0.168	**248.8**	**<.0001**
Hispanic[a]	-0.229	-0.248- -0.209	**521.6**	**<.0001**
Other/unknown[a] race/ethnicity	-0.147	-0.175- -0.120	**109.0**	**<.0001**
Rural[a]	0.021	0.004- 0.038	**5.6**	**0.02**
Other psychotropics[a]	-0.146	-0.181- -0.110	**65.5**	**<.0001**
Other mental health diagnosis[a]	-0.026	-0.043- -0.009	**9.4**	**<.01**
Long-acting medications[a]	0.605	0.578- 0.631	**1928.8**	**<.0001**
Short-acting medications[a]	0.301	0.284- 0.317	**1277.6**	**<.0001**
Stimulants[a]	0.208	0.171- 0.246	**118.91**	**<.0001**

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no other mental health diagnosis, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as a continuous variable in the model

4.6.3 Other mental health-related utilization

Objective 4c: *To determine and compare the healthcare utilization frequencies for other mental health-related office-based, inpatient, outpatient hospital, ED visits, and prescriptions between the RX and RX+PSY groups*

4.6.3.1 Other mental health-related office-based visits

H4c$_1$: *The number of other mental health-related office-based visits are significantly higher in the RX+PSY group as compared to the RX group* – **Rejected**

Table 4.34 presents a zero-inflated Poisson regression comparison of other mental health-related office-based visits between the pharmacotherapy and combination therapy groups in the overall cohort. After controlling for covariates, for patients with other mental health-related office-based visits, the expected number of other mental health-related office-based visits in the pharmacotherapy group was 1.256 times [exp (0.228)] the expected number of other mental health-related office-based visits in the combination therapy group (β = 0.228, x^2= 473.6, p < 0.0001). Thus, among those who have other mental health-related office-based visits, being in the pharmacotherapy group increases the expected number of other mental health-related office-based visits by 25.6%, holding other covariates constant, and this is statistically significant (p < 0.0001).

As for the covariates, patients with higher age, females, rural area residences, and short-acting medication users were significantly associated with a lower number of other mental health-related office-based visits. Conversely, patients with higher pre-index psychiatric visits, pre-index non-psychiatric visits, total pre-index costs, Hispanics, African American, other/unknown race race/ethnicity, and using other psychotropics were significantly associated with a higher number of other mental health-related office-based visits. The unit increments on

the scale for total pre-index costs were relatively small; therefore, a one unit change in pre-index costs may result in a very small change in post-index utilization.

4.6.3.2 Other mental health-related inpatient visits

***H4c$_2$**: The number of other mental health-related inpatient visits are significantly higher in the RX+PSY group as compared to the RX group* – **Rejected**

Table 4.35 presents a zero-inflated Poisson regression comparison of other mental health-related inpatient visits between pharmacotherapy and combination therapy groups in the overall cohort. After controlling for covariates, for patients with other mental health-related inpatient visits, the expected number of other mental health-related inpatient visits in the pharmacotherapy group was 1.735 times [exp (0.551)] the expected number of other mental health-related inpatient visits in the combination therapy group (β = 0.551, x^2= 6.6, p = 0.01). Thus, among those who have other mental health-related inpatient visits, being in the pharmacotherapy group increases the expected number of other mental health-related inpatient visits by 73.5%, holding other covariates constant, and this is statistically significant (p < 0.0001).

As for the covariates, rural residence status was significantly associated with a lower number of other mental health-related inpatient visits. Conversely, patients with higher pre-index psychiatric visits, pre-index non-psychiatric visits, total pre-index costs, African American race/ethnicity, and short-acting medication use were significantly associated with a higher number of other mental health-related inpatient visits. The unit increments on the scale for total pre-index costs were relatively small; therefore, a one unit change in pre-index costs may result in a very small change in post-index utilization.

4.6.3.3 Other mental health-related outpatient hospital visits

***H4c$_3$**: The number of other mental health-related outpatient hospital visits are significantly higher in the RX+PSY group as compared to the RX group* – **Failed to reject**

Table 4.36 presents a zero-inflated Poisson regression comparison of other mental health-related outpatient hospital visits between the pharmacotherapy and combination therapy groups in the overall cohort. After controlling for covariates, for patients with other mental health-related outpatient hospital visits, the expected number of other mental health-related inpatient visits in the pharmacotherapy group was 0.981 times [exp (-0.019)] the expected number of other mental health-related outpatient hospital visits in the combination therapy group (β = -0.019; x^2= 4.4; p = 0.04). Thus, among those who have other mental health-related outpatient hospital visits, being in the pharmacotherapy group decreases the expected number of other mental health-related outpatient hospital visits by 1.9%, holding other covariates constant, and this is statistically significant (p < 0.0001).

As for the covariates, patients with higher age, higher pre-index psychiatric visits, females, African American, rural area residents, and long- and short-acting medication users were significantly associated with lower other mental health-related outpatient hospital visits. Conversely, patients with higher pre-index non-psychiatric visits, total pre-index costs, Hispanic or other/unknown race/ethnicity, using other psychotropics, and stimulants were significantly associated with higher number of other mental health-related outpatient hospital visits. The unit increments on the scale for total pre-index costs were relatively small; therefore, a one unit change in pre-index costs may result in a very small change in post-index utilization.

4.6.3.4 Other mental health-related ED visits

***H4c$_4$**: The number of other mental health-related ED visits are significantly higher in the RX+PSY group as compared to the RX group* – **Could not test**

Since the number of events in both treatment groups was mostly zero, this hypothesis could not be tested.

4.6.3.5 Other mental health-related prescriptions

***H4c$_5$:** The number of other mental health-related prescriptions are significantly higher in the RX+PSY group as compared to the RX group* — **Failed to reject**

Table 4.37 presents a zero-inflated Poisson regression comparison of other mental health-related prescriptions between the pharmacotherapy and combination therapy groups in the overall cohort. After controlling for covariates, for patients with other mental health-related prescriptions, the expected number other mental health-related prescriptions in the pharmacotherapy group was 0.909 times [exp (-0.095)] the expected number of other mental health-related prescriptions in the combination therapy group (β = -0.095; x^2= 39.9; p <0.0001). Thus, among those who have other mental health-related prescriptions, being in the pharmacotherapy group decreases the expected number of other mental health-related prescriptions by 9.1%, holding other covariates constant, and this is statistically significant (p < 0.0001).

As for the covariates, Hispanic, African American race/ethnicity, other psychotropic users, short-acting, and stimulant medication users were significantly associated with a lower number of other mental health-related prescriptions. Conversely, patient with higher age and long-acting medication users were significantly associated with a higher number of other mental

health-related prescriptions. The unit increments on the scale for total pre-index costs were relatively small; therefore, a one unit change in pre-index costs may result in a very small change in post-index utilization.

Table 4.34: Zero-Inflated Poisson Regression: Comparison of other mental health-related office-based visits between the pharmacotherapy (RX) and combination (RX+PSY) groups (N = 10,255) – after controlling for covariates

Characteristics	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**0.228**	**0.208- 0.249**	**473.6**	**<.0001**
Covariates				
Age[b]	-0.097	-0.108- -0.085	**287.7**	**<.0001**
Pre-index psychiatric visits[b]	0.029	0.029- 0.029	**22303.3**	**<.0001**
Pre-index non-psychiatric visits[b]	0.017	0.015- 0.018	**383.3**	**<.0001**
Total pre-index costs[b]	0.000	0.000- 0.000	**48.8**	**<.0001**
Female[a]	-0.201	-0.225- -0.176	**259.3**	**<.0001**
African American[a]	0.229	0.179- 0.280	**78.5**	**<.0001**
Hispanic[a]	0.204	0.165- 0.243	**106.2**	**<.0001**
Other/unknown[a] race/ethnicity	0.379	0.336- 0.421	**309.8**	**<.0001**
Rural[a]	-0.157	-0.187- -0.126	**101.2**	**<.0001**
Other psychotropics[a]	0.177	0.114- 0.241	**29.5**	**<.0001**
Long-acting medications[a]	0.007	-0.022- 0.035	0.2	0.65
Short-acting medications[a]	-0.043	-0.066- -0.019	**12.5**	**<.01**
Stimulants[a]	0.041	-0.008- 0.090	**2.6**	**0.10**

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as a continuous variable in the model;

Excluded other mental health diagnosis since the outcome was defined based on other mental health diagnosis variable

Table 4.35: Zero-Inflated Poisson Regression: Comparison of other mental health-related inpatient visits between the pharmacotherapy (RX) and combination (RX+PSY) groups (N = 10,255) – after controlling for covariates

Characteristics	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**0.551**	**0.130- 0.972**	**6.6**	**0.01**
Covariates				
Age[b]	0.105	-0.140- 0.350	0.7	0.40
Pre-index psychiatric visits[b]	0.045	0.016- 0.073	**9.5**	**<.01**
Pre-index non-psychiatric visits[b]	0.068	0.024- 0.112	**9.2**	**<.01**
Total pre-index costs[b]	0.000	-0.000- 0.000	**4.5**	**0.03**
Female[a]	0.111	-0.326- 0.547	0.3	0.62
African American[a]	1.258	0.171- 2.344	**5.1**	**0.02**
Hispanic[a]	0.370	-0.406- 1.146	0.9	0.35
Other/unknown[a] race/ethnicity	-0.302	-1.316- 0.713	0.3	0.56
Rural[a]	-2.018	-3.068- -0.968	**14.2**	**<.01**
Other psychotropics[a]	-1.706	-4.248- 0.836	1.7	0.19
Long-acting medications[a]	0.145	-0.332- 0.621	0.4	0.55
Short-acting medications[a]	1.054	0.490- 1.618	**13.4**	**<.01**
Stimulants[a]	0.377	-0.644- 1.398	0.5	0.47

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as a continuous variable in the model;

Excluded other mental health diagnosis since the outcome was defined based on other mental health diagnosis variable

Table 4.36: Zero-Inflated Poisson Regression: Comparison of other mental health-related outpatient hospital visits between the pharmacotherapy (RX) and combination (RX+PSY) groups (N = 10,255) – after controlling for covariates

Characteristics	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**-0.019**	**-0.036- -0.001**	**4.4**	**0.04**
Covariates				
Age[b]	-0.037	-0.046- -0.027	**53.9**	**<.0001**
Pre-index psychiatric visits[b]	-0.006	-0.008- -0.005	**94.5**	**<.0001**
Pre-index non-psychiatric visits[b]	0.006	0.004- 0.008	**48.5**	**<.0001**
Total pre-index costs[b]	0.000	0.000- 0.000	**1898.5**	**<.0001**
Female[a]	-0.112	-0.134- -0.091	**104.6**	**<.0001**
African American[a]	-0.461	-0.540- -0.382	**130.7**	**<.0001**
Hispanic[a]	0.450	0.403- 0.497	**354.1**	**<.0001**
Other/unknown[a] race/ethnicity	0.290	0.238- 0.342	**118.6**	**<.0001**
Rural[a]	-0.584	-0.625- -0.543	**773.5**	**<.0001**
Other psychotropics[a]	0.144	0.095- 0.193	**33.6**	**<.0001**
Long-acting medications[a]	-0.077	-0.101- -0.052	**37.4**	**<.0001**
Short-acting medications[a]	-0.025	-0.046- -0.004	**5.3**	**0.02**
Stimulants[a]	0.156	0.112- 0.199	**49.4**	**<.0001**

*p < 0.05 (in bold); CI = Confidence Interval; x^2 = Chi-square;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as a continuous variable in the model;

Excluded other mental health diagnosis since the outcome was defined based on other mental health diagnosis variable

Table 4.37: Zero-Inflated Poisson Regression: Comparison of other mental health-related prescriptions between the pharmacotherapy (RX) and combination (RX+PSY) groups (N = 10,255) – after controlling for covariates

Characteristics	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**-0.095**	**-0.124- -0.066**	**39.9**	**<.0001**
Covariates				
Age[b]	0.021	0.004- 0.038	**5.7**	**0.02**
Pre-index psychiatric visits[b]	0.001	-0.001- 0.004	1.1	0.30
Pre-index non-psychiatric visits[b]	-0.001	-0.005- 0.003	0.3	0.57
Total pre-index costs[b]	0.000	0.000- 0.000	**148.0**	**<.0001**
Female[a]	-0.032	-0.065- 0.001	3.6	0.06
African American[a]	-0.118	-0.164- -0.073	**26.0**	**<.0001**
Hispanic[a]	-0.237	-0.276- -0.197	**138.6**	**<.0001**
Other/unknown[a] race/ethnicity	0.004	-0.043- 0.051	0.0	0.86
Rural[a]	-0.005	-0.041- 0.030	0.1	0.76
Other psychotropics[a]	-0.104	-0.185- -0.023	**6.3**	**0.01**
Long-acting medications[a]	0.081	0.031- 0.131	**10.1**	**<.01**
Short-acting medications[a]	-0.067	-0.100- -0.033	**14.8**	**<.01**
Stimulants[a]	-0.132	-0.190- -0.075	**20.3**	**<.0001**

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as a continuous variable in the model;

Excluded other mental health diagnosis since the outcome was defined based on other mental health diagnosis variable

4.7 Objective 5: Medical and prescription costs between the pharmacotherapy and combination therapy group

Objectives 5a-5c were to determine and compare healthcare cost between the pharmacotherapy and combination therapy groups after controlling for covariates. All costs were adjusted to 2013 dollar value using the medical consumer price index from the Bureau of Labor Statistics (BLS). In the adjusted analyses, medical, prescription, and total costs of preschoolers diagnosed with ADHD receiving pharmacotherapy was compared to medical, prescription, and total costs of preschoolers diagnosed with ADHD receiving combination therapy using separate generalized linear regression models for each cost category (i.e., all-cause, ADHD-related, and other mental health-related). A Modified Park test was conducted to identify the distribution and functional form for each cost category (Appendix VIII). A gamma distribution with a log-link was specified for all cost models.

Table 4.38 shows the results for mean medical, prescription, and total costs for the pharmacotherapy and combination therapy groups. The mean (±SD) all-cause medical costs were highest in the psychotherapy group $5,240.29 (±7,145.68) followed by the combination therapy group $4,163.19 (±6,235.77) and the pharmacotherapy group $3,402.86 (±6,149.12). Mean (±SD) all-cause prescription costs were highest in the combination therapy group $2,210.90 (±2,772.17) followed by the pharmacotherapy group $1,996.19 (±1,964.85), and the psychotherapy group $1,101.34 (±1,698.70). Mean all-cause total costs were highest in the combination therapy group $7,266.41 (±7,254.25) followed by the psychotherapy group $6,897.43 (±7,856.84), and the pharmacotherapy group $6,665.88 (±8,840.31).

The mean (±SD) ADHD-related medical costs were highest in combination therapy group $973.87 (±1,348.10) followed by the psychotherapy group $884.97 (±1,401.92) and the pharmacotherapy group $396.16 (±878.08). The mean (±SD) ADHD-related prescription costs were highest in the combination therapy group $1,151.03 (±893.16) followed by the pharmacotherapy group $1,112.26 (±901.72). The psychotherapy group did not have any ADHD-related medication use thus producing zero cost for the psychotherapy group.

The mean (±SD) other mental health-related medical costs were highest in the psychotherapy group $2,150.26 (±4,818.46) followed by the combination therapy group $1,508.27 (± 3,989.50) and the pharmacotherapy group $1,476.99 (±3,997.84). The mean (±SD) other mental health-related prescription costs were highest in the combination therapy group $327.31 (±1,026.28) followed by the psychotherapy group $213.96 (±903.13) and the pharmacotherapy group $185.08 (±875.03). The mean (±SD) other mental health-related total costs were highest in the psychotherapy group $2,401.31 (±4,936.03) followed by the combination therapy group $1,903.86 (±4,148.63) and pharmacotherapy group $1,820.69 (±4,274.53).

Table 4.38: Descriptive. All-cause, ADHD-related, and other mental health-related medical and prescription costs for pharmacotherapy, psychotherapy, and combination therapy groups

	Pharmacotherapy (n=5,904)			Psychotherapy (n=622)			Combination therapy (n=4,351)		
	Mean	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**
All-cause									
Medical costs[a]	$3,402.86	$6,149.12	$971.89	$5,240.29	$7,145.68	$2,282.51	$4,163.19	$6,235.77	$1,730.08
Prescription costs[b]	$1,996.19	$1,964.85	$1,632.04	$1,101.34	$1,698.70	$633.38	$2,210.90	$2,772.17	$1,761.07
Total costs[c]	$6,665.88	$8,840.31	$3,798.01	$6,897.43	$7,856.84	$3,698.10	$7,266.41	$7,254.25	$4,759.14
ADHD-related									
Medical costs[a]	$396.16	$878.08	$204.81	$884.97	$1,401.92	$466.91	$973.87	$1,348.10	$639.02
Prescription costs[b]	$1,112.26	$901.72	$930.61	$0.00	$0.00	$0.00	$1,151.03	$893.16	$979.64
Total costs[c]	$1,582.45	$1,337.77	$1,347.38	$1,001.94	$1,461.57	$571.57	$2,345.99	$1,766.00	$2,011.01
Other mental health-related									
Medical costs[a]	$1,476.99	$3,997.84	$0.00	$2,150.26	$4,818.46	$0.00	$1,508.27	$3,989.50	$0.00
Prescription costs[b]	$185.08	$875.03	$0.00	$213.96	$903.13	$0.00	$327.31	$1,026.28	$0.00
Total costs[c]	$1,820.69	$4,274.53	$15.03	$2,401.31	$4,936.03	$148.55	$1,903.86	$4,148.63	$110.43

SD = Standard deviation; ADHD = Attention Deficit Hyperactivity Disorder;

[a] Medical costs included office-based, outpatient hospital, inpatient, and emergency department costs for all-cause, ADHD-related, and other mental health-related categories;

[b] Prescription costs included prescription medication costs for all-cause, ADHD-related, and other mental health-related categories;

[c] Total costs included medical, prescription, and other medical costs (costs that could not be categorized in the medical cost categories);

Cost based on 2013 dollars

4.7.1 All-cause medical, prescription, and total costs

Objective 5a: *To determine and compare the all-cause medical (office-based, inpatient, outpatient hospital, and ED), prescription, and total costs between the RX and RX+PSY groups*

4.7.1.1 All-cause medical costs

H5a$_1$: *The all-cause medical costs are significantly higher in the RX+PSY group as compared to the RX group* – **Failed to reject**

Table 4.39 shows the results of a generalized linear regression model comparing all-cause medical costs between the pharmacotherapy and combination therapy groups in the overall cohort. All-cause medical costs in the pharmacotherapy group were 0.713 [exp(-0.338)] times those costs in the combination therapy group while controlling for covariates (β = -0.338; x^2= 290.1; p < 0.0001). Thus, all-cause medical costs in the pharmacotherapy group were 28.7% lower as compared to the all-cause medical costs in the combination therapy group.

As for the covariates, patient with higher age, females, and African American race/ethnicity were significantly associated with lower all-cause medical costs. Conversely, higher pre-index psychiatric visits, pre-index non-psychiatric visits, total pre-index costs, Hispanic, other/unknown race/ethnicity, rural residence status, other psychotropic drug use, and other mental health diagnosis were significantly associated with higher all-cause medical costs. The unit increments on the scale for total pre-index costs were relatively small; therefore, a one unit change in pre-index costs may result in a very small change in post-index utilization.

4.7.1.2 All-cause prescription costs

H5a$_2$: *The all-cause prescription costs are significantly higher in the RX+PSY group as compared to the RX group* – **Failed to reject**

Table 4.40 shows the results of a generalized linear regression model comparing all-cause prescription costs between the pharmacotherapy and combination therapy groups in the overall cohort. All-cause prescription costs in the pharmacotherapy group were 0.899 times [exp(-0.107)] those costs in the combination therapy group, while controlling for covariates (β = -0.107; x^2= 53.0; p < 0.0001). Thus, all-cause prescription costs in the pharmacotherapy group were 10.1% lower as compared to the all-cause prescription costs in the combination therapy group.

As for the covariates, patients with higher pre-index psychiatric visits, Hispanics, African Americans, rural area residents, and other psychotropic drug users were significantly associated with lower all-cause prescription costs. Conversely, higher pre-index non-psychiatric visits, total pre-index costs, other mental health diagnosis, and long-acting medications users were significantly associated with higher all-cause prescription costs. The unit increments on the scale for total pre-index costs were relatively small; therefore, a one unit change in pre-index costs may result in a very small change in post-index utilization.

4.7.1.3 All-cause total costs

H5a$_3$: *The all-cause total costs are significantly higher in the RX+PSY group as compared to the RX group* – **Failed to reject**

Table 4.41 shows the results of a generalized linear regression model comparing all-cause total costs between the pharmacotherapy and combination therapy groups in the overall cohort. All-cause total costs in the pharmacotherapy group were 0.841 times [exp(-0.173)] those costs in the combination therapy group, while controlling for covariates (β = -0.173; x^2= 182.0; p

< 0.0001). Thus, all-cause total costs in the pharmacotherapy group were 15.9% lower as compared to the all-cause total costs in the combination therapy group.

As for the covariates, patient with higher age, females, African American, and residing in rural or unknown area status were significantly associated with lower all-cause total costs. Conversely, higher pre-index non-psychiatric visits, total pre-index costs, Hispanic, and other/unknown race/ethnicity, other mental health diagnosis, and long-acting medications use were significantly associated with higher all-cause total costs. The unit increments on the scale for total pre-index costs were relatively small; therefore, a one unit change in pre-index costs may result in a very small change in post-index utilization.

Table 4.39: Generalized linear model: Comparison of all-cause medical costs between the pharmacotherapy (RX) and combination (RX+PSY) groups (N = 10,255) – after controlling for covariates

Characteristics	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**-0.338**	**-0.377- -0.299**	**290.1**	**<.0001**
Covariates				
Age[b]	-0.142	-0.166- -0.119	**138.8**	**<.0001**
Pre-index psychiatric visits[b]	0.004	0.001- 0.008	**7.4**	**0.01**
Pre-index non-psychiatric visits[b]	0.052	0.047- 0.058	**308.1**	**<.0001**
Total pre-index costs[b]	0.000	0.000- 0.000	**684.9**	**<.0001**
Female[a]	-0.053	-0.096- -0.010	**5.7**	**0.02**
African American[a]	-0.121	-0.185- -0.058	**14.2**	**<.01**
Hispanic[a]	0.346	0.290- 0.401	**148.6**	**<.0001**
Other/Unknown[a] race/ethnicity	0.330	0.257- 0.404	**77.1**	**<.0001**
Rural[a]	0.131	0.083- 0.179	**28.6**	**<.0001**
Other psychotropics[a]	0.205	0.114- 0.295	**19.6**	**<.0001**
Other mental health diagnosis[a]	1.011	0.965- 1.057	**1859.8**	**<.0001**
Long-acting medications[a]	0.012	-0.050- 0.074	0.1	0.71
Short-acting medications[a]	0.019	-0.027- 0.064	0.7	0.42
Stimulants[a]	0.039	-0.046- 0.125	0.8	0.37

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square; Generalized linear model with gamma distribution and log-link function;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no other mental health diagnosis, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as continuous variable in the model;

Medical costs included all-cause office-based, outpatient hospital, inpatient, and emergency department costs

Table 4.40: Generalized linear model: Comparison of all-cause prescription costs between the pharmacotherapy (RX) and combination therapy (RX+PSY) groups (N = 10,255) – after controlling for covariates

Characteristics	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**-0.107**	**-0.136- -0.078**	**53.0**	**<.0001**
Covariates				
Age[b]	0.016	-0.002- 0.033	3.0	0.08
Pre-index psychiatric visits[b]	-0.004	-0.006- -0.001	**9.8**	**<.01**
Pre-index non-psychiatric visits[b]	0.021	0.017- 0.024	**113.9**	**<.0001**
Total pre-index costs[b]	0.000	0.000- 0.000	**297.0**	**<.0001**
Female[a]	-0.029	-0.061- 0.003	3.2	0.07
African American[a]	-0.164	-0.210- -0.117	**46.9**	**<.0001**
Hispanic[a]	-0.214	-0.253- -0.175	**115.1**	**<.0001**
Other/Unknown[a] race/ethnicity	-0.048	-0.103- 0.006	3.1	0.08
Rural[a]	-0.150	-0.184- -0.116	**75.6**	**<.0001**
Other psychotropics[a]	-0.115	-0.182- -0.047	**11.1**	**<.01**
Other mental health diagnosis[a]	0.089	0.057- 0.120	**30.6**	**<.0001**
Long-acting medications[a]	0.446	0.400- 0.492	**358.8**	**<.0001**
Short-acting medications[a]	0.021	-0.012- 0.055	1.5	0.22
Stimulants[a]	0.029	-0.035- 0.092	0.8	0.37

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square; Generalized linear model with gamma distribution and log-link function;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no other mental health diagnosis, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as continuous variable in the model;

Prescription costs included prescription medication costs for all the medications (ADHD-related and non-ADHD related)

Table 4.41: Generalized linear model: Comparison of all-cause total costs between the pharmacotherapy (RX) and combination therapy (RX+PSY) groups (N = 10,255) – after controlling for covariates

Characteristics	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**-0.173**	**-0.198- -0.148**	**182.0**	**<.0001**
Covariates				
Age[b]	-0.082	-0.098- -0.067	**108.9**	**<.0001**
Pre-index psychiatric visits[b]	0.001	-0.001- 0.003	0.6	0.42
Pre-index non-psychiatric visits[b]	0.018	0.015- 0.021	**113.0**	**<.0001**
Total pre-index costs[b]	0.000	0.000- 0.000	**1312.1**	**<.0001**
Female[a]	-0.049	-0.077- -0.021	**11.9**	**<.01**
African American[a]	-0.120	-0.161- -0.080	**33.4**	**<.0001**
Hispanic[a]	0.051	0.016- 0.085	**8.2**	**<.01**
Other/Unknown[a] race/ethnicity	0.083	0.036- 0.131	**11.9**	**<.01**
Rural[a]	-0.186	-0.216- -0.156	**147.5**	**<.0001**
Other psychotropics[a]	-0.009	-0.067- 0.050	0.1	0.77
Other mental health diagnosis[a]	0.604	0.575- 0.632	**1703.1**	**<.0001**
Long-acting medications[a]	0.167	0.127- 0.207	**67.1**	**<.0001**
Short-acting medications[a]	0.024	-0.005- 0.054	2.6	0.11
Stimulants[a]	0.014	-0.041- 0.070	0.3	0.61

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square; Generalized linear model with gamma distribution and log-link function;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no other mental health diagnosis, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as continuous variable in the model;

Total costs included total of all-cause medical costs, prescription costs and other costs

4.7.2 ADHD-related medical, prescription, and total costs

Objective 5b: *To determine and compare the ADHD-related medical (office-based, inpatient, outpatient hospital, and ED), prescription, and total costs between the RX and RX+PSY groups*

4.7.2.1 ADHD-related medical costs

$H5b_1$: *The ADHD-related medical costs are significantly higher in the RX+PSY group as compared to the RX group* – **Failed to reject**

Table 4.42 shows the results of a generalized linear regression model comparing ADHD-related medical costs between the pharmacotherapy and combination therapy groups in the overall population. ADHD-related medical costs in the pharmacotherapy group were 0.446 times [exp(-0.808)] those costs in the combination therapy group, while controlling for covariates (β = -0.808; x^2= 1,661.9; p <.0001). Thus, ADHD-related medical costs in the pharmacotherapy group were 55.4% lower as compared to the ADHD-related medical costs in the combination therapy group.

As for the covariates, patients with higher age and higher pre-index psychiatric visits were significantly associated with lower ADHD-related medical costs. Conversely, higher pre-index non-psychiatric visits, total pre-index costs, Hispanics, and other/unknown race/ethnicity, rural area residence status, other mental health diagnosis, long- and short-acting medication users, and stimulant medication users were associated with higher ADHD-related medical costs. The unit increments on the scale for total pre-index costs were relatively small; therefore, a one unit change in pre-index costs may result in a very small change in post-index utilization.

4.7.2.2 ADHD-related prescription costs

H5b$_2$: *The ADHD-related prescription costs are significantly higher in the RX+PSY group as compared to the RX group* – **Failed to reject**

Table 4.43 shows the results of a generalized linear regression model comparing ADHD-related prescription costs between the pharmacotherapy and combination therapy groups in the overall cohort. ADHD-related prescription costs in the pharmacotherapy group were 0.966 times [exp(-0.035)] those costs in the combination therapy group, while controlling for covariates (β = -0.035; x^2= 4.5; p = 0.03). Thus, ADHD-related prescription costs in the pharmacotherapy group were 3.4% lower as compared to the ADHD-related prescription costs in the combination therapy group.

As for the covariates, female, African American, Hispanic, other/unknown race/ethnicity, rural residence status, and other psychotropic drug use were significantly associated with lower ADHD-related prescription costs. Conversely, patients with higher age, higher pre-index psychiatric visits, long- and short-acting medication users, and stimulant medication users were associated with higher ADHD-related prescription costs.

4.7.2.3 ADHD-related total costs

H5b$_3$: *The ADHD-related total costs are significantly higher in the RX+PSY group as compared to the RX group* – **Failed to reject**

Table 4.44 shows the results of a generalized linear regression model comparing ADHD-related total costs between the pharmacotherapy and combination therapy groups in the overall cohort. ADHD-related total costs in the pharmacotherapy group were 0.677 times [exp (-0.390)] those costs in the combination therapy group, while controlling for covariates (β = -0.390, x^2=

779.0, $p < .0001$). Thus, ADHD-related total costs in the pharmacotherapy group were 32.3% lower as compared to the ADHD-related total costs in the combination therapy group.

As for the covariates, females, Hispanics, African American, other/unknown race/ethnicity, rural residence status, and other psychotropic drug users were significantly associated with lower ADHD-related total costs. Conversely, patients with higher age, higher pre-index non-psychiatric visits, other mental health diagnosis, long- or short-acting, and stimulant medication users were significantly associated with higher ADHD-related total costs.

Table 4.42: Generalized linear model: Comparison of ADHD-related medical costs between the pharmacotherapy (RX) and combination therapy (RX+PSY) groups (N = 10,255) – after controlling for covariates

Characteristics	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**-0.808**	**-0.846- -0.769**	**1,661.9**	**<.0001**
Covariates				
Age[b]	-0.056	-0.081- -0.032	**20.7**	**<.0001**
Pre-index psychiatric visits[b]	-0.004	-0.007- -0.001	**6.1**	**0.01**
Pre-index non-psychiatric visits[b]	0.024	0.018- 0.029	**74.7**	**<.0001**
Total pre-index costs[b]	0.000	0.000- 0.000	**9.3**	**<.01**
Female[a]	-0.010	-0.053- 0.034	0.2	0.67
African American[a]	-0.023	-0.087- 0.040	0.5	0.47
Hispanic[a]	0.244	0.189- 0.299	**75.6**	**<.0001**
Other/Unknown[a] race/ethnicity	0.180	0.107- 0.254	**23.0**	**<.0001**
Rural[a]	0.149	0.102- 0.197	**38.6**	**<.0001**
Other psychotropics[a]	0.029	-0.062- 0.120	0.4	0.54
Other mental health diagnosis[a]	0.313	0.269- 0.357	**192.4**	**<.0001**
Long-acting medications[a]	0.180	0.117- 0.242	**31.8**	**<.0001**
Short-acting medications[a]	0.116	0.070- 0.162	**24.8**	**<.0001**
Stimulants[a]	0.118	0.031- 0.205	**7.0**	**0.01**

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square; Generalized linear model with gamma distribution and log-link function;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no other mental health diagnosis, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as continuous variable in the model;

[a] Medical costs included ADHD-related office-based, outpatient hospital, inpatient, and emergency department costs

Table 4.43: Generalized linear model: Comparison of ADHD-related prescription costs between the pharmacotherapy (RX) and combination therapy (RX+PSY) groups (N = 10,255) – after controlling for covariates

Characteristics	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**-0.035**	**-0.067- -0.003**	**4.5**	**0.03**
Covariates				
Age[b]	0.123	0.103- 0.143	**145.7**	**<.0001**
Pre-index psychiatric visits[b]	0.003	0.001- 0.006	**5.5**	**0.02**
Pre-index non-psychiatric visits[b]	0.002	-0.002- 0.006	0.7	0.41
Total pre-index costs[b]	0.000	0.000- 0.000	0.3	0.61
Female[a]	-0.080	-0.116- -0.044	**19.1**	**<.0001**
African American[a]	-0.213	-0.265- -0.160	**63.1**	**<.0001**
Hispanic[a]	-0.185	-0.228- -0.141	**68.5**	**<.0001**
Other/Unknown[a] race/ethnicity	-0.187	-0.248- -0.126	**36.1**	**<.0001**
Rural[a]	-0.055	-0.093- -0.017	**8.1**	**<.01**
Other psychotropics[a]	-0.236	-0.312- -0.161	**37.6**	**<.0001**
Other mental health diagnosis[a]	0.017	-0.018- 0.052	0.9	0.34
Long-acting medications[a]	0.811	0.759- 0.862	**942.3**	**<.0001**
Short-acting medications[a]	0.110	0.072- 0.148	**32.3**	**<.0001**
Stimulants[a]	0.165	0.094- 0.236	**20.8**	**<.01**

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square; Generalized linear model with gamma distribution and log-link function;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no other mental health diagnosis, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as continuous variable in the model

[a] Prescription costs included prescription costs for ADHD-related medications

Table 4.44: Generalized linear model: Comparison of ADHD-related total costs between the pharmacotherapy (RX) and combination therapy (RX+PSY) groups (N = 10,255) – after controlling for covariates

Characteristics	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**-0.390**	**-0.417- -0.363**	**779.0**	**<.0001**
Covariates				
Age[b]	0.064	0.047- 0.081	**53.9**	**<.0001**
Pre-index psychiatric visits[b]	-0.001	-0.003- 0.002	0.4	0.54
Pre-index non-psychiatric visits[b]	0.006	0.003- 0.010	**13.1**	**<.01**
Total pre-index costs[b]	0.000	0.000- 0.000	2.9	0.09
Female[a]	-0.056	-0.086- -0.026	**13.1**	**<.01**
African American[a]	-0.127	-0.171- -0.082	**31.0**	**<.0001**
Hispanic[a]	-0.070	-0.107- -0.032	**13.4**	**<.01**
Other/Unknown[a] race/ethnicity	-0.061	-0.112- -0.009	**5.3**	**0.02**
Rural[a]	-0.050	-0.082- -0.017	**9.1**	**<.01**
Other psychotropics[a]	-0.144	-0.208- -0.080	**19.3**	**<.0001**
Other mental health diagnosis[a]	0.124	0.094- 0.155	**64.8**	**<.0001**
Long-acting medications[a]	0.513	0.470- 0.557	**528.1**	**<.0001**
Short-acting medications[a]	0.102	0.070- 0.134	**38.5**	**<.0001**
Stimulants[a]	0.123	0.062- 0.183	**15.9**	**<.0001**

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square; Generalized linear model with gamma distribution and log-link function;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no other mental health diagnosis, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as continuous variable in the model;

Total costs included ADHD-related medical costs, prescription costs, and other ADHD-related medical costs

4.7.3 Other mental health-related medical, prescription, and total costs

Objective 5c: *To determine and compare the other mental health-related medical costs (office-based, inpatient, outpatient hospital, and ER), prescription costs, and total costs between the RX and RX+PSY groups*

4.7.3.1 Other mental health-related medical costs

H5c$_1$: *The other mental health-related medical costs are significantly higher in the RX+PSY group as compared to the RX group*- **Failed to reject**

Table 4.45 shows the results of a generalized linear regression model comparing other mental health-related medical costs between the pharmacotherapy and combination therapy groups in the overall cohort. Other mental health-related medical costs in the pharmacotherapy group were 0.691 times [exp(-0.370)] those costs in the combination therapy group, while controlling for covariates (β = -0.370, x^2= 1.1, p < 0.0001). Thus, other mental health-related medical costs in the pharmacotherapy group were 30.9% lower as compared to the other mental health-related medical costs in the combination therapy group.

As for the covariates, patients with higher age, females, and rural residence status were significantly associated with lower other mental health-related medical costs. Conversely, higher pre-index psychiatric visits, pre-index total costs, Hispanic, and other/unknown race/ethnicity were significantly associated with higher other mental health-related medical costs.

4.7.3.2 Other mental health-related prescription costs

H5c$_2$: *The other mental health-related prescription costs are significantly higher in the RX+PSY group as compared to the RX group*– **Failed to reject**

Table 4.46 shows the results of a generalized linear regression model comparing other mental health-related prescription costs between the pharmacotherapy and combination therapy groups in the overall cohort. Other mental health-related prescription costs in the pharmacotherapy group were 0.513 times [exp(-0.668)] those costs in the combination therapy group, while controlling for covariates (β = -0.668, x^2= 7.5, p < 0.0001). Thus, other mental health-related prescription costs in the pharmacotherapy group were 48.7% lower as compared to the other mental health-related prescription costs in the combination therapy group.

As for the covariates, patients with higher age, higher pre-index psychiatric and non-psychiatric visits, Hispanic race/ethnicity, and rural residence status were significantly associated with lower other mental health-related prescription costs. Conversely, higher total pre-index costs, other/unknown race/ethnicity, and long-acting medication users were significantly associated with higher other mental health-related prescription costs. The unit increments on the scale for total pre-index costs were relatively small; therefore, a one unit change in pre-index costs may result in a very small change in post-index utilization.

4.7.3.3 Other mental health-related total costs

H5c$_3$: *The other mental health-related total costs are significantly higher in the RX+PSY group as compared to the RX group–* **Failed to reject**

Table 4.47 shows the results of a generalized linear regression model comparing other mental health-related total costs between the pharmacotherapy and combination therapy groups

in the overall cohort. Other mental health-related total costs in the pharmacotherapy group were 0.633 times [exp(-0.458)] those costs in the combination therapy group, while controlling for covariates (β = -0.458, x^2= 6.8, p =0.03). Thus, other mental health-related total costs in the pharmacotherapy group were 36.7% lower as compared to the ADHD-related prescription costs in the combination therapy group.

As for the covariates, patient with higher age, females, and rural area residents were significantly associated with lower other mental health-related total costs. Conversely, higher pre-index psychiatric visits, total pre-index costs, Hispanic, and other/unknown race/ethnicity were significantly associated with higher other mental health-related total costs. The unit increments on the scale for total pre-index costs were relatively small; therefore, a one unit change in pre-index costs may result in a very small change in post-index utilization.

Table 4.45: Generalized linear model: Comparison of other mental health-related medical costs between the pharmacotherapy (RX) and combination therapy (RX+PSY) groups (N = 10,255) – after controlling for covariates

Parameter	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**-0.370**	**-0.544- -0.195**	**1.1**	**<.0001**
Covariates				
Age[b]	-0.416	-0.516- -0.317	**44.0**	**<.0001**
Pre-index psychiatric visits[b]	0.036	0.018- 0.053	**9.6**	**<.0001**
Pre-index non-psychiatric visits[b]	0.019	-0.006- 0.044	0.4	0.14
Total pre-index costs[b]	0.000	0.000- 0.000	**291.1**	**<.0001**
Female[a]	-0.307	-0.498- -0.115	**16.0**	**<.01**
African American[a]	0.278	-0.010- 0.566	3.8	0.06
Hispanic[a]	1.232	0.969- 1.494	**21.7**	**<.0001**
Other/Unknown[a] race/ethnicity	1.121	0.793- 1.450	**11.4**	**<.0001**
Rural[a]	-0.562	-0.796- -0.328	**73.4**	**<.0001**
Other psychotropics[a]	0.059	-0.355- 0.474	1.4	0.78
Long-acting medications[a]	-0.118	-0.391- 0.155	2.0	0.40
Short-acting medications[a]	-0.018	-0.219- 0.182	2.0	0.86
Stimulants[a]	0.017	-0.361- 0.395	0.4	0.93

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square; Generalized linear model with gamma distribution and log-link function

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as continuous variable in the model;

Medical costs included other mental health-related office-based, outpatient hospital, inpatient, and emergency department costs;

Excluded other mental health diagnosis because the outcome was defined based on the other mental health diagnosis variable

Table 4.46: Generalized linear model: Comparison of other mental health-related prescription costs between the pharmacotherapy (RX) and combination therapy (RX+PSY) groups (N = 10,255) – after controlling for covariates

Parameter	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**-0.668**	**-0.842- -0.495**	**7.5**	**<.0001**
Covariates				
Age[b]	-0.206	-0.307- -0.106	**0.1**	**<.0001**
Pre-index psychiatric visits[b]	-0.021	-0.036- -0.006	**8.9**	**0.01**
Pre-index non-psychiatric visits[b]	-0.026	-0.045- 0.006	**2.5**	**0.01**
Total pre-index costs[b]	0.000	0.000- 0.000	**32.4**	**<.0001**
Female[a]	-0.119	-0.304- 0.067	2.6	0.21
African American[a]	0.072	-0.204- 0.347	0.5	0.61
Hispanic[a]	-0.569	-0.790- -0.347	**15.1**	**<.0001**
Other/Unknown[a] race/ethnicity	0.432	0.118- 0.747	**3.9**	**0.01**
Rural[a]	-0.270	-0.468- -0.071	**5.4**	**0.01**
Other psychotropics[a]	0.063	-0.340- 0.466	2.2	0.76
Long-acting medications[a]	0.392	0.128- 0.657	**1.6**	**<.01**
Short-acting medications[a]	-0.089	-0.286- 0.106	19.4	0.37
Stimulants[a]	-0.247	-0.613- 0.120	1.4	0.19

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square; Generalized linear model with gamma distribution and log-link function;

[a] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[b] Recorded as continuous variable in the model;

Prescription costs included prescription costs for other mental health-related medications (antipsychotics, anticonvulsants, anxiolytics, antimanic, and antidepressants);

Excluded other mental health diagnosis because the outcome was defined based on the other mental health diagnosis variable

Table 4.47: Generalized linear model: Comparison of other mental health-related total costs between the pharmacotherapy (RX) and combination therapy (RX+PSY) groups (N = 10,255) – after controlling for covariates

Parameter	Estimate	95% CI	x^2	p-value*
Treatment group[a]				
Pharmacotherapy	**-0.458**	**-0.591- -0.326**	**6.8**	**0.03**
Covariates				
Age[b]	-0.344	-0.419- -0.269	**89.3**	**<.0001**
Pre-index psychiatric visits[b]	0.027	0.015- 0.039	**25.1**	**<.0001**
Pre-index non-psychiatric visits[b]	0.005	-0.012- 0.023	10.1	0.54
Total pre-index costs[b]	0.000	0.000- 0.000	**476.5**	**<.0001**
Female[a]	-0.282	-0.423- -0.141	**30.1**	**<.0001**
African American[a]	-0.172	-0.039- 0.383	0.2	0.11
Hispanic[a]	0.501	0.320- 0.681	**91.9**	**<.0001**
Other/Unknown[a] race/ethnicity	0.632	0.394- 0.870	**38.8**	**<.0001**
Rural[a]	-0.632	-0.798- -0.468	**25.6**	**<.0001**
Other psychotropics[a]	-0.125	-0.430- 0.181	0.8	0.42
Long-acting medications[a]	-0.055	-0.257- 0.147	3.8	0.59
Short-acting medications[a]	-0.026	-0.175- 0.123	3.7	0.73
Stimulants[a]	0.086	-0.193- 0.366	0.9	0.54

*p < 0.05 (in bold); CI = Confidence Interval; x^2= Chi-square; Generalized linear model with gamma distribution and log-link function;
[a] Reference categories: Combination therapy group, males, whites, urban residents, no psychotropic use, no long-acting medication use, no short-acting medication use, and non-stimulant use;
[b] Recorded as continuous variable in the model;
Total costs included other mental health-related medical costs, prescription costs, and other costs

4.7.4 Cost estimates

Table 4.48 shows the adjusted mean cost estimates of all-cause, ADHD-related, and other mental health-related costs for the pharmacotherapy and combination therapy group. The adjusted mean all-cause (medical, prescription, and total) costs, ADHD-related (medical and total) costs, and other mental health-related (medical, prescription, and total) costs were significantly higher in the combination therapy group as compared to pharmacotherapy group.

Table 4.48: Generalized linear model. Mean adjusted cost estimates for all-cause, ADHD-related, and other mental health-related medical, prescription, and total costs between the pharmacotherapy and combination therapy groups

Characteristics	Pharmacotherapy (n=5,904)		Combination therapy (n = 4,351)		z	p-value
	Mean	SE	Mean	SE		
All-cause costs						
Medical costs[a]	$3,233.23	$61.95	$4,554.06	$100.04	**-13.46**	**<.0001**
Prescription costs[b]	$2,019.20	$25.33	$2,249.70	$32.81	**-5.69**	**<.0001**
Total costs[c]	$6,465.85	$72.60	$7,660.07	$100.75	**-10.39**	**<.0001**
ADHD-related costs						
Medical costs[a]	$400.97	$9.55	$993.04	$27.41	**-19.68**	**<.0001**
Prescription costs[b]	$1,109.36	$12.93	$1,150.86	$19.42	**-2.08**	**0.04**
Total costs[c]	$1,587.26	$17.77	$2,351.86	$30.60	**-21.78**	**<.0001**
Other mental health-related costs						
Medical costs[a]	$1,579.29	$240.78	$2,285.66	$373.11	**-3.34**	**<.01**
Prescription costs[b]	$183.46	$11.07	$357.93	$25.81	**-6.38**	**<.0001**
Total costs[c]	$1,594.71	$108.77	$2,522.20	$202.58	**-5.74**	**<.0001**

SE = Standard Error; ADHD = Attention Deficit Hyperactivity Disorder;
[a] Medical costs included office-based, outpatient hospital, inpatient, and emergency department costs for all-cause, ADHD-related, and other mental health-related categories;
[b] Prescription costs included prescription medication costs for all-cause, ADHD-related, and other mental health-related categories;
[c] Total costs included medical, prescription, and other medical costs
Costs were estimated based on 2013 dollars

The results of the hypotheses tests conducted for the study are summarized in **Table 4.49**.

Table 4.49: Results of hypothesis testing

Objectives and Hypotheses	Test results
Objective 1 – To determine the annual prevalence and incidence of ADHD in the Texas Medicaid preschool population	
1a: To determine the treated **prevalence** of ADHD in preschoolers <6 years of age enrolled in Texas Medicaid	No hypothesis
1b: To determine the treated **incidence** of ADHD in preschoolers <6 years of age enrolled in Texas Medicaid	No hypothesis
Objective 2 – To determine and compare the baseline characteristics between RX, PSY, and RX+PSY groups	
2a: To determine and compare the baseline demographic, clinical, and prior utilization characteristics between the pharmacotherapy only (RX), psychotherapy only (PSY), and pharmacotherapy + psychotherapy combined (RX+PSY) groups	No hypothesis
Objective 3 – To assess the treatment patterns of preschoolers (2 to <6 years of age) with ADHD	
3a: To determine the time to "first pharmacotherapy," "first psychotherapy," and "first combination therapy"	No hypothesis
3b: To compare the time to first pharmacotherapy, psychotherapy, and combination therapy in preschoolers with ADHD and to compare time to pharmacotherapy with respect to gender, race/ethnicity, medication duration of action	
$H_0(3b)_1$: There is no difference in time-to-initiation of pharmacotherapy ("first RX"), psychotherapy ("first PSY"), and "first combination therapy"	Rejected
$H_0(3b)_2$: There is no significant difference in the **time-to-initiation of RX in male vs. female** ADHD patients	Failed to reject
$H_0(3b)_3$: There is no significant difference in the **time-to-initiation of RX in different race/ethnicity groups** diagnosed with ADHD	Rejected for Hispanic vs. White and for Others/unknown vs. White
$H_0(3b)_4$: There is no significant difference in the **time-to-initiation of RX with respect to long-acting (LA) vs. short-acting (SA) medications** in ADHD patients	Rejected
$H_0(3b)_5$: There is no significant difference in the **time-to-initiation of RX by physician specialty**	Could not test
3c: To assess the factors associated with receiving RX, PSY, or RX+PSY, after controlling for covariates	No hypothesis
3d: To compare adherence, persistence, augmentation, and switching between the RX and the RX+PSY groups	
$H_0(3d)_1$: There is no significant difference in the **likelihood of medication adherence** between the RX and the RX+PSY groups, after controlling for covariates	Rejected
$H_0(3d)_2$: There is no significant difference in **time to discontinuation** between the RX and the RX+PSY groups, after controlling for covariates	Failed to reject
$H_0(3d)_3$: There is no significant difference in the **likelihood of medication augmentation** between the RX and the RX+PSY groups, after controlling for covariates	Rejected

Table 4.49: Results of hypothesis testing (continued)

Objectives and Hypotheses	Test results
$H_0(3d)_4$: There is no significant difference in the **likelihood of switching** between the RX and the RX+PSY groups, after controlling for covariates	Rejected
Objective 4 – To determine and compare healthcare utilization between the RX and the RX+PSY groups	
4a: To determine and compare the healthcare utilization frequencies for all-cause office-based, inpatient, outpatient hospital, emergency department (ED) visits, and prescriptions between the RX and the RX+PSY groups	
$H(4a)_1$: The number of **all-cause office-based visits** is significantly higher in the RX+PSY group as compared to the RX group	Failed to reject
$H(4a)_2$: The number of **all-cause inpatient visits** is significantly higher in the RX+PSY group as compared to the RX group	Failed to reject
$H(4a)_3$: The number of **all-cause outpatient hospital visits** is significantly higher in the RX+PSY group as compared to the RX group	Failed to reject
$H(4a)_4$: The number of **all-cause ED visits** is significantly higher in the RX+PSY group as compared to the RX group	Failed to reject
$H(4a)_5$: The number of **all-cause prescriptions** is significantly higher in the RX+PSY group as compared to the RX group	Failed to reject
4b: To determine and compare the healthcare utilization frequencies for ADHD-related office-based, inpatient, outpatient hospital, ED visits, and prescriptions between the RX and RX+PSY groups	
$H(4b)_1$: The number of **ADHD-related office-based visits** is significantly higher in the RX+PSY group as compared to the RX group	Failed to reject
$H(4b)_2$: The number of **ADHD-related inpatient visits** is significantly higher in the RX+PSY group as compared to the RX group	Failed to reject
$H(4b)_3$: The number of **ADHD-related outpatient hospital visits** is significantly higher in the RX+PSY group as compared to the RX group	Failed to reject
$H(4b)_4$: The number of **ADHD-related ED visits** is significantly higher in the RX+PSY group as compared to the RX group	Could not test due to small sample size
$H(4b)_5$: The number of **ADHD-related prescriptions** is significantly higher in the RX+PSY group as compared to the RX group	Rejected

Table 4.49: Results of hypothesis testing (continued)

Objectives and Hypotheses	Test results
4c: To determine and compare the healthcare utilization frequencies for other mental health-related office-based, inpatient, outpatient hospital, ED visits, and prescriptions between the RX and RX+PSY groups	
H(4c)$_1$: The number of **other mental health-related office-based visits** is significantly higher in the RX+PSY group as compared to the RX group	Rejected
H(4c)$_2$: The number of **other mental health-related inpatient visits** is significantly higher in the RX+PSY group as compared to the RX group	Rejected
H(4c)$_3$: The number of **other mental health-related outpatient hospital visits** is significantly higher in the RX+PSY group as compared to the RX group	Failed to reject
H(4c)$_4$: The number of **other mental health-related ED visits** is significantly higher in the RX+PSY group as compared to the RX group	Could not test
H(4a)$_5$: The number of **other mental health-related prescriptions** is significantly higher in the RX+PSY group as compared to the RX group	Failed to reject
Objective 5: To determine and compare healthcare costs between the RX and the RX+PSY groups	
5a: To determine and compare the all-cause medical (office-based, inpatient, outpatient hospital, and ED), prescription, and total costs between the RX and RX+PSY groups	
H(5a)$_1$: The **all-cause medical costs** are significantly higher in the RX+PSY group as compared to the RX group	Failed to reject
H(5a)$_2$: The **all-cause prescription costs** are significantly higher in the RX+PSY group as compared to the RX group	Failed to reject
H(5a)$_3$: The **all-cause total costs** are significantly higher in the RX+PSY group as compared to the RX group	Failed to reject
5b: To determine and compare the ADHD-related medical (office-based, inpatient, outpatient hospital, and ED), prescription, and total costs between the RX and RX+PSY groups	
H(5b)$_1$: The **ADHD-related medical costs** are significantly higher in the RX+PSY group as compared to the RX group	Failed to reject
H(5b)$_2$: The **ADHD-related prescription costs** are significantly higher in the RX+PSY group as compared to the RX group	Failed to reject
H(5b)$_3$: The **ADHD-related total costs** are significantly higher in the RX+PSY group as compared to the RX group	Failed to reject
5c: To determine and compare the other mental health-related medical costs (office-based, inpatient, outpatient hospital, and ED), prescription drug costs, and total costs between the RX and RX+PSY groups	
H(5c)$_1$: The **other mental health-related medical costs** are significantly higher in the RX+PSY group as compared to the RX group	Failed to reject
H(5c)$_2$: The **other mental health-related prescription costs** are significantly higher in the RX+PSY group as compared to the RX group	Failed to reject
H(5c)$_3$: The **other mental health-related total costs** are significantly higher in the RX+PSY group as compared to the RX group	Failed to reject

CHAPTER 5: DISCUSSION

Chapter Overview

This chapter provides a detailed discussion of the study results. The chapter begins with a brief review of the study objectives. This is followed by a discussion of the study results, comparisons with previous research, and possible explanations for study findings. The chapter concludes with a discussion regarding study limitations, implications, and suggestions for future research.

5.1 Review of study objectives

In an attempt to contribute to the literature on ADHD treatment in preschoolers, the aim of the current study was to understand the prevalence, incidence, treatment patterns (i.e., adherence, persistence, augmentation, and switching), resource utilization (i.e., office-based, outpatient hospital, inpatient, emergency department visits, and prescriptions), and costs (i.e., medical, prescription, and total costs) of ADHD in preschoolers using paid claims dated between January 2008 and December 2013 in the Texas Medicaid dataset. Historically, the prevalence of ADHD in Texas has been higher than the national average and thus, it is important to understand the burden of ADHD in preschoolers.[37] Additionally, ADHD is among the conditions with the highest expenditures for Texas Medicaid making it important to study the factors associated with resource use and costs in this population.[123] Apart from being the first study to assess preschoolers with ADHD in Texas, to our knowledge, this is the only study providing a comprehensive overview and comparison of pharmacotherapy, psychotherapy, and combination therapy treatments.

5.2 Patient demographic, clinical, and prior utilization characteristics

In the sample of 10,877 preschoolers with ADHD in this study, the patient demographic, clinical, and prior utilization characteristics were similar in the overall and treatment pattern cohorts. According to the Centers for Disease Control (CDC), the average age of current ADHD diagnosis was reported to be 6.2 years in patients between 4 and 17 years of age with mild, moderate, and severe forms of ADHD.[37] The mean (± SD) age of ADHD diagnosis in the current study was estimated at 4.7 (± 0.9) years which is 1.5 years lower than the CDC estimate; however, it corresponded to the age of diagnosis reported by the CDC for severe forms of ADHD (4.4 years). Since the current study included preschoolers from 2 to < 6 years of age, it is likely that the difference in age ranges considered for the mean age calculations contributed to the lower age reported in the current study compared to the CDC estimate. It is also possible that patients in the current study were more severe, thus, being diagnosed at an early age; however, this relationship could not be evaluated because a direct measure of ADHD severity was not available in the dataset.

In our study, males (72.9%) comprised a much higher proportion of preschoolers diagnosed with ADHD as compared to females (27.1%), which is in agreement with previous studies using the Texas Medicaid dataset.[83,84] Although the predisposition to an ADHD diagnosis in males and females in the population is unknown, the higher proportion of males in the current study may be explained in part by differences in symptom presentation in males and females. Previous research provides evidence that males are more likely to be diagnosed with the hyperactive/impulsive ADHD subtype exhibiting more "externalizing symptoms" (i.e., running, hitting, and impulsivity), whereas females are more likely to be diagnosed with the inattentive

subtype exhibiting more "internalizing symptoms" (e.g., depression, anxiety, and low self-esteem).[124] The externalizing symptoms might be more obvious resulting in screening and diagnosis, which may explain the higher proportion of male patients observed in the current study.

With respect to race/ethnicity, the CDC reports that ADHD is more prevalent nationally in Whites followed by African Americans and other race/ethnicity groups.[125–127] In the current study, a majority of the preschoolers diagnosed with ADHD were Hispanic. A higher proportion of Hispanic preschoolers was not unexpected, as Hispanics represent the highest proportion of enrollees in the Texas Medicaid program. In addition, the proportion of Hispanics diagnosed with ADHD was similar to that found in a study conducted by Lawson et al. (2012) using Texas Medicaid data from 2006 to 2007 (52.3%).[84]

In the current study, ADHD patients were more likely to reside in urban areas as compared to rural areas. In a study conducted using the Medical Expenditure Panel Survey (MEPS) data, Anderson et al. (2013) reported that children residing in rural areas were more likely to be diagnosed with ADHD.[128] However, the authors emphasized that the differences did not persist after controlling for demographic characteristics.

ADHD is often associated with comorbid mental health conditions and treatments. In the current study, approximately 5% of the patients had other psychotropic medication use. Previous studies have also reported psychotropic medication use in preschoolers. In a study conducted to determine the prevalence of psychotropic drug use in preschool aged youth using multi-state Medicaid program data and salaried group model health maintenance organization (HMO) data, Zito et al. (2000) found that 1.23% (n = 1,865) of preschoolers between the ages of 2 and 4 were

being prescribed psychotropic medications. Similar trends have been reported in other studies conducted on the preschool population using US managed care and MarketScan Research datasets.[90,129,130] In a study using US managed care claims data, Van Brunt et al. (2005) reported the use of bupropion, antidepressants, antipsychotics, antimanics, and anxiolytics in preschool patients diagnosed with ADHD.[90] In a recent systematic review, Birnbaum et al. (2013) concluded that 30.5% of preschoolers treated with antipsychotics were reported to have a diagnosis of ADHD.[88] In a study examining trends of psychotropic drug utilization of Medicaid preschool patients diagnosed with ADHD, Fullerton et al. (2012) reported that the probability of filling at least one antipsychotic medication in 2005 was two times that in 1996.[131] Further exploration of psychotropic drug use in the preschool population will help uncover patterns of medication use. In addition to the psychotropic medication use, nearly one-third of the patients had other mental health diagnoses, which is in agreement with previous studies.[132,133]

Investigation of other factors related to ADHD treatments has been reported in the literature. The current study explored the treatment characteristics of preschoolers diagnosed with ADHD. A majority of the patients in the current study were taking long-acting (89.0%) medications whereas short-acting medications were prescribed in approximately 40% of the cases, which is consistent with previous studies conducted by Lawson et al. (2012) and Barner et al. (2011) using the Texas Medicaid dataset.[83,84] Similar to previous studies, patients in the current study also had a higher proportion of stimulant medication use than non-stimulant medications.[83,84] Studies have shown that simulants are associated with more favorable outcomes in alleviating the core symptoms of hyperactivity, impulsivity, inattentiveness, and associated aggressiveness exhibited in patients with ADHD. Therefore, stimulants may be a preferred choice of treatment even in the preschool population.

The mean numbers of pre-index psychiatric visits were similar in both the overall (1.4 ± 6.7) and the treatment pattern (1.8 ± 7.6) cohorts. The mean numbers of pre-index non-psychiatric visits were higher than the mean number of pre-index psychiatric visits in both cohorts (3.3 ± 4.4 vs. 4.6 ± 5.3). A study by Chan et al. (2002) conducted using Medical Expenditure Panel Survey (MEPS) data from 1996 estimated that the average number of outpatient visits for patients with ADHD was (5.97 ± 0.60), followed by home health (2.08 ± 2.04) visits and ED visits (0.23 ± 0.05).[134] In another study using a large not-for-profit staff model HMO dataset, Guevara et al. (2001) reported a higher number of primary care visits (3.84 ± 3.30), followed by mental health visits (1.35 ± 3.11) and ED visits (0.08 ± 0.33).[135] These studies, however, were conducted in the school-aged population and may not be directly comparable to our results. Although no known study has estimated costs in preschoolers before ADHD diagnosis, the current study estimated the mean total pre-index costs at $2,372.16 in the overall cohort and at $2,552.42 in the treatment pattern cohort.

5.3 Study objectives

The present study addressed five major objectives covering 33 hypotheses. A discussion for each objective is presented in the following sections.

5.3.1 Objective 1: Prevalence and incidence

***Objective 1a**: To determine the prevalence of ADHD in preschoolers <6 years of age enrolled in Texas Medicaid*

***Objective 1b:** To determine the incidence of ADHD in preschoolers <6 years of age enrolled in Texas Medicaid*

This part of the study provides insight into the prevalence and incidence of ADHD in preschoolers in a state Medicaid pediatric population. To summarize, the treated prevalence of ADHD in preschoolers rose steadily from 2008 to 2012; however, the treated incidence estimates were stable across those years. ADHD prevalence increased in Texas Medicaid preschoolers through the five study years, with an estimated 2.1, 3.9, 5.9, 7.6, and 8.5 cases per 1,000 preschool enrollees meeting inclusion criteria during 2008, 2009, 2010, 2011, and 2012, respectively. These estimates are lower than the most recent national estimates that reported a prevalence estimate of 11.0% in the national population and 10.1% in Texas among children and adolescents between 4 and 17 years of age.[37] A direct comparison seems unwarranted since the age range (< 6 years) of the population under consideration in the current study is different from the age range (4-17 years) reported by the CDC. Nonetheless, certain factors may help explain the differences. The lower prevalence rates found in the present study could be associated with challenges in establishing a correct diagnosis of ADHD in preschoolers since they have naturally high energy levels and impulsivity. Additionally, the extensive set of inclusion and exclusion criteria used in the current study were different from the methodology used by the CDC to

estimate prevalence. For instance, we required that the patients should be continuously enrolled with at least 2 medication claims for the entire year to be included in the prevalence and incidence estimates. This would have excluded those patients who received a diagnosis for ADHD and were not continuously enrolled or did not receive any medication for ADHD.

The incidence was estimated at 2.4, 2.6, 2.7, and 2.1 cases per 1,000 preschoolers (<6 years of age) for 2009, 2010, 2011, and 2012, respectively. The incidence estimates of ADHD in the preschool population were relatively stable and were lower than the incidence estimates reported by previous studies. A study assessing the incidence of psychiatric disorders using the Teen Health 2000 data revealed that the incidence of ADHD was 1.2%.[136] A meta-regression analysis of 135 studies by Polanczyk et al. (2014) reported that differences in reported ADHD prevalence and incidence estimates could be mostly explained by methodological differences characterizing these studies. As discussed earlier, these methodological differences may explain the lower incidence estimates in the Texas Medicaid population.[137]

Increasing proportions of preschoolers were found to be diagnosed with ADHD each year, which could be associated with an actual increase in prevalence or with increasing awareness of the condition. Increasing awareness may influence the prevalence rate by increasing diagnosis of the previously undiagnosed cases. Additionally, increasing awareness in the general population (e.g., teachers, parents, and day care personnel) regarding the symptoms of ADHD may have led to higher screening and evaluation rates by healthcare professionals. According to Sax et al. (2003), teachers were foremost in suggesting a diagnosis of ADHD (46.4%), followed by parents (30.2%), primary care physicians (11.3%), school personnel other than teachers (6.0%), consultants such as child psychiatrists or psychologists (3.1%), and other

specified categories (3.0%).[138] The higher rates of screening and evaluation may have influenced the prevalence rates over time.

In Texas, the STAR Health program was implemented on April 01, 2008; it covers children <18 years of age under the Department of Family and Protective Services (DFPS).[139] STAR Health provides a full-range of Medicaid-covered medical and behavioral health services for children in DFPS conservatorship and young adults in DFPS paid placements. A report submitted to a subcommittee of the Senate Committee on Homeland Security and Governmental Affairs by the National Alliance on Mental Illness (NAMI) highlighted that children in foster care settings often experience high rates of mental illness, including ADHD, which may be associated with genetic, environmental (i.e., *in utero* exposure to drugs and alcohol), and social determinants (i.e., abuse, neglect, removal from their families and homes, multiple placements, poverty, and related experiences).[140] Additionally, the AAP implemented a new set of clinical practice guidelines for diagnosis and evaluation of ADHD in children and adolescents in 2011. The age range of diagnosis was expanded to include patients from 4 to 18 years of age as compared to 6 to 12 years of age in the previous guidelines.[29] Thus, expanding coverage to include foster care children and modifications in the age range for diagnosis of ADHD also may have contributed to the increase in prevalence estimates in the latter years of the current study. Additionally, coverage of ADHD in the public press and media may have shifted the attention to diagnosis of ADHD, thereby resulting in higher prevalence and incidence rates.

Due to lack of availability of accurate enrollment information for preschoolers enrolled in Texas Medicaid, prevalence and incidence estimates were calculated using an estimate of 1.2 million enrollees (average enrollment from 2012-2013) provided by Texas Medicaid. This may have influenced the prevalence and incidence rates in either direction depending on the actual

enrollment numbers in each year. Additionally, the increase in estimated prevalence rates despite stable incidence estimates could be due to the cross-sectional nature of the data. Although we estimated treated prevalence, to our knowledge it is the only study that provides epidemiology estimates of preschoolers (<6 years) using the Texas Medicaid population. Considering that Medicaid/SCHIP enrolled children provide coverage to nearly 50% of the total children in the state of Texas, these estimates could be useful to the Texas state government. [141]

5.3.2 Objective 2: Comparison of treatment groups with respect to patient demographic, clinical, and prior utilization characteristics

***Objective 2a**: To determine and compare the baseline demographic, clinical, and prior utilization characteristics between the pharmacotherapy only (RX), psychotherapy only (PSY), and pharmacotherapy + psychotherapy combined (RX+PSY) groups*

The second objective of the study was to compare the patient demographic, clinical, and prior utilization characteristics between the treatment groups. The explanations provided in section 5.2 are also applicable to this section.

In the current study, we identified 10,877 patients between 2 and 6 years of age receiving treatment for ADHD. Of these patients, a higher proportion were male, Hispanic, residing in urban areas, did not receive psychotropic medications, did not have a mental health diagnosis, used long-acting medications, had a higher mean number of pre-index non-psychiatric visits, and had a higher mean total pre-index cost in the psychotherapy group. Although the age range in the previous studies conducted using Texas Medicaid dataset were different from the present study, the proportions were still comparable. In a study using the Texas Medicaid dataset, Lawson et al. (2012) reported similar trends in the treatment of school-aged children and adults.[84] Furthermore, in the current study Hispanics comprised the largest group of preschoolers receiving treatment for ADHD. This trend was reflected in the study by Lawson et al. (2012) where the proportion of Hispanic patients receiving therapy was higher as compared to the other race/ethnicities.[84]

The results of the current study highlight that a higher proportion of patients received pharmacotherapy (n = 5,904; 54.3%) followed by combination therapy (n = 4,351; 40.0%) and psychotherapy (n = 622; 5.7%). The results of the current study are similar to those found by Stein et al. (2012) where a higher proportion of patients received pharmacotherapy compared to

combination therapy.[80] Conversely, a study by Visser et al. (2015) reported that 25.4% of the patients received medication therapy alone, 31.9% received behavior therapy alone, 21.2% received combination therapy, and 21.4% received no treatment.[142] However, the medication only cohort in the Visser et al. study was defined based on data from the past week. In the current study, we assessed therapies used over a 1-year timeframe, which may have reduced bias associated with short observation periods. Also, Visser et al. included a 'no treatment' group which would alter the percentages.

5.3.3 Objective 3: Time-to-initiation

Objective 3a: *To determine the time to "first pharmacotherapy," "first psychotherapy," and "first combination therapy"*

Objective 3b: *To compare the time to first pharmacotherapy, psychotherapy and combination therapy in preschoolers with ADHD and to compare time to pharmacotherapy with respect to gender, race/ethnicity, and medication duration of action*

The third objective of the current study was to assess the time-to-initiation of pharmacotherapy, psychotherapy, and combination therapy. Results showed that 66.0% of preschoolers were initiated on pharmacotherapy (n = 7,184), followed by 32.3% on psychotherapy (n = 3,513) and 1.7% on combination therapy (n = 180). The results for average time-to-initiation of therapy suggest that preschoolers with ADHD initiated psychotherapy (43.0 ± 89.7 days) relatively early on followed by combination therapy (68.9 ± 92.7 days) and pharmacotherapy (107.4± 112.1 days). The median time-to-initiation also revealed a similar trend (15.0 vs. 28.0 vs. 67.0 days) in all the treatment groups. This finding is in agreement with the recent guidelines, which suggest that a satisfactory trial with psychotherapy should be conducted before adding pharmacotherapy.[32,53] Also, implementing psychotherapy can reduce the need for medication treatment in many preschoolers with ADHD.

In addition to the aforementioned guidelines, there might be other reasons for not prescribing a pharmacologic agent to preschoolers or factors that influence the initiation of therapy. First, the preschool population is different from the school-aged population in that preschoolers undergo rapid neuronal, emotional, and cognitive developmental changes in a very short span of time.[106] This phase of high development makes them more vulnerable to developmental side effects, which may have long-term consequences. Second, medications in preschoolers may show differential therapeutic response and side effect profiles.[102,143,144] In

addition to a differential therapeutic response, concerns have also been raised about the adverse effects associated with use of ADHD medications in preschoolers. Previous studies in preschoolers have reported a high rate (30%) of adverse effects associated with ADHD medication use including irritability, mood changes, reduced appetite, difficulty falling asleep, and a reduction in growth velocity.[143,144] These adverse effects were more prominent in the preschool population as compared to school-aged children with a similar ADHD profile. Third, parents' preferences for and choice of treatment are also important factors in determining time to initiation of therapy. In the PATS study, very few parents opted for the medication treatment arm even though the trials with behavioral therapy were not adequate and patients met the strict criteria for ADHD diagnosis, which gave the option of treatment with medication.[102,143] Lastly, most of the ADHD medications are available as tablets/capsules and preschoolers might be inexperienced in swallowing pills, thus leading to challenges associated with administration of medication. Despite the lack of evidence on prescribing pharmacologic agents to preschoolers, a majority of the patients in the current study were initiated on pharmacotherapy. However, whether such use is justified still remains a point of contention among experts. Long-term population-based studies will help in understanding the outcomes associated with medication use in preschoolers with ADHD.

In accordance with our stated hypothesis, we did not find any difference in the time-to-pharmacotherapy by gender. Perhaps the differences in pharmacotherapy that have been reported in the school-aged population start occurring after the age of 6 years. However, significant differences were observed by race/ethnicity which may be related to cultural differences regarding perspectives on the condition and its treatment. For instance, previous research has shown that Hispanics have delayed acceptance of medication therapies as compared to other

race/ethnicities.[145,146] Although difference by medication duration of action was significant, it was too small to have any meaningful implication.

5.3.3.2 Predictors of treatment

Objective 3c: *To assess the factors associated with receiving RX, PSY, or RX+PSY, after controlling for covariates*

One of the objectives of the current study was to assess the predictors of treatment membership in the overall cohort. With increasing age, patients were less likely to receive psychotherapy therapy as compared to pharmacotherapy. In a previous study assessing the difference in children receiving behavioral therapy only versus combined treatment for ADHD, Pelham et al. (1980) reported that the age of patients receiving combined treatment was higher than the age of patients receiving behavioral therapy only.[147] Also, as discussed in section 5.3.3, an increase in age may have increased prescribers confidence in the safety of medications. In addition to the aforementioned explanations, psychotherapy visits impose a significant burden on the caregiver and use of medications may help in reducing this burden.[133,148,149] Furthermore, with increasing age, parents', teachers', and children's performance expectations typically increase which may increase the need and intake of medications.[150,151]

The current study found that patients with higher pre-index non-psychiatric visits were more likely to undergo psychotherapy as compared to pharmacotherapy. Diagnosis of ADHD requires a thorough evaluation of patients' symptoms. It is even more challenging to determine the diagnosis of ADHD in preschoolers who usually have naturally high level of energy, activity, and impulsivity.[152] This might have resulted in non-psychiatric visits. The presence of pre-index non-psychiatric visits may also suggest that parents were visiting healthcare professionals to

evaluate and understand the behavioral patterns of their child. This eventually may have led to referral and/or diagnosis of ADHD and subsequent initiation of psychotherapy.

Additionally, patients with other mental health diagnosis were more likely to receive psychotherapy as compared to pharmacotherapy. This is similar to the findings published in literature.[142] In a study assessing the parent-reported prevalence of ADHD treatments among a national sample of Children with Special Health Care Needs (CSHCN) dataset, Visser et al. (2015) reported that patients with co-occurring conditions were more likely to undergo psychotherapy as compared to patients without co-occurring conditions. Additionally, age of the patients (**Table 4.4**) in the psychotherapy group was lower than the age of the patients in the pharmacotherapy group. Thus, use of medications in very young preschoolers may not have been viewed as the best treatment option by their physician.

The current study also found that compared to patients not receiving psychotropics, patients receiving other psychotropics were more likely to undergo psychotherapy than pharmacotherapy. This is contrary to previous research where patients were more likely to receive other psychotropic medications if they were being prescribed medications for ADHD. However, this observation was based on studies in school-aged children and may not be applicable to preschoolers due to concerns about tolerability of medications in this population. Thus, patients receiving other psychotropics might actually respond more favorably to psychotherapy than to addition of another medication.

African American, Hispanic, and other/unknown race/ethnicity groups were more likely to receive combination therapy as compared to pharmacotherapy. Previous research shows that combination therapy is recommended for patients who are more severe and require intense

therapy.[153] In addition, patients with other mental disorders were more likely to undergo combination therapy than pharmacotherapy as compared to patients without other mental health disorders, which is in agreement with previous studies.[89,154]

Objective 3d: *To compare adherence, persistence, switching, and augmentation of pharmacotherapy between the RX and the RX+PSY groups*

5.3.3.3 Medication adherence

Of the 10,877 preschoolers identified with ADHD, 8,833 patients receiving pharmacotherapy were included in the treatment pattern cohort. Of those 8,833 patients, 5,382 patients were categorized in the pharmacotherapy only group and 3,451 patients were categorized in the combination therapy group. Both groups were observed for a 12-month period after their index medication claim.

Overall, medication adherence in the pharmacotherapy and combination therapy groups were low. Mean adherence [i.e., proportion of days covered (PDC)] for the entire treatment pattern cohort was 0.48 ± 0.30 (i.e., 48%) with a median value of 0.46. Although none of the previous studies have estimated medication adherence in a strictly preschooler population, adherence estimates of the combined age group (i.e., preschoolers and school-aged children) do exist. Adherence estimates of school-aged children varied between 52.0% and 86.1% in a one-year period.[155–158] A study by Barner et al. that (2012) used a cut-off of 80% to measure adherence (measured as MPR), reported adherence rates that were similar to the current study. Mean adherence (MPR) reported in the study varied between 37.2% (for stimulant users) to 52.5% (for non-stimulant users).[83]

Unadjusted analysis of the difference in mean medication adherence (i.e., t-test) between the pharmacotherapy and combination therapy groups revealed that adherence was higher in the combination therapy group as compared to the pharmacotherapy group. The results for adherence rate (linear regression) and likelihood of adherence (logistic regression) analysis indicate that the difference in adherence between the pharmacotherapy and the combination therapy groups were still significant, while controlling for covariates. It is possible that differences in patient/parent preferences for prescription drug treatment may explain the results, and/or that differences in disease severity might be playing a role. Additionally, it is likely that there is a selection effect where by patients who are more severe require a more intensive treatment approach including a combination of pharmacotherapy and psychotherapy.[159] Thus, severe patients may have a greater need to be adherent as compared to patients who might be relatively less severe. And patients receiving combination therapy may receive more monitoring and encouragement as part of their psychotherapy. Additionally, it is likely that adherence in combination therapy was better than in the pharmacotherapy group due to some unobserved variables. However, the difference in mean adherence between the pharmacotherapy and combination therapy group was too small to have any meaningful clinical implication.

Covariates that were significantly associated with higher odds of being adherent included increasing age and long-acting medication use. Conversely, the covariates significantly associated with lower odds of being adherent included female gender, Hispanic, African American, and other/unknown race/ethnicity, and stimulant medication user. Previous studies have shown that increasing age is one of the main predictors of non-adherence in patients with ADHD.[157,158] Treatment guideline recommendations regarding medication use in patients > 6 years of age might have increased prescriber confidence towards medication prescribing as age

increased.[30,32] The directionality of likelihood of adherence for all other variables is in agreement with the existing literature.[157,158,160] We could only account for the factors that were available in the database. The lack of data for other factors such as adverse events, patient/parent preference, and treatment response meant that they could not be accounted for in the model. However, this study is based on retrospective observational claims data and no causal inferences can be made.

5.3.3.4 Medication persistence

Results showed that the mean persistence was 139.0 ± 127.3 days in the overall treatment pattern cohort. Several of the explanations described earlier in Section 5.3.3.2 and 5.3.3.3, also apply to the findings from these analyses of persistence. The persistence estimate was within the range (95.4 ± 92.6 to 153.3 ± 124.3) reported by Barner et al. using the Texas Medicaid dataset.[83] In the current study, the mean persistence was lower in the pharmacotherapy group (137.1 ± 127.3 days) as compared to the combination therapy group (141.8 ± 127.2 days) which is similar to the relationship found for adherence. However, the difference was too small to have any meaningful clinical implication. Unadjusted analysis of the difference in mean medication persistence (i.e., t-test) between the pharmacotherapy and combination therapy groups showed no significant difference. Adjusted analysis, after controlling for covariates, indicated that the difference in persistence was still not significant.

Regarding covariates, female gender, Hispanic, African American, and Other/Unknown race/ethnicity, and stimulant medication use were significantly associated with higher hazard rates of discontinuation. Conversely, age, rural residence status, and long-acting medication use were significantly associated with lower hazard rates of discontinuation.

Overall adherence (mean PDC) and persistence in the current study is low and could be associated with patient and caregiver/parent-related factors. For instance, adherence in preschoolers could be a reflection of parents'/caregivers' opinions about medication therapy and may represent parents' attitudes towards long-term medication use in preschoolers. Parents may be hesitant for their children to receive stimulant medications due to concerns about side effects, stigma, and the logistics of administering medications to young children. In addition, Schedule II drugs (i.e., methylphenidate and amphetamine) require a new prescription every 30 days which could impose a major burden on the caregiver. (In Texas, prescribers can issue multiple prescriptions authorizing the patient to receive a total of up to a 90-day supply under certain conditions.)

5.3.3.5 Medication augmentation and switching

An examination of the augmentation patterns in the treatment pattern cohort revealed medication augmentation in 10.5% of the patients during the study period. In a comparison study of commercially insured and Medicaid children ≥ 6 years of age, Molife et al. (2012) demonstrated that combination therapy (> 1 ADHD medication class in the same month) was used in 10.3% and 24.0% of the commercially and Medicaid insured groups, respectively.[161] In another study conducted using a large national US health plan, Hodgkins et al. (2012) reported an augmentation rate of 8.3%. The augmentation rates were highest for mixed amphetamine salts-extended release (11.4%), followed by lisdexamfetamine dimesylate (8.9%), and osmotic-release oral system methylphenidate (6.0%).[162] The estimates in the current study (10.5%) are similar to the augmentation rates among school-aged children for the commercial population, but lower than the augmentation rates in the Medicaid population as reported by Molife et al. (2012).

The augmentation rate observed in the current study is somewhat surprising, considering the reservations that exist regarding prescribing medications to preschoolers. However, approximately one-third of the preschoolers identified in the current study were also diagnosed with comorbid mental health conditions which might be an indication of higher severity and may have played a role in the augmentation trends observed.

Examination of the switching patterns in the treatment pattern cohort revealed that 31.8% of the patients switched from their index medication. The rate of switching in our study is similar to that found by Lawson et al. (26.9% to 27.8%) and Winterstien et al. (23.9% to 26.8%) conducted using the Texas Medicaid and Florida Medicaid datasets, respectively.[84,163] The results of the current study were not surprising since preschoolers might require more frequent dose adjustments or even medication class changes. Switching is usually influenced by drug effectiveness, differences and similarities in duration of use, and side-effects. Perhaps in the preschool population these effects might be monitored more closely and may be associated with switching in cases where potential benefits were judged to outweigh potential risks.

A multivariate analysis of augmenters and switchers revealed that patients in the pharmacotherapy group were less likely to augment or switch as compared to the combination therapy group. As discussed earlier, combination therapy users might be more severe and may have more frequent opportunities for dose/treatment monitoring. In the case of severe patients, sub-optimal response to drug therapy may have encouraged the physician to add another medication or to switch to an alternate medication. Also, regular psychotherapy visits along with pharmacotherapy visits may allow for closer monitoring of medication use and more frequent opportunities for therapy augmentation.

5.3.4 Objective 4: Healthcare utilization

Objective 4a: *To determine and compare the healthcare utilization frequencies for all-cause office-based, inpatient, outpatient hospital, ED visits, and prescriptions between the RX and the RX+PSY groups*

Objective 4b: *To determine and compare the healthcare utilization frequencies for ADHD-related office-based, inpatient, outpatient hospital, ED visits, and prescriptions between the RX and RX+PSY groups*

Objective 4c: *To determine and compare the healthcare utilization frequencies for other mental health-related office-based, inpatient, outpatient hospital, ED visits, and prescriptions between the RX and RX+PSY groups*

Texas Medicaid covers nearly 50% of the pediatric population in Texas, which means that pediatric expenditures constitute a considerable proportion of Medicaid spending.[141] We explored the healthcare utilization for preschoolers with ADHD and compared the pharmacotherapy and combination therapy groups, to provide estimates of the relative healthcare resource utilization burden for the two treatment groups in the state Medicaid program.

Our findings indicated that preschoolers with ADHD receiving combination therapy had significantly higher healthcare utilization compared to preschoolers receiving pharmacotherapy. It is likely that the additional psychotherapy component in the combination therapy group increased the healthcare utilization in the combination therapy group as compared to medication therapy alone. This trend was also reflected in the treatment pattern results (sections 5.3.2.2, 5.3.2.3, and 5.3.3.4) where the combination therapy group showed better adherence and persistence. Consequently, more visits may have allowed for closer treatment monitoring thus, leading to increased augmentation and switching in the combination therapy cohort where the response might be suboptimal or a more intensive treatment was needed.

While utilization patterns for all service use categories (i.e., office-based, outpatient hospital, inpatient, emergency department visits, and prescriptions) were different for the treatment groups, it is important to note that the utilization was higher in the combination therapy group as compared to the pharmacotherapy group in all the categories except for ADHD-related prescriptions, other mental health-related office and inpatient visits. Few studies have been conducted comparing healthcare utilization in preschoolers with respect to type of therapy (i.e., RX, PSY, and RX+PSY).

In addition to the medical visit resource use categories, all-cause and other mental health-related prescriptions use were also higher in the combination therapy group. Previous research has shown that children with ADHD are more prone to other acute and chronic conditions such as asthma, injuries, infections, and mental health comorbidities which may be associated with increased healthcare utilization including prescription medications for the treatment of those conditions.[164–167]

In summary, although the age of the patients in the current study is different from reported studies conducted in school-aged children, some of the practice trends may remain consistent irrespective of the age group being treated. Additionally, the psychotherapy component may lead to higher healthcare utilization.

5.3.5 Objective 5: Healthcare costs

Objective 5a: *To determine and compare the all-cause medical (office-based, inpatient, outpatient hospital, and ED), prescription, and total costs between the RX and RX+PSY groups*

Objective 5b: *To determine and compare the ADHD-related medical (office-based, inpatient, outpatient hospital, and ED), prescription, and total costs between the RX and RX+PSY groups*

Objective 5c: *To determine and compare the other mental health-related medical (office-based, inpatient, outpatient hospital, and ED), prescription, and total costs between the RX and RX+PSY groups*

For objective 5, we explored the healthcare costs for preschoolers with ADHD and compared the pharmacotherapy and combination therapy groups to provide estimates of the relative economic burden. Healthcare costs were estimated for patients based on the overall cohort. Patients in the combination therapy group had higher medical, prescription, and total healthcare costs in all the three categories (i.e., ADHD-related, all-cause, and other mental health-related). Differences were highest in the all-cause categories, followed by ADHD-related and other mental health-related categories. Interestingly, prescription medication costs in the ADHD-related category were higher than the ADHD-related medical costs. The prescription costs in all other categories (i.e., all-cause and other mental healthcare-related) were lower than the medical costs.

A limited number of studies have been conducted comparing the cost estimates between pharmacotherapy and combination therapy groups. Vanoverbeke et al. (2003), estimating costs for methylphenidate-IR, methylphenidate-ER, and behavioral therapy over a one-year time period, reported that psychotherapy was the most expensive alternative with a cost estimate of $3,049 (based on 2001 dollars) followed by the MPH-ER ($2,115), and MPH-IR ($2,163)

groups.[168] Leinwand et al. (2011) modelled costs of medication and combination therapy with respect to gender and comorbidities.[169] The authors reported higher costs for combination therapy users as compared to medication therapy users for both males and females. Medication costs ranged from $832 to $839 whereas costs for the combination therapy group ranged from $6,703 to $6,742. Results of these two studies showing that the cost estimate for the psychotherapy group was highest are consistent with the findings of the current study showing that costs for the combination therapy group (which includes psychotherapy) were higher than those for the pharmacotherapy group.

In a cost-effectiveness analysis comparing methylphenidate (instant release), dextroamphetamine, behavioral therapy, combination, and no treatment costs, Zupancic et al. (1999) estimated the total cost for the combination therapy group to be $2,510 (based on 2001 dollars) as compared to $559 with methylphenidate alone.[170,171] The cost estimates for combination therapy and pharmacotherapy followed a similar trend in the current study with higher costs in the combination therapy group as compared to pharmacotherapy group.

According to the information provided by the American Academy of Pediatrics (2015), the average cost of each Medicaid-eligible child in Texas is estimated at $3,045 per year.[141] As evident from the results of the current study, the medical and total all-cause costs for preschoolers with ADHD were higher than the average cost for each Medicaid-eligible child. The findings of this study could help identify high spending categories (i.e., medical and/or prescription) that could lead to potential cost savings and delivery of more efficient care. Thus, early intervention could help prevent future costs and could lead to a decline in Medicaid spending.

5.5 Limitations

The results of this study should be viewed in light of a few limitations. First limitation is the use of administrative claims data in identifying ADHD in preschoolers. It is possible that some ADHD cases were misclassified either due to misdiagnosis, miscoding, or inaccuracies introduced through the inclusion criteria. It is reported that children often present with symptoms and risk profile of multiple mental health conditions, which makes it difficult to accurately establish an ADHD diagnosis. If children were falsely classified, we cannot reclassify them correctly without a chart review or clinical data to confirm the diagnosis. Nevertheless, more preschoolers are possibly being diagnosed with ADHD because of the increased attention on ADHD in the scientific and lay literature in recent times, which may have an influence on diagnosis rate. Similarly, increased awareness of ADHD among clinicians, counselors, parents, and other caregivers could have resulted in the diagnosis of formerly undiagnosed pediatric patients with the condition, which may explain the high prevalence in the current study.

A second limitation of the study is that incidence rate may not be representative of new cases if diagnoses existed prior to enrollment in Texas Medicaid. Similarly, prevalence rates may not be accurate if patients sought care outside of the Medicaid program.[172] In addition, the incidence and prevalence estimates are based on enrollment estimates provided by Texas Medicaid for limited years. These enrollment estimates may have contributed to inaccurate prevalence and incidence estimates.

A third limitation is that the current study only evaluated preschoolers receiving treatment for ADHD. It does not include patients who did not receive therapy for ADHD. Consequently, it did not include patients who were being treated with medication without a

diagnosis of ADHD. This may have underestimated the prevalence, incidence, utilization, and costs of the patients.

A fourth limitation of the study is the small sample size in the psychotherapy group. Although these results cannot be extrapolated to the entire preschool population, they provide an estimate of spending on preschoolers in Texas Medicaid associated with an ADHD diagnosis.

Fifth, we could only control for factors that were available in the dataset. Other patient characteristics such as education, level of understanding or clinical factors including side-effects and adverse events, and physician specialty were not available and thus, could not be controlled for in the study. These variables, if present, may provide more insight into the nature of the condition in preschoolers.

Sixth, classification of combination therapy initiators based on having claims for an ADHD medication and psychotherapy on the same day may be too restrictive as there might be some lag between psychotherapy and medication use.

5.4 Conclusions, implications, and future directions

The prevalence rate of ADHD in preschoolers increased steadily from 2008 to 2012. In contrast, the incidence rates were stable for those years. Most of the patients received medication therapy followed by combination therapy, and psychotherapy. A comparison of treatments revealed that the combination therapy group had a higher healthcare burden (i.e., utilization and cost) as compared to the pharmacotherapy group.

Early treatment intervention during the preschool years may help in reducing the overall disease burden. Previous research has shown that patients diagnosed with ADHD early-on may have long-term behavioral manifestations. Therefore, the use of combination therapy may provide a better management alternative leading to better adherence and persistence with the ultimate goal of achieving symptom control and improving daily functioning.[173] Additionally, the current study also shows that adherence in the Texas Medicaid preschool population is low. Further discussion of the desirability of adherence and persistence in the preschool population is warranted. Also, future studies could be conducted to identify factors and clinical outcomes associated with poor adherence and persistence. The current study also identifies utilization and cost categories that could be targeted to avoid the additional long-term healthcare cost to the payers such as Medicaid and society at large.

Additionally, this study has important implications for Texas Medicaid. Stimulant medications are among the highest medication expenditure categories for Texas Medicaid. Identification and early treatment may avert some of the costs that would be incurred by Texas Medicaid if these patients remain untreated. Considering that Texas Medicaid covers 46.3% of the pediatric population in Texas, treatment of their condition could contribute to a sizeable

burden on the healthcare system.[141] Economic burden information provided in the current study could be useful to Medicaid as decision makers identify and consider cost-effective strategies.

Findings from the current study add to the limited available research regarding ADHD in preschoolers; however, future studies could be conducted to add more information regarding treatment in preschoolers. Since this study was conducted using the Texas Medicaid dataset, future studies could utilize other data sources to validate the findings and add new information. These results would be valuable for stakeholders including, insurance companies, providers, and patients to understand the long-term impact of early treatment in preschoolers.

One of the interesting observations was the cut-off period for adherence and the definitions for persistence and adherence. Since preschoolers are vulnerable to ill effects of medications, parents often take their children off medications for a certain period. Methodological studies could be conducted to determine the impact of drug holidays on the outcomes. In this study, we found that even though time-to-initiation of psychotherapy was lower, a majority of the patients were represented in the pharmacotherapy only group. Longitudinal studies could determine if this pattern of treatment continues or if there is a shift from one treatment alternative to another over a period of time.

In order to get a more in-depth understanding of treatment patterns in preschoolers, a thorough evaluation of switching and augmentation by each medication class and duration of action could be conducted. This additional information might help tailor medication therapy according to the requirements of each patient for a more personalized approach.

The current study evaluated only patients who received treatment for ADHD. Instead of Medicaid data, future research could utilize survey datasets such as MEPS or Children with

Special Health Care Needs (CSHCN) to include a no-treatment arm so as to provide a more holistic evaluation of the treatment and non-treatment trends in preschoolers with ADHD. In addition, it is evident from the current research that there are various interactions that could be evaluated (e.g., interaction of age and comorbidity). Future research could explore this aspect in further detail to add more information regarding the condition.

APPENDICES

Appendix I

Types of medications used for the management of Attention Deficit Hyperactivity Disorder in patients

Drug	Action	Generic Names	Brand Names
Methylphenidates	Short Acting	SA Methylphenidate	Ritalin, Methylin
		SA Dexmethylphenidate	Focalin
	Long Acting	LA Methylphenidate	Ritalin LA, Ritalin SR, Metadate CD, Metadate ER, Methylin ER, Daytrana, Concerta
		LA Dexmethylphenidate	Focalin XR
Amphetamines	Short Acting	SA Dextroamphetamine	Dexedrine, Dextrostat, Procentra
		SA Dextroamphetamine and Amphetamine Salts	Adderall
	Long Acting	LA Dextroamphetamine and Amphetamine Salts	Adderall XR
		Lisdexamphetamine	Vyvanse
Non-Stimulants	Long Acting	LA Guanfacine	Intuniv
		LA Clonidine	Kapvay
		Atomoxetine	Strattera

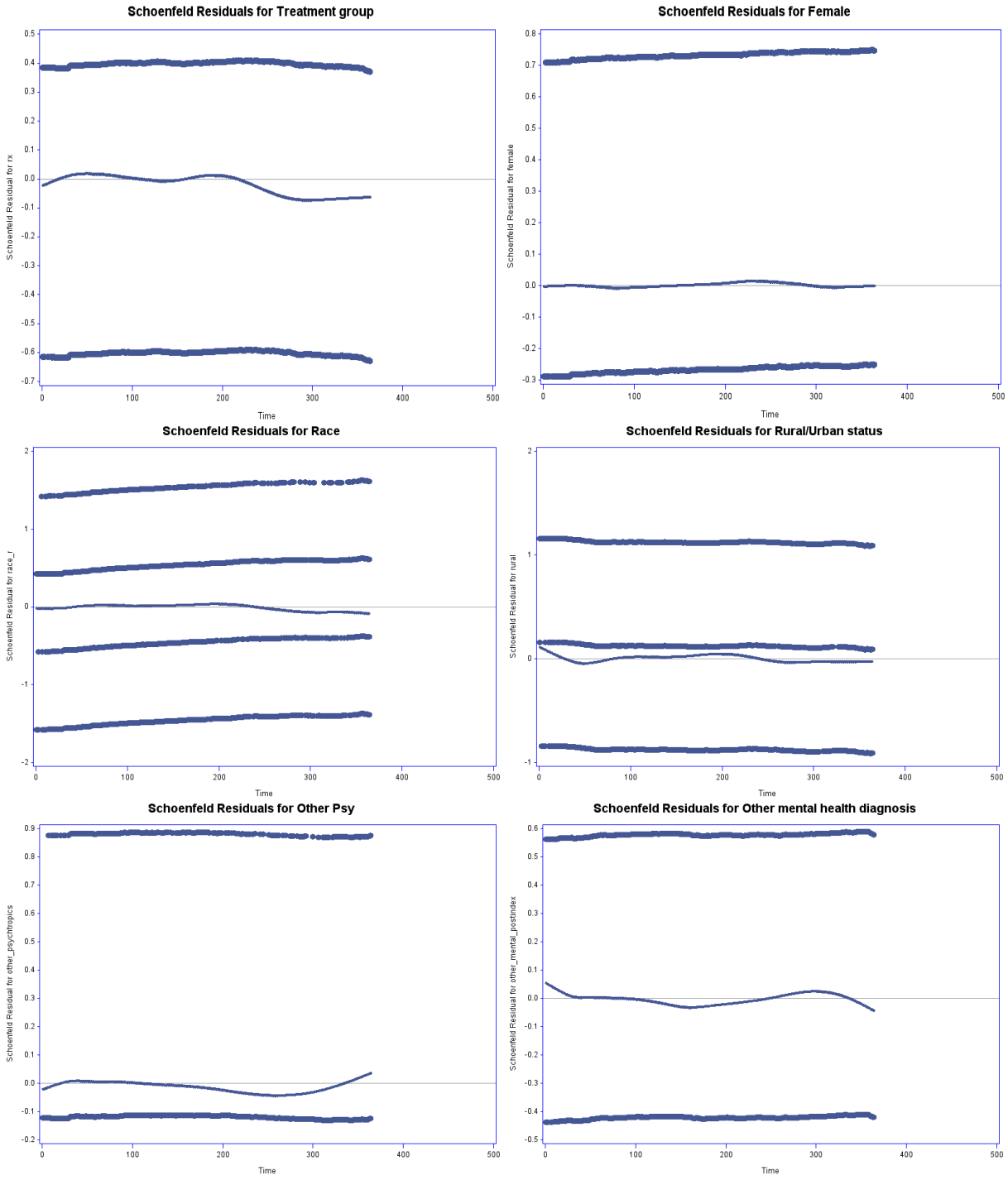
Appendix II

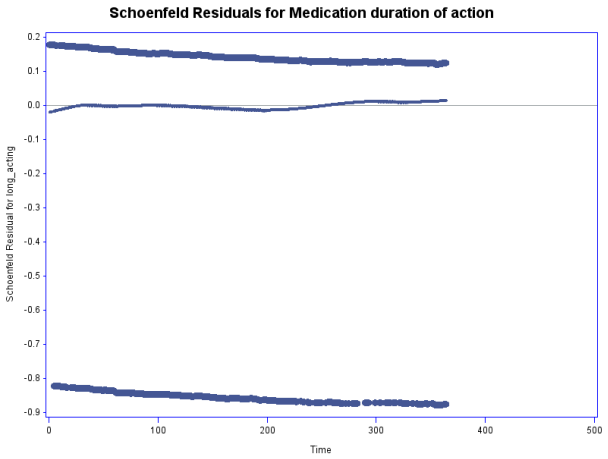
List of current procedural terminology (CPT) codes used to identify psychotherapy in patients with ADHD

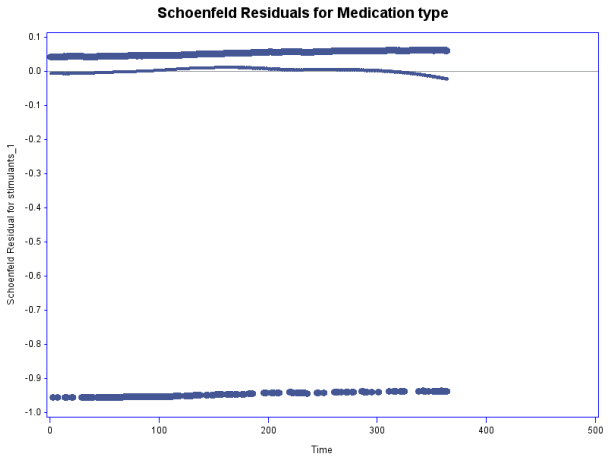
CPT codes	Description
1050X	Individual counseling services by LMSW-ACPs and LPCs, per hour
1052X	Family counseling services by LMSW-ACPs and LPCs, per hour
90805	Individual psychotherapy with E/M, 20-30 min
90847	Family psychotherapy with patient present
90806	45-50 minute psychotherapy
90804	Individual psychotherapy 20-30 min (changed after 2012)
90837	Individual psychotherapy 53+ minutes (implemented in 2013) (prior to 2013 it was coded as 90808 & 90821)
97150	Group therapy services
90807	Individual psychotherapy 45-50 min (changed after 2012)
1152X	Family counseling services by LMFT, per hour
90833	Psychotherapy 30 (16-37*) min (used after 2012)
90808	Individual psychotherapy (75-80 min)
1150X	Individual counseling services by LMSW-ACP and LPCs, per hour
90832	Psychotherapy 30 (16-37*) min (used after 2012)
90834	Psychotherapy 45 (38-52*) min
90811	Interactive individual psychotherapy with E/M 20-30 min
90836	Psychotherapy patient&/family with E/M services 45 min
90812	Interactive individual psychotherapy (45-50 min)
90853	Group psychotherapy
1051X	Group counseling services by LMSW-ACPs and LPCs, per hour
90810	Interactive individual psychotherapy 20-30 min
90817	Individual psychotherapy 20-30 min (changed after 2012)
90809	Individual psychotherapy with E/M 20-30 min
90815	Interactive individual psychotherapy with E/M (75-80 min)
90838	Psychotherapy patient and/family w/E&M services 60 min
90816	Individual psychotherapy 20-30 min (changed after 2012)
90818	Individual psychotherapy 45-50 min (changed after 2012)
90814	Interactive individual psychotherapy (75-80 min)
90819	Individual psychotherapy 45-50 min (changed after 2012)
90822	Individual psychotherapy (75-80 min)

Appendix III

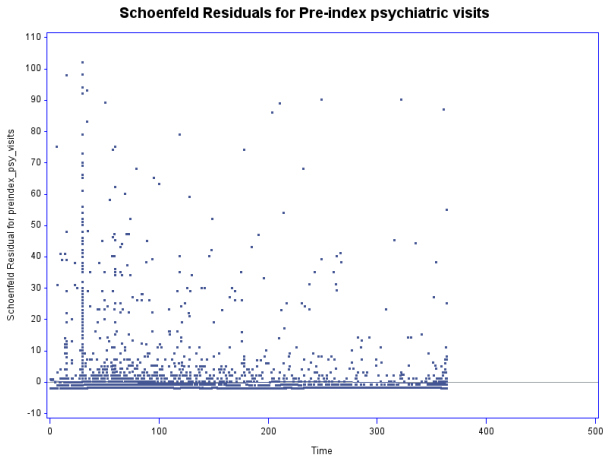
Schoenfeld Residual plots testing the proportional hazards assumption in the Cox proportional hazards regression model

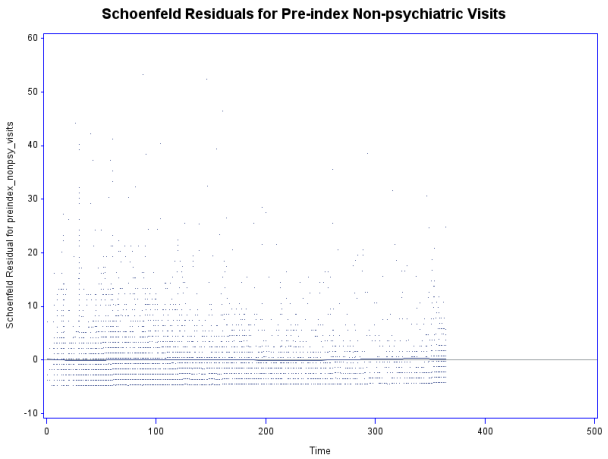


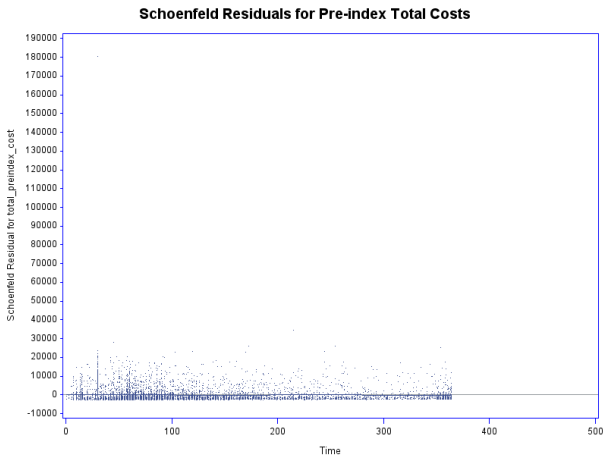

Schoenfeld Residuals for Medication duration of action
Schoenfeld Residual for long_acting
Time


Schoenfeld Residuals for Medication type
Schoenfeld Residual for stimulants_1
Time


Schoenfeld Residuals for Age at Diagnosis
Schoenfeld Residual for ageatdiag
Time


Schoenfeld Residuals for Pre-index psychiatric visits
Schoenfeld Residual for preindex_psy_visits
Time


Schoenfeld Residuals for Pre-index Non-psychiatric Visits
Schoenfeld Residual for preindex_nonpsy_visits
Time


Schoenfeld Residuals for Pre-index Total Costs
Schoenfeld Residual for total_preindex_cost
Time

Appendix IV

Sensitivity analysis for persistence – 60-day gap

Cox-proportional hazards regression. Determinants of persistence (60-day gap) between combination therapy and pharmacotherapy groups in preschoolers diagnosed with ADHD

Characteristics	HR	95% CI	x^2	p-value
Pharmacotherapy	1.041	0.994 – 1.090	2.9	0.09
Covariates				
Age[a]	0.921	0.896 – 0.947	**34.2**	**<.0001**
Pre-index psychiatric visits[a]	0.999	0.995 – 1.002	0.7	0.40
Pre-index non-psychiatric visits[a]	1.003	0.999 – 1.008	2.1	0.15
Total pre-index costs[a]	1.000	1.000 – 1.000	0.7	0.42
Female[b]	1.087	1.033 – 1.143	**10.5**	**<0.01**
African Americans[b]	1.269	1.178 – 1.367	**39.3**	**<.0001**
Hispanics[b]	1.247	1.171 – 1.329	**47.2**	**<.0001**
Others/Unknown[b]	1.177	1.080 – 1.282	**13.8**	**<0.01**
Rural[b]	0.953	0.903 – 1.006	3.1	0.08
Other psychotropics[b]	1.001	0.932 – 1.075	0.0	0.98
Other mental health diagnosis[b]	0.973	0.924 – 1.024	1.1	0.29
Long-acting medications[b]	0.912	0.856 – 0.971	**8.1**	**<0.01**
Stimulants[b]	1.125	1.013 – 1.249	**4.8**	**0.03**

*p < 0.05 (in bold); HR = Hazard Ratio; CI = Confidence Interval; x^2= Chi-square;

[a] Recorded as a continuous variable in the model;

[b] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no other mental health diagnosis, no long-acting medication use, no short-acting medication use, and non-stimulant use;

[a] Persistence was calculated over a 365-day period with a 60-day allowable gap

Appendix V

Sensitivity analysis for persistence – 90-day gap

Cox-proportional hazards regression. Determinants of persistence (90-day gap) between combination therapy and pharmacotherapy groups in preschoolers diagnosed with ADHD

Parameter	HR	95% CI	x^2	p-value*
Pharmacotherapy	1.030	0.984 – 1.079	1.6	0.21
Covariates				
Age[a]	0.918	0.893 – 0.944	**37.2**	**<.0001**
Pre-index psychiatric visits[a]	0.998	0.995 – 1.001	1.7	0.19
Pre-index non-psychiatric visits[a]	1.002	0.997 – 1.007	0.6	0.43
Total pre-index costs[a]	1.000	1.000 – 1.000	1.4	0.23
Female[b]	1.070	1.017 – 1.125	**7.0**	**0.01**
African Americans[b]	1.183	1.098 – 1.274	**19.6**	**<.0001**
Hispanics[b]	1.205	1.131 – 1.283	**33.4**	**<.0001**
Others/Unknown[b]	1.139	1.045 – 1.241	**8.8**	**<.01**
Rural[b]	0.944	0.894 – 0.996	**4.4**	**0.04**
Other psychotropics[b]	0.992	0.924 – 1.066	0.0	0.83
Other mental health diagnosis[b]	0.970	0.921 – 1.021	1.4	0.24
Long-acting medications[b]	0.961	0.902 – 1.024	1.5	0.22
Stimulants[b]	1.105	0.995 – 1.228	3.5	0.06

*p < 0.05 (in bold); HR = Hazard Ratio; CI = Confidence Interval; x^2 = Chi-square;

[a] Recorded as a continuous variable in the model;

[b] Reference categories: combination therapy group, males, whites, urban residents, no psychotropic use, no other mental health diagnosis, no long-acting medication use, no short-acting medication use, and non-stimulant use; Persistence was calculated over a 365-day period with a 90-day allowable gap

Appendix VI

Distribution coefficients for ADHD-related, all-cause, and other mental health-related visits

Categories	Coefficient	p-value*
All-cause		
Office-based visits	1.44	**<0.0001**
Inpatient visits	1.26	0.09
Outpatient hospital visits	1.80	**<0.0001**
ER visits	1.26	**0.01**
ADHD-related		
Office-based visits	1.30	0.20
Inpatient visits	1.27	0.44
Outpatient hospital visits	1.73	**0.02**
ER visits	1.89	0.09
Other mental health related		
Office-based visits	1.51	**<0.0001**
Inpatient visits	6.37	0.11
Outpatient hospital visits	1.72	**<0.0001**
ER visits	0.99	1.00

*Values greater than or less than 1 yet not significantly different from 1 indicate that the confidence interval includes 1

Appendix VII

Vuong test to identify the best model for ADHD-related, all-cause, and other mental health-related healthcare utilization outcomes

All-cause office				ADHD-related office			Other mental health-related office		
Vuong Statistic	**Z**	**Pr>|Z|**	**Model**	**Z**	**Pr>|Z|**	**Model**	**Z**	**Pr>|Z|**	**Model**
Unadjusted	12.20	<.0001	zip	12.20	<.0001	zip	19.62	<.0001	zip
Akaike Adjusted	12.20	<.0001	zip	12.20	<.0001	zip	19.62	<.0001	zip
Schwarz Adjusted	12.17	<.0001	zip	12.17	<.0001	zip	19.61	<.0001	zip
All-cause inpatient				**ADHD-related inpatient**			**Other mental health-related inpatient**		
Vuong Statistic	**Z**	**Pr>|Z|**	**Model**	**Z**	**Pr>|Z|**	**Model**	**Z**	**Pr>|Z|**	**Model**
Unadjusted	16.80	<.0001	zip	16.80	<.0001	zip	15.72	<.0001	zip
Akaike Adjusted	16.80	<.0001	zip	16.80	<.0001	zip	15.72	<.0001	zip
Schwarz Adjusted	16.78	<.0001	zip	16.78	<.0001	zip	15.73	<.0001	zip
All-cause outpatient hospital				**ADHD-related outpatient hospital**			**Other mental health-related outpatient hospital**		
Vuong Statistic	**Z**	**Pr>|Z|**	**Model**	**Z**	**Pr>|Z|**	**Model**	**Z**	**Pr>|Z|**	**Model**
Unadjusted	29.77	<.0001	zip	29.77	<.0001	zip	29.33	<.0001	zip
Akaike Adjusted	29.76	<.0001	zip	29.76	<.0001	zip	29.33	<.0001	zip
Schwarz Adjusted	29.76	<.0001	zip	29.76	<.0001	zip	29.33	<.0001	zip
All-cause ER				**ADHD-related ER[a]**			**Other mental health-related ER[a]**		
Vuong Statistic	**Z**	**Pr>|Z|**	**Model**						
Unadjusted	8.97	<.0001	zip						
Akaike Adjusted	8.94	<.0001	zip						
Schwarz Adjusted	8.84	<.0001	zip						
All-cause prescriptions				**ADHD-related prescriptions**			**Other mental health-related prescriptions**		
Vuong Statistic	**Z**	**Pr>|Z|**	**Model**	**Z**	**Pr>|Z|**	**Model**	**Z**	**Pr>|Z|**	**Model**
Unadjusted	-0.03	0.98	poi	-0.01	1.00	poi	40.14	<.0001	zip
Akaike Adjusted	-29560.20	<.0001	poi	-80038.00	<.0001	poi	40.13	<.0001	zip
Schwarz Adjusted	-136502.00	<.0001	poi	-369595.00	<.0001	poi	40.12	<.0001	zip

ZIP = Zero-inflated Poisson regression; poi = Poisson regression; ED = Emergency Department; ADHD= Attention Deficit Hyperactivity Disorder;

[a] Could not test between the two models (ZIP vs. Poisson) due to zero values for covariates in pharmacotherapy and combination therapy groups

Appendix VIII

Distribution coefficients for ADHD-related, all-cause, and other mental health-related costs

	Coefficient	p-value
All-cause		
Medical costs	1.67	<0.0001
Prescription costs	2.37	0.47
Total costs	1.97	0.72
ADHD-related		
Medical costs	-0.41	<0.0001
Prescription costs	0.66	<0.0001
Total costs	0.60	0.57
Other mental health-related		
Medical costs	1.76	<0.0001
Prescription costs	1.55	<0.0001
Total costs	1.81	<0.0001

*Values far from 2 yet non-significant indicate that the confidence interval included a value of 2

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