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A Comparison of Non-ADHD-Related Health Care Costs Associated with Different Medication Treatment Modalities among Adults with ADHD

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A Comparison of Non-ADHD-Related Health Care Costs Associated with Different Medication Treatment Modalities among Adults with ADHD

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An abstract of
A Thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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2011

ABSTRACT

Attention-Deficit/Hyperactivity Disorder (ADHD), a common mental health disorder among adults, affects many aspects of a person's life including work and daily task performance, interpersonal relationships, time perception, and likelihood of injuries and driving accidents. The principal form of therapy used is stimulant and non-stimulant psychotropic medication. Theoretically, effective medication therapy would control the disorder's inattentive and impulsive components, leading to improved health status due to reduced injury rate, reduced daily stress, and better self-management of health. This improved health status could be reflected in a reduced need for non-ADHD-related healthcare resources and reduce non-ADHD-related costs. This study seeks to evaluate whether the type of ADHD medication taken is associated with non-ADHD-related costs.

This retrospective study used five years of medical and pharmacy claims data from Thomson Reuters' MarketScan® database to compare non-ADHD-related costs among adults aged 18-64 receiving five different types of ADHD medication therapy: brand name Adderall, generic Adderall, brand name non-Adderall stimulants, generic non-Adderall stimulants, and atomoxetine (Strattera) (a non-stimulant which did not exist in a generic version during the study period). Additionally, those taking generic stimulants were compared to those taking brand name stimulants.

In the full population of adults with ADHD aged 18-64 (n=4,123) there were no significant differences in non-ADHD-related costs across the five medication groups or when comparing those taking generic versus brand name stimulants. Post hoc analyses of the subpopulation aged 18-25 (n= 1,248) indicated that those taking atomoxetine (Strattera) had significantly greater non-ADHD-related costs than those taking brand name Adderall ($p<.01$), generic Adderall ($p<.01$), or brand name non-Adderall stimulants ($p<.01$). There was no significant difference between those taking generic versus brand name stimulants. One possible explanation for these findings is that the impact of health issues related to injuries and accidents may be easier to detect in this age group, making it easier to identify variation in outcomes among the five different treatment groups. This study lays groundwork for future studies in adults with ADHD that seek to compare the effectiveness of different types of medication in control of ADHD symptoms, a key element of improving the ADHD patient's quality of life.

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DEDICATIONS AND ACKNOWLEDGEMENTS

DEDICATIONS

To my mother, Professor Melitta Tengler de McLure, MA, PhD candidate, protozoologist, (1936-1978), who did all her statistical tests by hand.

To my partner Stephen Murtagh, mental health professional in training without whose support completing my degree would have been impossible. I know your patients will be the better for your work with them.

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I: Introduction, Background, and Statement of Problem

"People keep saying to me who I chat to, 'Oh that's all behind, leave it behind, you've got this now, now look to the future,' and I'm like, 'Yeah, hang on, I've just spent 34 years underachieving. I feel like part of my life has been a lie.'"

"I have—if you like—unrealized potential to work, to do even better and produce more success because I can . . . I am much more positive about the future and I can see much more potential in myself."

Quotes from persons identified as having ADHD as adults. (Young et al. 2008)

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a disorder that has an impact on many domains of a person's life. These are as diverse as work, personal relationships, driving, money management, and rate of injury (Biederman and Faraone 2006; Kessler et al. 2005; Eakin et al. 2004; Barkley, Murphy, and Fischer 2008; Richards et al. 2006; Merrill et al. 2009). Although ADHD has long been studied in children, the population in which it was identified and for whom all case definitions have been developed up to the present, it is only in the last two decades or so that its presence in adults has been identified and seriously studied. This project seeks to contribute to the body of knowledge on adults with ADHD and how they are affected by treatment with different forms of medication.

BACKGROUND ON ADHD

ADHD Definition and Types

The American Psychiatric Association defines ADHD as "a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequently displayed and more severe than is typically observed in persons at a comparable level of development (APA 2000)." The three forms of ADHD currently identified in DSM-IV are the predominantly inattentive type, the predominantly hyperactive type and the combined type, which meets criteria for both the inattentive and the hyperactive type.

Some of the characteristics of the inattentive type of ADHD include failure to pay attention to details, difficulty in sustaining attention during activities, appearance of not listening when spoken to, and easy distractibility.

The hyperactive ADHD person is characterized by physical fidgeting (the jumping/shaking knee is a very common manifestation in both adults and children) and impulsivity (with symptoms such as interrupting during conversations, having difficulties in waiting for one's turn, and making significant decisions without appropriate deliberation).

In addition to the established concepts of hyperactivity and inattention, more recent theory as put forward by Barkley (2010) describes ADHD as a "deficit in executive function, which can be broadly defined as a set of neurocognitive processes that allow for the organization of behavior across time so as to attain future goals. [The four areas of functioning specifically affected include] nonverbal working memory, verbal working memory, planning and problem-solving, and emotional self-regulation" (p. E17).

Effects of ADHD in Adults

As previously mentioned, ADHD in adults affects many aspects of an adult's life, including challenges in work performance, maintenance of interpersonal relationships both in and outside the household and partnership/ marriage, time perception, ability to perform daily tasks, and heightened likelihood of driving accidents and injuries(Biederman and Faraone 2006; Merrill et al. 2009; Kessler et al. 2005; Shifrin, Proctor, and Prevatt 2010; Eakin et al. 2004). It is also possible that a person with ADHD would have more difficulty in maintaining health when confronted with metabolic diseases such as diabetes which require a significant element of self-management (Sanchez, Chronis, and J. Hunter 2006).

ADHD and Psychiatric Comorbidities

The most frequent mental health comorbidities in the adult person with ADHD are depression, anxiety, substance abuse, and sleep disorders (McIntosh et al. 2009; Friedrichs et al. 2010; Secnik, Swensen, and Lage 2005).

Treatment for Adults with ADHD

Although there are non-medication approaches (such as cognitive behavioral therapy and coaching) that are used to help with the effects of impaired impulse control and attentiveness in the adult with ADHD , the principal form of therapy used is medication, which can be divided into stimulants and non-stimulants (Barkley 2011). The most common stimulant prescribed in the US is Adderall (mixed

amphetamine salts)[1]. Adderall is available both in brand name and generic formulations and in instant release (IR) and extended release (ER) versions. The other stimulants principally prescribed are methylphenidate (Ritalin, Concerta), dexmethylphenidate (Focalin), and lisdexamphetamine (Vyvanse). The only non-stimulant medication currently approved as a treatment for adults with ADHD is atomoxetine (Strattera) which has been available since 2003 in the US. Upon its launching, it was the first new type of medication for ADHD which had become available in 25 years (Barkley 2011).

Anti-depressive medications such as Desipramine have also been used to treat ADHD (Verbeeck, Tuinier, and Bekkering 2009) (Spencer, Biederman, and Wilens 2004). These are outside the scope of this study.

ADHD in Adults – Diagnosis and Onset

Formal diagnosis of ADHD requires meeting a complex series of criteria detailed in DSM-IV-TR (full criteria are provided in *Appendix A – DSM-IV Criteria for Diagnosis of ADHD)*. These include nine criteria for inattentiveness (e.g., failure to complete work) and nine criteria for hyperactivity/ impulsiveness (e.g., fidgeting, interrupting in conversations). A patient must meet at least six of one of these sets of criteria to be diagnosed with ADHD. The subdivision into hyperactive-impulsive, inattentive, or combined type depends on whether the first, the second or both set of criteria have been met.

One significant aspect of ADHD as compared to other mental health conditions is that formal diagnosis also requires presence of symptoms by age seven. This means that, under current definitions (APA 2000), there is no such diagnosis as "adult onset" ADHD. Instead, one can only refer to "adult

[1] Specifically dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulphate

diagnosed" ADHD (i.e., although present since childhood, it has only been diagnosed in adulthood). With increasing awareness of adult ADHD, these childhood-based diagnosis criteria are a topic of discussion in the field (Barkley 2009). It is likely that DSM-5 will change the required age at which symptoms need to be present to 12 and relax other criteria for adult diagnoses (APA 2010).

Study Objective

This study examines whether non-ADHD-related medical and pharmacy costs vary depending on what type of ADHD medication is used to treat the adult with ADHD, as reflected in a retrospective claims data analysis of a large, commercially insured population.

Non-ADHD-related cost outcomes for five treatment modalities will be compared. These include brand name Adderall (a product of Shire Pharmaceuticals, this is the most-commonly prescribed medication for ADHD in adults), generic Adderall, brand name non-Adderall stimulants, generic non-Adderall stimulants, and atomoxetine (brand name Strattera), the only non-stimulant.

Additionally, non-ADHD-related cost outcomes will be compared for those taking generic vs. brand name stimulants (e.g., excluding atomoxetine (Strattera), which is not a stimulant).

Theoretical Framework

In theory, effective medication control of ADHD would lead to reduced non-ADHD- related medical and pharmaceutical costs, given that adequate control of the inattentive and impulsive components of the disease could lead to a reduced risk of injury, reduced daily stress in the person's life, and improved control in the case of metabolic diseases such as diabetes which benefit from person self-management.

Additionally there is a question as to whether generic medications used to treat ADHD have similar results than the brand name, given the Food and Drug Administration's (FDA's) allowed variation in bioavailability (FDA 2008).

Research Questions

Research Question 1: Is there a statistically significant difference in total non-ADHD-related medical and prescription costs among adults aged 18-64 with ADHD receiving the following types of medication treatment for ADHD: brand name Adderall, generic Adderall, brand name non-Adderall stimulants, generic non-Adderall stimulants, or atomoxetine (Strattera)?

Associated Null Hypothesis: There is no significant difference in total non-ADHD related medical and prescription costs among adults aged 18-64 with ADHD receiving medications from these five groups.

Research Question 2: Is there a statistically significant difference in total non-ADHD-related medical and prescription costs between adults aged 18-64 with ADHD receiving brand name stimulant treatment for ADHD and those receiving generic stimulant treatment for ADHD?

Associated Null Hypothesis: There is no significant difference in total non-ADHD related medical and prescription costs between adults aged 18-64 with ADHD receiving brand name stimulant treatment for ADHD and those receiving generic stimulant treatment for ADHD.

Significance Statement

Although there have been previous retrospective claims-based studies which compare total costs for ADHD adults treated with different types of medication, the most recent one only had data up to 2004 (Wu et al. 2007). This would provide limited data on atomoxetine (Strattera) since it was only approved and released in 2003. Additionally, no study has attempted to see if there is a significant difference in results in non-ADHD-related costs due to whether the medication taken is brand name or

generic. This is an important aspect to review given the increased trend in health plans towards requiring generic medication.

Definition of Terms

ADHD. Attention Deficit Hyperactivity Disorder.

ADHD, Inattentive Type. Form of ADHD that displays predominantly characteristics of inattention.

ADHD, Hyperactive Type. Form of ADHD that displays predominantly hyperactive-impulsive manifestations.

ADHD, Combined Type. Form of ADHD that displays characteristics both of inattention and of hyperactive-impulsive behavior.

Atomoxetine (Strattera). The only non-stimulant medication to be approved for treatment of ADHD in adults. It was approved by the FDA in 2003.

AWP - Average Wholesale Price. National average of wholesale prices charged to pharmacies for drugs by drug companies.

Axis I. Axis in DSM-IV used to report all clinical disorders except personality disorders and mental retardation.

DSM-IV-TR. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Manual published by the American Psychiatric Association that classifies and assigns codes to all mental health disorders.

HEDIS. Healthcare Effectiveness Data and Information Set. Evaluation standards published by the National Commission for Quality Assurance (NCQA).

IPSD. Index Prescription Start Date.

ICD-9-CM. International Classification of Diseases – 9th Edition – Clinical Modification

Methylphenidate. Form of CNS stimulant medication used to treat ADHD.

Mixed amphetamine salts (Adderall). Stimulant medication used to treat ADHD. It is a mixture of dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate.

Presenteeism. As opposed to absenteeism, this refers to being present at one's employment but not appropriately productive.

II: Review of the Literature

Introduction

A literature review was conducted using PubMed and PsycInfo for published journals. Additional sources used included the Center for Disease Control (CDC)'s ADHD website (CDC 2011) and bibliographies/ references found at the end of identified articles. This literature review was been organized by subtopics relevant to this research within the general topic of adult ADHD.

Prevalence and Treatment of ADHD in the US

Per a recent CDC report, 5.4 million children 5-17 years of age in the US have ever been diagnosed with ADD as of 2007 (CDC 2011). Between 2003 and 2007, the percentage of children aged 4-17 years with a parent-reported ADHD diagnosis increased from 7.8 to 9.5% (MMWR 2010).

As stated by Kessler et al., ADHD in adults has only recently become the focus of widespread clinical attention, and this neglect has led to its being left out of significant major US psychiatric epidemiological surveys (Kessler et al. 2006). This, along with other factors such as reluctance to self-report and the childhood-oriented nature of the criteria has led to difficulties in establishing prevalence.

Although originally identified exclusively as a childhood condition, it is now known that ADHD symptoms carry on into adulthood for a significant proportion of those who have had ADHD in childhood. Estimates of this proportion range from 50% to 80% (Barkley 2007; Mannuzza et al. 1993).

One 2006 telephone survey study estimated a 2.9% prevalence when using strict DSM-IV criteria (referred to in the study as "narrow ADHD") and 16.4% when using sub-threshold criteria (referred to in the study as "broad ADHD") (Faraone and Biederman 2005). Kessler's more recent survey-based study

estimates prevalence in adults aged 18+ at 4.44% and this is currently the generally accepted estimate (Kessler et al. 2006).

In Kessler's study sample, only 10.9% of respondents with a diagnosis of ADHD had received treatment for ADHD in the previous twelve months (Kessler et al. 2006). Using 2009 estimated US Census data (*U.S. Census Bureau - Population Finder*)[2] , these prevalence and treatment figures would translate into over nine million adults with ADHD, of which less than one million had received treatment.

ADHD Distribution and Symptomatology by Sex

In childhood, there is a considerably higher prevalence of diagnosed ADHD among boys (13.2%) than among girls (5.6%)(CDC 2011). This may be a factor of different behavioral patterns in females versus males, which leads to earlier reporting of males to clinics (Biederman et al. 1999; Rasmussen and Levander 2009). There is conflicting research as to whether this evens out in adulthood. The Kessler study of adults with ADHD showed that being male is still a significant factor in being diagnosed with ADHD (OR 1.6, 95% CI 1.0,2.5) (Kessler et al. 2006).

SOCIAL CONSEQUENCES OF ADHD

Barkley's study based at the University of Massachusetts Medical center compared a large sample of clinic-referred adults with ADHD to adults with other disorders and to a community control group (Barkley, Murphy, and Fischer 2008)(p. 39).This study found impairment in many domains of

[2] (Total 2009 Estimated Population 307 million x 75.4% age 18 and over = 231 million)

function, including education, home responsibilities, occupation, and dating or marriage. (Barkley, Murphy, and Fischer 2008) (p.141). It also important to note that "clear evidence of clinically significant impairment in social, academic, or occupational functioning" is one of the required criteria for diagnosing ADHD, so it is expected to see evidence of these types of impairment in a diagnosed population.

ADHD and Educational Attainment

The effects of ADHD such as distractibility and impulsivity create challenges both for the child and for the adult in the academic arena. As would be expected, research in the area of education and adult ADHD tends to be conducted among the college-aged student population.

Mannuzza et al.'s early (1993) study of "adult outcome of hyperactive boys" showed "significantly compromised educational attainments" which were "dependent on the continuation of ADHD symptoms (Mannuzza et al. 1993)." Heiligenstein et al.'s 1999 study comparing students with ADHD (n=26) and a control group of students without ADHD (n=28) showed that students with ADHD had lower average GPAs (2.5 vs. 3.2), and increased likelihood of being on academic probation (0.38 vs. 0.07). In Barkley's UMass study, the majority of adults with ADHD reported being impaired in educational activity (Barkley, Murphy, and Fischer 2008) (p.141).

ADHD and Employment

ADHD can lead to significant loss of productivity in terms of both absenteeism and presenteeism (Hilton et al. 2009; Kessler et al. 2005). The adult with ADHD can have difficulty in initiating, managing or completing complex projects on time in an efficient or organized manner. The high-functioning ADHD

adult may still have difficulties when confronting particularly challenging tasks such as passing medical boards or completing a dissertation (Nadeau 2005)

A correlation has been found between work productivity and ADHD in the US, with estimates ranging from 28.3 to 35.0 days of annual lost work performance (including absenteeism and presenteeism) (de Graaf et al. 2008; Kessler et al. 2009)– this last figure would lead to an estimate of 120 million days of work lost annually in the US (Kessler et al. 2005).

Household incomes among persons with ADHD have been demonstrated to be significantly lower than those of controls (Biederman and Faraone 2006).

A recent "domain-overlapping" study of the work performance of college students with ADHD shows significantly increased likelihood of being fired (M = 0.5, SD = 1.1) for college students with ADHD as compared to the non-ADHD control group (M = 0.2, SD = 0.5). Additionally, when asked to self-rate their work performance, students with ADHD were more likely to rate their work performance as poorer than those without ADHD ((M = 2.5, SD = 0.8) vs. (M = 2.0, SD = 0.9))(Shifrin, Proctor, and Prevatt 2010).

ADHD in Marriage/ Partnerships

All the symptoms of ADHD such as distractibility and impulsivity can have a negative impact on the primary relationships of the adult with ADHD. Additionally, the process of starting and adjusting to medication therapy can pose challenges to the other members of the ADHD adult's family. As stated by Eakin et al., although there is extensive anecdotal evidence of the effect of ADHD on relationships, there has been limited formal research conducted in this specific domain among adults with ADHD (Eakin et al. 2004).

Earlier studies (Biederman et al. 1993; Murphy and Barkley 1996) found an increased rate of marriage and divorce when comparing adults with ADHD with non-ADHD controls. Barkley's UMass

study, however, reported that they did "not find differential rates of marriage or higher rates of divorce among the children growing up with ADHD or among the clinical-referred adults with ADHD"(Barkley 2011).

Eakin et al.'s 2004 study reported significantly poorer marital adjustment (in areas of satisfaction, consensus, affectional expression, and cohesion) and significantly poorer general family functioning (Eakin et al. 2004).

One qualitative study of partners of those who had been diagnosed with ADHD as an adult reflected that the partner had had to go through a similar process of psychological adaption as the ADHD person. Additionally partners noted improvement in problem areas once the patient was medicated, but noted that medication, while helping, was not a panacea (Young, Gray, and Bramham 2009).

ADHD and Psychiatric Comorbidities

The most common psychiatric comorbidities for ADHD are depression, anxiety, substance abuse and sleep disorders; (Barkley 2011; Wilens 2007). Kessler et al.'s 2006 study found that 38.3 % of the respondents with ADHD had a mood disorder (18.6% major depressive disorder, 19.4% bipolar disorder, 12.8% dysthymia). The same study found that 47.1% of respondents with ADHD had at least one type of anxiety disorder and that 15.2% had at least one type of substance abuse disorder (Kessler et al. 2006). These high rates are confirmed by other studies that show significant rates of mental health comorbidity in persons with ADHD (Biederman et al. 1993; Secnik, Swensen, and Lage 2005; Friedrichs et al. 2010).

Increased Health Risks for Adults with ADHD

ADHD and Increased Rate of Injury

Although there is a large body of research linking ADHD to increased rate of injury in children there are not many studies in adults. The grounds for an increased injury rate have not been clearly determined, although one could hypothesize that elements of distraction or impulsivity would lead to increased "accident-proneness" (Swensen et al. 2004). Marcus et al.'s Medicaid claim-based study of adolescents with ADHD had a finding that approached significance - those with a higher rate of "medication possession ratios" (e.g., those that have prescriptions on hand as evidenced by filling prescriptions as expected) had a lower risk of accidents (HR = 0.9, p = 0.07) (Marcus et al. 2008).

One factor that could contribute to an increased rate of injury would be the increased rate of driving incidents/ accidents for persons with ADHD, which has been established in multiple studies (Richards et al. 2006; Barkley 2004).

Swensen et al.'s retrospective claim-based study of adults (aged 18 and above), children (aged under 12) and adolescents (aged 12 to 18) found that having at least one diagnosis of ADHD was a significant predictor of having at least one accident claim in adults (38% vs. 18% for non-ADHD controls, $p<.05$) although they found that costs were equal among both groups if you compared only patients that had had accidents (whether they had ADHD or not). Merrill et al.'s retrospective claim study for 1998-2005 shows an increased rate of specific types of injury for adults with ADHD vs. adults without ADHD, including intracranial injury (RR = 3.8, 95% CI = 2.8, 5.3), internal injury of thorax, abdomen, and pelvis (RR = 3.1, 95% CI = 1.4, 7.0), and burns (RR = 1.96, 95% CI = 1.1, 3.6) (Merrill et al. 2009).

ADHD in Adults and Non-Psychiatric Comorbidities

There is little research in the area of adult ADHD and its relationship to non-psychiatric, non-injury-related comorbidities. One of the few existing studies reported a significant increase in the likelihood of having asthma among adults with ADHD compared to those without ADHD ($p<.01$)(Secnik, Swensen, and Lage 2005).

Although one could hypothesize that adults (and children) with diabetes would have difficulties in self-managing the disease, thus leading to worse diabetic outcomes, surprisingly there has only been one study that refers to this. This is a case study of two young adolescents - one was a 12-year-old African-American/Hispanic male on oral and injected insulin therapy and the other was an 11-year, 4-month-old Caucasian male on an insulin pump. Customized behavioral management intervention was posited to improve compliance with diabetes management and lead to improved diabetes outcomes such as lowering of glyocsylated hemoglobin (HbA1c). In the first case, compliance with treatment regimen was shown to improve, and the subject's HbA1c level dropped from 10.2 to 8.5 after 12 weeks of therapy. In the second case, compliance also improved throughout the intervention. The HbA1c level, however, increased slightly from 8.7 to 9.1 at 12 weeks, but then decreased to 8.2 at week 24 (Sanchez, Chronis, and J. Hunter 2006).

Stimulant drugs such as methylphenidate are associated with a rise in blood pressure and heart rate. Although there have been limited safety evaluations (Adler, Wilens, et al. 2009; Adler, Zimmerman, et al. 2009; Godfrey 2009; Biederman et al. 2005), there are no specific studies on the relationship between ADHD medication use and incidence of cardiac conditions in adults.

HEALTHCARE COSTS IN PERSONS WITH ADHD

There are limited studies on healthcare costs for adults with ADHD, although, as would be expected, there are frequent studies in the pediatric population. Adults with ADHD have been determined to have higher healthcare costs than those without ADHD, including costs for prescriptions, inpatient and outpatient costs, and total costs (Secnik, Swensen, and Lage 2005). Compared to other diseases, one study put total medical costs of persons with ADHD at less than those for diabetes or depression but more than those for a seasonal allergy (Hinnenthal, Perwien, and Sterling 2005). This study used mutually exclusive groups, thus not taking into account the frequency of depression as a comorbidity for ADHD.

Wu et al.'s retrospective claim study of adults with ADHD (data collected from 1999-2004) compared costs associated with extended-release methylphenidate (OROS-MPH), mixed amphetamine salts extended release (MAS-XR), and atomoxetine. They found that "After adjusting for patient characteristics including substance abuse, depression, and the Charlson Comorbidity Index, adults treated with OROS-MPH had, on average, slightly lower medical and total medical and drug costs than those treated with MAS-XR or atomoxetine over the 6-month period after drug therapy initiation." (Wu et al. 2007) . This is one of the most recent studies evaluating drug costs and has provided some of the structure used to design this study. This study builds on the previous study by evaluating non-ADHD-related costs (as opposed to just total costs), including more data since the introduction of atomoxetine (Strattera) for use in the adult ADHD population in 2003, and comparing groups taking generic stimulant medication to those taking brand name stimulant medication.

III: METHOD

Data Source

The Thomson Reuters MarketScan® claims database was used. This database is available commercially or under special license for research purposes. The version used covered between 10.6 million (2004) and 26.9 million (2008) employees and their dependents enrolled in commercial insurance as provided by larger employers in the U.S. The files accessed had been specifically modified to exclude patients who had no prescription benefits under their insurance. Most of the persons in the MarketScan® database are age 64 and under.

The Emory Institutional Review Board (IRB) determined that this project did not require IRB review because it did not meet the definition(s) of "research" involving "human subjects" or the definition of "clinical investigation" as set forth in Emory policies and procedures and federal rules, specifically because in this project, the data being analyzed would be non-identifiable data from de-identified datasets.

For each of the five years of data used in this study (2004-2008), three initial data files were available:

The *medical claims file* included all inpatient and outpatient claims for the enrollees. In addition to the deidentified person ID, significant data elements included ICD-9-CM diagnoses (primary and eight others), age, sex, service location (inpatient vs. outpatient) and charges, payments, adjustments, and person copays for each claim. Procedure codes and DRG codes for inpatient claims were also available but were not used in this analysis (with the exception of

some DRG codes that were used by the HCUP program for assignment of Elixhauser comorbidity codes to inpatient claims).

The *drug claims file* included all outpatient pharmacy claims for enrollees. In addition to the person ID, significant data elements included the National Drug Code (NDC), date medication was dispensed, total Average Wholesale Cost (following Red Book data), net amount paid by insurer, and generic or brand indicator.

The *enrollment/ costs file* had one record for each covered person. In addition to the person ID, significant data elements included 12 enrollment indicator variables, one for each month of the year. It is important to note that persons were not tracked across plans, which meant that if a person switched plans he or she would obtain a new ID in this database, so it would be impossible to follow them from plan to plan. This meant that to meet our enrollment requirements for inclusion a person had to be enrolled for a minimum of 16 months in the same plan. If a person stayed with the same plan from year to year, he or she would keep the same person id from year to year.

Database and Statistical Software

SAS statistical software version 9.2 (SAS Institute Inc., Cary, NC, USA) was used to build the analysis database and for some early analysis. Stata version 11.2 (StataCorp LP, College Station, TX, USA) was used for the final statistical analysis.

ADHD – Code Assignment

In DSM-IV-TR, ADHD is coded on Axis I (Clinical disorders, including major mental disorders, and learning disorders). The numeric codes used are the same ones that are used in the International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM). The ICD-9-CM/ DSM-IV codes used for ADHD are 314.00 for the predominantly inattentive type and 314.01 for both the hyperactive-impulsive and the combined types.

It is worth noting that a third code exists (314.9 Attention-Deficit/Hyperactivity Disorder, Not Otherwise Specified). This is assigned to those patients who have prominent symptoms that only partially meet the formal ADHD criteria (e.g., have an age of onset higher than seven). Previous studies have not used this code, as it does not meet formal criteria for the ADHD diagnosis. It has not been used in this study either.

ADHD National Drug Code (NDC) List

An ADHD drug NDC list file was developed based both on research on the FDA's online NDC code database (FDA 2011) and on the NCQA's list of 428 NDC codes that are to be used to identify medications prescribed for ADHD (NCQA). An indicator variable was added which indicated a preliminary drug type grouping – Adderall, non-Adderall stimulants, and atomoxetine (Strattera), the only non-stimulant medication used. Later in the process the generic/ brand indicator available in the MarketScan® database was merged with this indicator to create the final five study groups (brand name Adderall, generic Adderall, brand name non-Adderall stimulants, generic non-Adderall stimulants, and atomoxetine (Strattera). No group was created for atomoxetine generic since atomoxetine (Strattera) was not available as a generic drug during the study period.

Elixhauser Comorbidity Indicator Assignments

The "Comorbidity Software , v. 3.6" (HCUP.2011) SAS-based program was obtained from the Agency for Healthcare Research and Quality (AHRQ's) Healthcare Utilization Project (HCUP) and was used to assign comorbidity indicators to patients in the final study sample. This publicly available SAS-based program applies 29 comorbidity indicator flags based on Elixhauser et al.'s "Comorbidity Measures for Use with Administrative Data" (Elixhauser et al. 1998). See Appendix *B - List of Elixhauser Comorbidity Indicators Assigned by HCUP Software* for a list of the comorbidity indicators.

HEDIS Inclusion Criteria

The following criteria are based on NCQA HEDIS guidelines (NCQA) *[Follow-up care for Children Prescribed ADHD Medication (ADD)]* . Although they have been designed for use in evaluating follow-up care for children with ADHD, they are also a useful way to identify adequate medication coverage in adults with ADHD. The criteria used are:

- Have an Index Prescription Start Date (IPSD) for an ADHD medication.
- Have a period of 120 days (4 months) prior to the IPSD during which time the member has no ADHD medications dispensed (new or refill). This requires at least four months of insurance enrollment before the IPSD to ensure no ADHD prescriptions were filled during this look back period.
- During the 300 days following the IPSD, have at least 210 days of medication coverage.

Determination of Non-ADHD-Related Costs

The following process was used to identify costs as "Non-ADHD-Related" and apply a Non-ADHD-Related indicator to each claim. Once all medical claims (inpatient and outpatient) for the final population sample had been extracted, all claims that had either of the two relevant ICD-9-CM codes (314.00, 314.01) in any of the nine diagnosis fields were excluded. The Net Amount Paid by the insurer on the remaining claims (after any copays or deductibles) were added up for each person and determined to be that person's "non-ADHD-related" medical costs for the year. The decision to use the Net Amount Paid was based on the methods used in Wu et al's 2007 study (Wu et al. 2007).

For prescription claims, once all the prescription claims had been extracted for the population sample, an ADHD-related/ non-ADHD-related indicator was added to each claim based on whether or not the claim's NDC number was present in the list of NDC codes determined above (in *ADHD National Drug Code (NDC) List)* . The Average Wholesale Price (AWP) was added up separately for each person's ADHD-related and non-ADHD-related claims for the 12 months studied. AWP, as obtained from the *Drug Topics Red Book,* is a standard cost indicator frequently used to evaluate prescription claim cost (Muennig 2008).

Adjustment for Inflation

Since the claims spanned a period of five years (2004-2008), it was necessary to bring all cost figures up to 2008 (the last year of data studied). Semi-annual inflation indices from the Consumer Price Index (CPI) (*Consumer Price Index - CPI Tables* 2011) from the first half of 2004 through the first half of 2008 were applied to inflate all costs to their equivalent in the second half of 2008. The CPI Medical Care

Services index was used for medical costs and the Medical Care Commodities inflation index was used for pharmaceutical costs.

POPULATION AND SAMPLE

The data source comprised five years (2004-2008) of medical and pharmacy claims obtained from Thomson Reuters' MarketScan® database (details above). The population ranges from 10.6 million enrollees in 2004 to 26.9 million enrollees in 2008 (average 17.0 million enrollees).

Inclusion Criteria

The study population was defined as adults meeting the following inclusion criteria:

- Age 18-64
- At least one diagnosis of ADHD (DSM-IV/ ICD-9 code 314.00 or 314.01)
- Met HEDIS criteria detailed above for ADHD medication initiation and coverage and met following enrollment criteria:
  - Enrolled for four months prior to the IPSD in order to ensure there were no ADHD prescriptions in these four months
  - Enrolled for at least 12 months starting with the IPSD month in order to ensure that 12 months of data were obtainable

Exclusion Criteria

- Prescriptions for more than one type of ADHD medication during the 12 month/ (365 day) post-IPSD evaluation period (e.g., switching from Adderall to atomoxetine or an overlapping period during which they had prescriptions for more than one type of medication).

- Age less than 18 on IPSD (a small number of persons (n=8) were initially identified as being in the correct age range but had actually turned 18 during the study period).

RESEARCH DESIGN

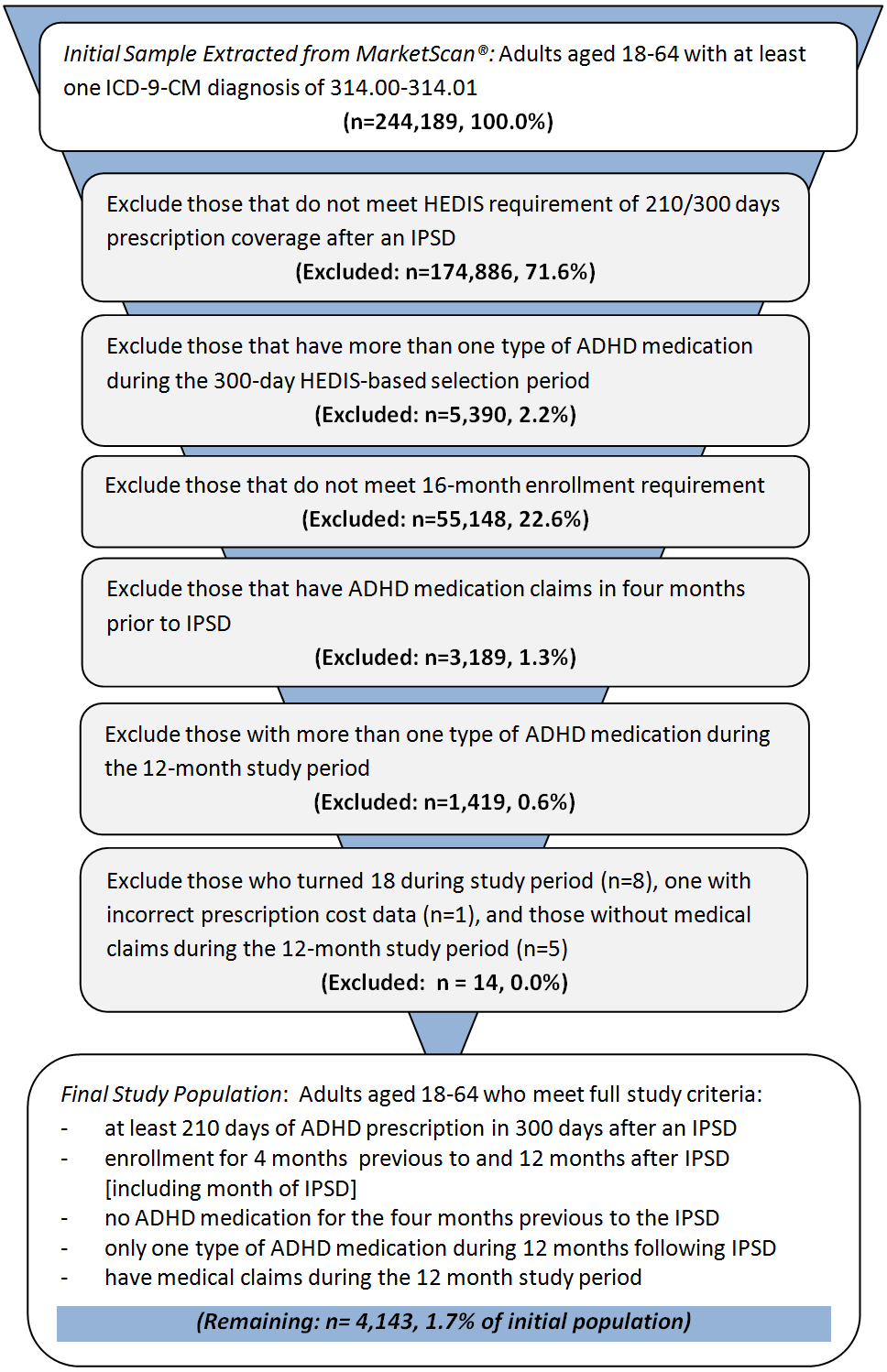
This is a retrospective cross-sectional study based on existing medical and pharmacy claims data.

PROCEDURES

Development of Analytic Database/ Population Sample

The population sample selection process is summarized in Figure 1 below. After selecting those patients aged 18-64 with at least one claim with an ADHD diagnosis (n=244,189), the HEDIS criteria already referred to were applied in sequence. Subsequently, those who were on more than one type of medication during the 12 months of claims studied were excluded. Finally, 14 cases that had other problems such as corrupted/miscoded cost data, age less than 18 at some point during the study period, or no medical claims during the study period were excluded, leaving us with a population sample of 4,143 patients/cases.

FIGURE 1 – SAMPLE SELECTION FROM POPULATION OF APPROXIMATELY 13 MILLION ENROLLEES



Note: IPSD = Index Prescription Start Date

STUDY VARIABLES

Outcome Variables

Total Costs. Total costs represent average total costs (both ADHD-related and non-ADHD related) including medical and prescription for the 12 month study period for each patient/"case".

Total Non-ADHD-Related Costs. These are average costs for Non-ADHD-Related medical and prescription costs as defined earlier.

Total Medical Costs. These are total costs (both inpatient and outpatient) excluding prescription claims, whether ADHD-related or not.

Total Non-ADHD-Related Medical Costs. This variable represents medical-only costs (e.g., excluding prescription) that have been determined to be non-ADHD-related as per criteria provided above.

Demographic Variables

Age. There are indications that ADHD prevalence decreases with age both due to a lower rate of identification and to possible diminution of symptoms with age(Simon et al. 2009). Age is presented both as a continuous variable (Age) and as a five-tiered ordinal categorical value that divides the population into five age groups: 18-25, 26-35, 36-44, 46-55, and 56-64.

Female (Sex). For this dichotomous variable, a value of "1" indicates that the patient is female and a value of "0" indicates that the patient is male.

MHSA. This dichotomous variable indicates whether an individual is covered by his or her insurance plan for mental health and substance abuse services. It is included under the assumption that ADHD-related mental health service claims would be more likely to be present in this database if the patient had this type of coverage, thus leading to a higher reported cost. A value of "1" indicates that the patient has this type of coverage and a value of "0" indicates that the patient does not have this type of coverage.

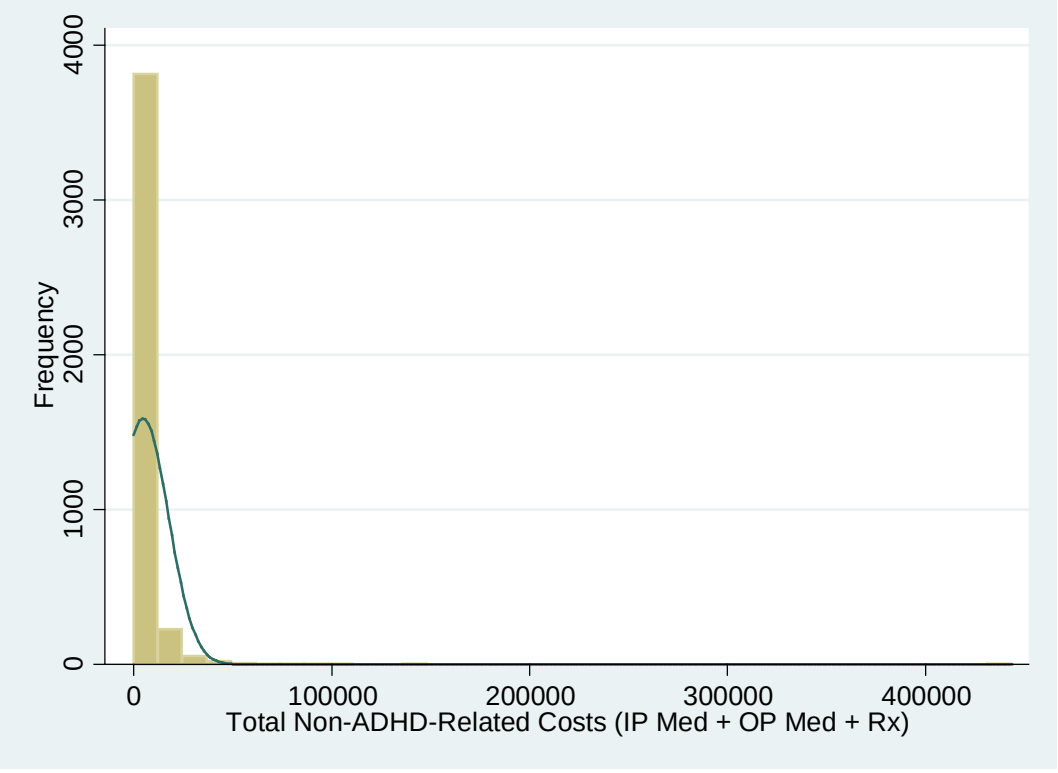
Comorbidities

The Elixhauser Comorbidity software Combined Medical Comorbidities Indicator assigns 29 dichotomous comorbidity indicators based on ICD-9-CM diagnoses found on claims. These were divided up into 25 "non-mental-health" comorbidities and 4 mental health comorbidities. The 25 non-mental-health comorbidities were combined into one continuous ordinal variable ranging from 0 to 25 that was named the "Combined Medical Comorbidities Indicator" (see *Appendix B - List of Elixhauser Comorbidities Assigned by HCUP Software* for the list of comorbidities that were combined into this variable). The four comorbidities related to mental health diagnoses (alcohol abuse, substance abuse, psychoses, and depression) remained as dichotomous variables for which a value of "1" indicated that the diagnosis had been identified in at least one of the medical claims for this individual.

DATA ANALYSIS

One of the known challenges for analyzing health care utilization cost data is its lack of normal distribution(Diehr et al. 1999). Health care cost data is frequently skewed to the right, with a small percentage of patients accounting for a large proportion of costs. This database was no exception to the rule, as identified by a simple frequency plotting of our total non-ADHD-related costs outcome data on a histogram produced in Stata (Figure 2). Note that the distribution is particularly skewed by two outlier cases in which calculated total non-ADHD-related costs are more than $400,000 (with the next highest case at $143,000). These were kept in the study population since they appeared to be fully valid cases with no reason to be excluded.

FIGURE 2 – DISTRIBUTION - TOTAL NON-ADHD-RELATED COSTS



The skewed nature of healthcare cost outcome distributions is well known, and historically multiple approaches have been taken to deal with this. In some situations Ordinary Least Squares (OLS) methodology has been used, even though the underlying assumptions of a normal distribution and homoscedasticity for OLS have not been met (Tyree, Lind, and Lafferty 2006). The most common approaches to working with this type of data, though, have generally included conducting a log transformation of the dependent variable prior to OLS regression estimation or the estimation of a generalized linear model using the gamma distribution with a log link function (Tyree, Lind, and Lafferty 2006).

For this study, we estimated generalized linear models with log links and gamma distribution distributions using the *glm* procedure in Stata version 11.2. Subsequently, we estimated marginal effects for the variables of interest at the mean value of the covariates using the *mfx* procedure. Finally, Wald tests were estimated to compare the four non-reference groups using Stata's *test* procedure.

Additionally, post-hoc analyses using the same Stata procedures/ statistical methods for the same two research questions were performed on the subpopulation of adults aged 18-25 (n=1,248). We examined this population separately because it represented the largest age sub-group within the total population (30.1%) and would be more likely to include patients who had already been identified as having ADHD as children. Additionally, we were interested in analyzing this subpopulation because it would be more likely to be affected by injury-related costs (theoretically those most amenable to reduction by use of adequate medication control). Finally, one would expect fewer comorbidities for a younger, healthier population (with the exception of alcohol and substance abuse).

IV: RESULTS

POPULATION STATISTICS

Population descriptive statistics are presented in Table 1. Of the 244,200 adults aged 18-64 with at least one diagnosis of ADHD identified in the five years of MarketScan® data available, 4,143 (1.9%) met the criteria discussed above for inclusion into the analytic sample. Values are provided both for the total sample population of 4,143 and for the five studied subgroups (brand name Adderall, generic Adderall, brand name non-Adderall stimulants, generic non-Adderall stimulants, and atomoxetine (Strattera)).

All outcome variables are expressed in terms of annual average costs in inflation-adjusted US dollars. These are presented for the total sample and for each of the five medication treatment groups. The Net Amount Paid on the claim was used to determine cost for all medical claims (both inpatient and outpatient) and Average Wholesale Price (AWP) was to determine costs for all prescription claims.

For purposes of this study, medical costs were defined as being non-ADHD-related if they did not have at least one ICD-9-CM diagnosis of 304.00 or 304.01 on the claim. Prescription costs were determined to be non-ADHD-related if the NDC number used on a prescription claim was not on the list of ADHD drugs developed earlier on.

TABLE 1 – DESCRIPTIVE STATISTICS - ADULTS AGED 18-64 WITH AT LEAST ONE DIAGNOSIS OF ADHD RECEIVING DIFFERENT TYPES OF ADHD MEDICATION

	Total (n = 4,143)	Adderall Brand (n= 1,692)	Adderall Generic (n=542)	Non-Adderall Stimulant Brand (n = 981)	Non-Adderall Stimulant Gen. (n=374)	Strattera/ Atomoxetine (n=554)
*OUTCOME VARIABLES**						
Total Costs	6,850.6 (15,219.4)	6,640.9 (14,284.8)	5,249.5 (6,518.7)	7,278.9 (22,317.4)	7,143.6 (9,840.2)	8,101.4 (10,808.5)
Total Non-ADHD-Related Costs	4,749.7 (12,798.9)	4,437.9 (13,752.5)	3,797.5 (6,010.3)	4,957.4 (15,851.7)	5,886.7 (9,270.2)	5,497.9 (10,359.5)
Total Medical Costs	3,420.2 (14,300.3)	3,292.6 (13,509.8)	2,564.2 (4,731.2)	3,804.2 (21,571.1)	3,648.6 (8,122.3)	3,813.1 (9,021.7)
Total Non-ADHD-Related Medical Costs	2,879.4 (11,867.1)	2,835.4 (13,070.0)	2,146.5 (4,204.3)	3,037.6 (15,046.8)	3,070.6 (7,531.2)	3,321.8 (8,653.4)
Total Outpatient Medical Costs	2,650.7 (8,539.4)	2,723.2 (12,138.6)	2,124.9 (3,522.5)	2,558.6 (4,739.1)	2,891.1 (4,950.0)	2,944.2 (5,170.6)
Total Non-ADHD-Related Outpatient Medical Costs	2,353.7 (8,502.7)	2,454.0 (12,121.5)	1,840.4 (3,411.3)	2,231.5 (4,657.6)	2,585.1 (4,891.1)	2,609.9 (5,081.6)
Total Prescription Costs	3,430.4 (3,568.3)	3,348.3 (3,187.1)	2,685.4 (3,537.0)	3,474.7 (3,384.9)	3,495.0 (4,388.2)	4,288.3 (4,179.7)
Total Non-ADHD-Related Prescription Costs	1,870.2 (3,333.7)	1,602.5 (2,881.6)	1,651.0 (3,442.5)	1,919.8 (3,115.4)	2,816.0 (4,280.1)	2,176.1 (3,965.9)
Total ADHD-Related Prescription Costs	1,560.2 (966.2)	1,745.8 (976.5)	1,034.4 (565.1)	1,554.9 (903.4)	678.9 (542.6)	2,112.3 (955.2)

TABLE 1 – (CONTINUED) DESCRIPTIVE STATISTICS - ADULTS AGED 18-64 WITH AT LEAST ONE DIAGNOSIS OF ADHD RECEIVING DIFFERENT TYPES OF ADHD MEDICATION

	Total (n = 4,143)	Adderall Brand (n= 1,692)	Adderall Generic (n=542)	Non-Adderall Stimulant Brand (n = 981)	Non-Adderall Stimulant Gen. (n=374)	Strattera/ Atomoxetine (n=554)
EXPLANATORY VARIABLES						
DEMOGRAPHICS						
Age	35.1 (12.1)	32.6 (11.8)	36.3 (11.8)	38.8 (12.8)	38.8 (12.8)	37.9 (11.8)
Age 18-25	30.1%	35.5%	38.2%	24.5%	20.6%	22.4%
Age 26-35	21.6%	22.0%	25.5%	21.0%	20.1%	18.4%
Age 36-45	24.9%	22.9%	19.0%	28.9%	24.0%	30.5%
Age 46-55	17.9%	15.5%	12.6%	20.7%	24.1%	21.1%
Age 56-64	5.5%	4.1%	4.8%	5.0%	11.2%	7.6%
Female (Sex = 1)	51.9%	54.2%	56.8%	47.2%	50.0%	50.0%
Mental Health/ Substance Abuse coverage	69.3%	68.1%	68.3%	69.6%	70.9%	72.2%
COMORBIDITIES						
Combined Medical Comorbidities Indicator **	0.4 (0.8)	0.3 (0.7)	0.4 (0.7)	0.4(0.7)	0.5 (1.0)	0.5 (0.9)
Individual Mental Health Comorbidities ***						
Alcohol abuse	1.4%	1.4%	1.3%	1.2%	1.1%	2.0%
Drug abuse	1.3%	1.5%	0.9%	1.1%	0.8%	1.8%
Psychoses	12.7%	11.5%	10.9%	14.3%	17.1%	12.6%
Depression	13.8%	12.5%	13.7%	14.4%	13.6%	16.8%

**Results reported as mean (standard deviation) for continuous variables, percentage for proportions; all cost figures represent annual US dollars adjusted for inflation to the second half of 2008*

*** 25 Elixhauser medical (e.g., non-mental-health) comorbidities combined into one variable with range from 0-25 (See Appendix B for details)*

**** For mental health comorbidity variables, (1= yes)*

When examining the type of ADHD medication taken by the sample population, the largest group comprises those taking brand name Adderall at 40.1% - this group was used as the reference group. Brand name non-Adderall stimulants represent 23.7% of the sample, atomoxetine (Strattera) 13.4%, generic Adderall 13.1%, and generic non-Adderall stimulants 9.0%. If we consolidate these groups, we see that 64.5% were taking brand name stimulants (brand name Adderall and brand name non-Adderall stimulants), 22.1% were taking generic stimulants (generic Adderall and generic non-Adderall stimulants). The remaining 13.4% were taking atomoxetine (Strattera), a non-stimulant medication.

Total costs averaged $6,850.6 (SD = 15,219.4) for the entire sample population. The atomoxetine (Strattera) group showed the highest average total costs at $8,104.4 (SD = 10,808.5). This would be expected given that total costs include medication costs, and costs for atomoxetine (Strattera) appear to be the highest (see "Total ADHD-Related Prescription Costs "). Total Non-ADHD-Related Costs averaged $4,749.7 (SD = 12,798.9) with the generic non-Adderall stimulants group showing the highest average costs at $5,886.7 (SD = 9.270.2).

When examining sample demographics, the population's average age was 35.1 (SD = 12.1). If we examine the distribution by age groups, we find that the highest proportion of patients was in the age 18-25 group (30.1%) followed by the age 36-45 group (24.9%) and the age 26-35 group (21.6%). The prevalence decreases dramatically for the age 56-65 group (5.5%). As expected in the adult population, prevalence among sexes was even in all groups except among those taking generic Adderall. In this group, the prevalence of female individuals was slightly higher than in the other groups (56.8%).When examining other sample characteristics, insurance coverage for Mental Health and Substance Abuse Services (MHAS) is 69.3% for the total population sample, and appears to be fairly even across the five medication groups. The average value of the Combined Medical Comorbidities Indicator is 0.4 (SD = 0.8) for the total group, and shows even distribution across the five medication groups.

Of particular note in this population is the relatively high prevalence of identified depression (13.8% in the study sample vs. 5.4% reported by NHIC in the US population) (Pratt and Brody 2008). Depression is frequently identified as a comorbidity with ADHD, so this high level would be expected (Kessler et al. 2006; Barkley 2011). The identified level of substance abuse in this study is surprisingly low (1.3%) when compared with the 8.9% figure for those 12 and above in the general population published by the Substance Abuse and Mental Health Services Administration in 2009 (USDHHS.2009) and with the 4.8% rate for any substance use disorder among adults with ADHD cited in Kessler et al's 2006 study.

FINDINGS

Primary Research Question

Table 2 presents results for the primary research question for this study that seeks to assess whether there is a statistically significant difference in average total non-ADHD-related costs among patients in the five different treatment groups. The first section of the table compares average total non-ADHD-related costs between the four non-reference groups and brand name Adderall, the reference group. Examining the findings associated with each medication group, one sees that none of the coefficients or marginal effects are statistically significant at $\alpha = 0.05$. Additionally, all the 95% Confidence Intervals contain 0.

TABLE 2 – TOTAL NON-ADHD-RELATED COSTS FOR ADULTS AGED 18-64 TAKING FIVE DIFFERENT TYPES OF ADHD MEDICATION

	Total Non-ADHD-Related Costs Model 1 – Comparing with Adderall Brand (Reference)			
	Coefficient	**95% CI**	**Marginal Effect**	**95% CI for Marginal Effect**
Adderall Generic[a]	-0.12	-0.35 to 0.12	-408.76	-1,205.75 to 388.23
Non-Adderall Stimulant Brand[a]	0.04	-0.23 to 0.15	-139.36	-834.74 to 556.03
Non-Adderall Stimulant Generic[a]	0.10	-0.17 to 0.37	385.37	-713.77 to 1,484.51
Strattera/ Atomoxetine[a]	0.11	-0.13 to 0.34	422.50	-520.06 to 1,365.06
Age	0.02***	0.01 to 0.03	71.50***	45.86 to 97.14
Sex (Female = 1)	0.23**	0.08 to 0.38	852.93**	299.95 to 1,405.91
MHSA coverage	0.26**	0.10 to 0.43	934.72**	370.58 to 1,498.87
COMORBIDITIES				
Combined Medical Comorbidities Indicator	0.58 ***	0.47 to 0.69	2,155.83***	1,675.51 to 2,636.16
Mental Health Comorbidities				
Alcohol abuse	0.24	-0.39 to 0.88	1,017.56	-1,971.23 to 4,006.35
Drug abuse	0.52	-0.14 to 1.19	2,541.82	-1,562.09 to 6,645.72
Psychoses	0.57***	0.34 to 0.79	2,633.29***	1,301.61 to 3,964.97
Depression	0.39***	0.17 to 0.61	1,675.53**	576.87 to 2,774.19
-Const	6.88***	6.60 to 7.16		

Notes: N = 4,153, MHSA = MHSA coverage = Mental Health and Substance Abuse coverage by insurance company
**p < .05, ** p < .01, *** p < 0.001, † approaching statistical significance*
a – Reference value omitted - Adderall Brand Name

Table 3 shows results of Wald Chi-square tests used to compare results for the six remaining permutations among the non-reference groups. None of the results was statistically significant at $\alpha = 0.05$.

TABLE 3 – TOTAL NON-ADHD-RELATED COSTS FOR ADULTS AGED 18-64 TAKING FIVE DIFFERENT TYPES OF ADHD MEDICATION - WALD CHI-SQUARE TEST COMPARING THE FOUR NON-REFERENCE GROUPS

	Total Non-ADHD-Related Costs – Comparing Non-Reference Groups	
	Wald χ^2	p-value
Adderall Generic vs. Non-Adderall Stimulant Brand Name	0.4	0.545
Adderall Generic vs. Non-Adderall Stimulant Generic	1.7	0.187
Adderall Generic vs. Strattera/ Atomoxetine	2.4	0.125
Non-Adderall Stimulant Brand Name vs. Non-Adderall Stimulant Generic	0.9	0.351
Non-Adderall Stimulant Brand Name vs. Strattera/ Atomoxetine	1.3	0.255
Non-Adderall Stimulant Generic vs. Strattera/Atomoxetine	0.0	0.956

Based on these results, one fails to reject the associated null hypothesis that there is no significant difference in total non-ADHD related medical and prescription costs among adults aged 18-64 with ADHD receiving medications from these five groups at $\alpha = 0.05$.

It is worth nothing that, as would be expected, psychoses and depression have a statistically significant effect on total non-ADHD-related costs (ME=$2633.2, 95% CI=$1,301.61, $3,965.0 for Psychoses; ME=$1,675.5, 95% CI = $576.9, $2,774.2 for Depression).

Secondary Research Question

Table 4 presents results for this study's secondary research question that attempts to assess a difference in non-ADHD-related costs between patients taking brand name stimulant medication and those taking generic ADHD medication. Examining the indicator for those taking generic stimulant medication (versus the reference brand name stimulant medication) one sees that none of the

coefficients or marginal effects are statistically significant at α = 0.05. Additionally, all the 95% Confidence Intervals contain 0.

Based on these results, one fails to reject the associated null hypothesis that there is no significant difference in total non-ADHD related medical and prescription costs between adults aged 18-64 with ADHD receiving brand name stimulant medications and those receiving generic stimulant medications at α = 0.05.

TABLE 4 – TOTAL NON-ADHD-RELATED COSTS FOR ADULTS AGED 18-64 TAKING GENERIC STIMULANT ADHD MEDICATION VS. BRAND NAME STIMULANT ADHD MEDICATION (ATOMOXETINE (STRATTERA) EXCLUDED)

	Total Non-ADHD-Related Costs – Stimulant Generic vs. Brand Name Model 2			
	Coefficient	**95% CI**	**Marginal Effect**	**95% CI for Marginal Effect**
Stimulant Generic[a]	-0.01	-0.19 to 0.17	-31.67	-683.17 to 619.83
Age	0.02***	0.01 to 0.03	78.15***	53.12 to 103.18
Sex (Female = 1)	0.28**	0.12 to 0.44	1,011.78**	433.00 to 1,590.55
MHSA coverage	0.26**	0.08 to 0.43	877.40**	299.61 to 1,455.19
COMORBIDITIES				
Combined Medical Comorbidities Indicator	0.59***	0.47 to 0.71	2,103.53***	1,673.38 to 2,533.67
Mental Health Comorbidities				
Alcohol abuse	0.34	-0.37 to 1.05	1,458.31	-2,105.27 to 5,021.90
Drug abuse	0.48	-0.26 to 1.21	2,177.87	-2,030.69 to ,6386.43
Psychoses	0.59***	0.35 to 0.83	2,689.84***	1,298.21 to ,4081.48
Depression	0.41**	0.17 to 0.65	1,711.13**	536.95 to 2,885.30
-Const	6.75***	6.45 to 7.05		

Notes: N = 3,589, MHSA = MHSA coverage = Mental Health and Substance Abuse coverage by insurance company
**p < .05, **p < .01, ***p < 0.001*
a – Reference value omitted - Stimulant Brand Name

Additional Findings – Post hoc Analysis of 18- to 25-Year-Old Subpopulation

The post hoc analysis of the 18- to 25-year-old subpopulation provided the following results.

As suspected, when a brief analysis comparing age groups was done, we found that the highest rate of patients having at least one injury-related claim (ICD-9-CM – 800.00 – 995.49) was indeed in the 18- to 25-year -old age group (30.0%), followed by the 36-45 and 26-35 age groups (23.1% and 21.5% respectively). This validates our principal reason for undertaking additional post-hoc analysis in this sub-population.

Additionally, the identified prevalence of alcohol use in the 18- to 25-year-old population at 1.9% was higher than the identified prevalence of alcohol use in the whole sample population at 1.4%. Similarly, the prevalence of identified drug abuse at 1.9% in the 18- to 25-year-old population was higher than the total sample population prevalence of 1.3%.

Comparing the Five Medication Groups in 18- to 25-Year-Olds

Table 5 presents results for adults aged 18-25. For an adult with ADHD in this subpopulation, there is a considerable statistically significant increase in non-ADHD-related costs (ME = $1,754.8, 95% CI = $431.8, $3,077.7) for those patients taking atomoxetine (Strattera) compared to those taking brand name Adderall, our reference.

TABLE 5 – TOTAL-NON-ADHD-RELATED COSTS FOR ADULTS AGED 18-25 TAKING FIVE DIFFERENT TYPES OF ADHD MEDICATION

	Total Non-ADHD-Related Costs (Age 18-25 only) Model 3			
	Coefficient	**95% CI**	**Marginal Effect**	**95% CI for Marginal Effect**
Adderall Generic[a]	0.02	-0.28 to 0.33	50.04	-570.54 to 670.62
Non-Adderall Stimulant Brand[a]	0.00	-0.29 to 0.29	-6.11	-582.16 to 569.93
Non-Adderall Stimulant Generic[a]	0.19	-0.27 to 0.64	409.08	-665.03 to 1,483.19
Strattera/Atomoxetine[a]	0.63**	0.25 to 1.01	1,754.80**	431.88 to 3,077.71
Age	0.02	-0.03 to 0.07	39.24	-64.70 to 143.19
Sex (Female = 1)	0.27*	0.05 to 0.49	545.08*	95.83 to 994.34
MHSA coverage	0.41**	0.16 to 0.65	742.21**	309.61 to 1,174.81
COMORBIDITIES				
Combined Medical Comorbidities Indicator	0.86***	0.59 to 1.12	1,703.28***	1,175.01 to 2,231.55
Mental Health Comorbidities				
Alcohol abuse	0.04	-0.75 to 0.83	73.93	-1,556.92 to 1,704.79
Drug abuse	0.79†	-0.02 to 1.60	2,371.95	-1,113.71 to 5,857.62
Psychoses	0.88***	0.51 to 1.24	2,565.55**	1,010.63 to 4,120.48
Depression	0.64**	0.28 to 1.00	1,671.07**	424.89 to 2,917.26
-Const	6.45***	5.31 to 7.59		

Notes: N = 1,248 , MHSA = MHSA coverage = Mental Health and Substance Abuse coverage by insurance company
**p < .05, ** p < .01, *** p < 0.001, † approaching statistical significance*
a – Reference value omitted - Adderall Brand Name

Additionally, comparison of the four non-reference groups using Wald's Chi-square test (Table 6) showed a statistically significant difference between those taking generic Adderall and those taking atomoxetine (Strattera) ($\chi^2 = 7.6$, $p<.01$), and between those taking brand name non-Adderall stimulants and those taking atomoxetine (Strattera)($\chi^2 = 8.9$, $p<.01$).

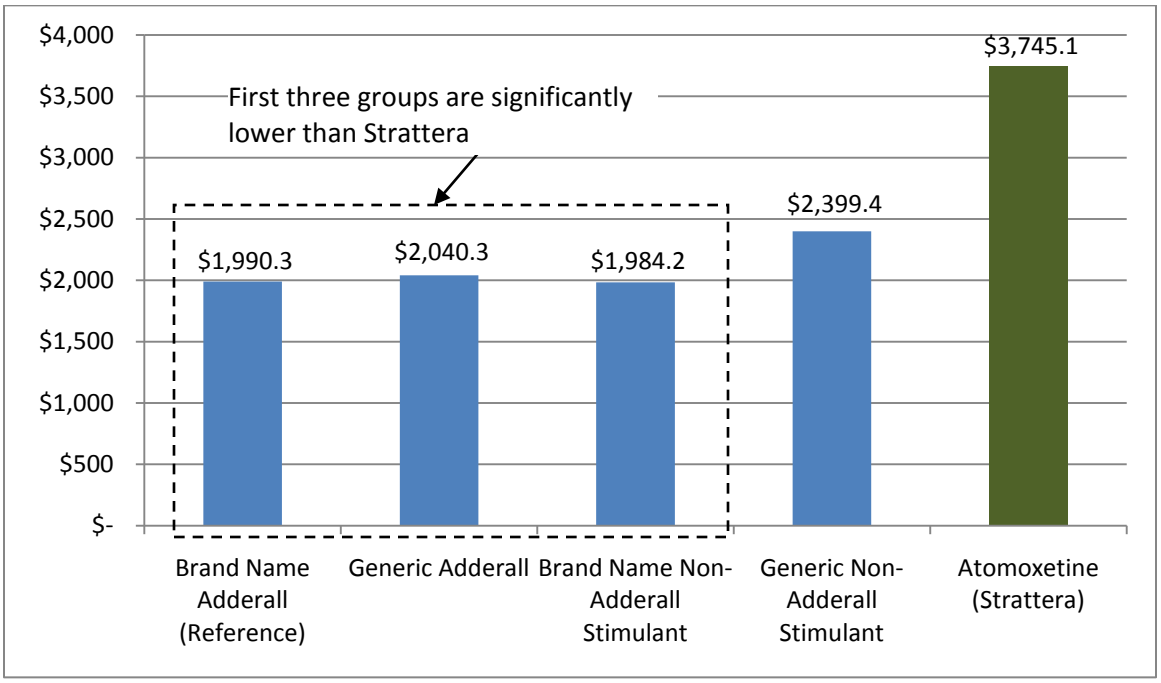
In both of these cases, the adjusted average total non-ADHD-related costs were higher for those taking atomoxetine (Strattera) - in the first (comparing to generic Adderall) by $1,704.8 and in the second (comparing to brand name non-Adderall stimulants) by $1,760.9.

Table 6 – Total-Non-ADHD-Related Costs for Adults Aged 18-25 Taking Five Different Types of ADHD Medication – Wald Chi-Square Test Comparing the Four Non-Reference Groups

	Total Non-ADHD-Related Costs – Comparing Non-Reference Groups	
	Wald χ^2	p-value
Adderall Generic vs. Non-Adderall Stimulant Brand	0.0	0.880
Adderall Generic vs. Non-Adderall Stimulant Generic	0.4	0.531
Adderall Generic vs. Strattera/ Atomoxetine	7.6	0.006
Non-Adderall Stimulant Brand vs. Non-Adderall Stimulant Generic	0.6	0.449
Non-Adderall Stimulant Brand vs. Strattera/ Atomoxetine	8.9	0.003
Non-Adderall Stimulant Generic vs. Strattera/Atomoxetine	2.5	0.110

Figure 3 presents a comparison of the adjusted mean non-ADHD-related total annual costs for adults aged 18-25 in each of the five medication groups.

Figure 3 – Adjusted Mean Total Non-ADHD-Related Costs for Adults Aged 18- 25 in Five Comparison Medication Groups



Note: Results reported as mean annual US dollars adjusted for inflation to the second half of 2008.

Comparing Total Non-ADHD-Related Costs in 18- to 25-Year-Olds Taking Generic versus Brand Name Stimulant ADHD Medication

The results for this analysis, provided in Table 7, show no statistically significant difference in non-ADHD-related for those 18- to 25-year-olds who are taking generic ADHD stimulant medications versus for those who are taking brand name ADHD stimulant medications. As in the analysis done for the full sample population, atomoxetine (Strattera) was specifically excluded from the analysis given that it was only available as a brand name product during the study period.

TABLE 7 – TOTAL NON-ADHD-RELATED MEDICAL COSTS FOR ADULTS AGED 18-25 TAKING GENERIC STIMULANT ADHD MEDICATION VS. BRAND NAME STIMULANT ADHD MEDICATION

	Total Non-ADHD-Related Costs – Stimulant Generic vs. Brand Name (Age 18-25 only) Model 4			
	Coefficient	**95% CI**	**Marginal Effect**	**95% CI for Marginal Effect**
Stimulant Generic[a]	0.08	-0.14 to 0.31	164.76	-305.67 to 635.20
Age	0.03	-0.02 to 0.08	57.80	-33.63 to 149.24
Sex (Female = 1)	0.35**	0.15 to 0.54	692.87**	285.49 to 1,100.26
MHSA coverage	0.42***	0.20 to 0.65	763.13***	381.61 to 1,144.65
COMORBIDITIES				
Combined Medical Comorbidities Indicator	0.96***	0.71 to 1.21	1,874.02***	1385.34 to 2,362.70
Mental Health Comorbidities				
Alcohol abuse	0.11	-0.61 to 0.83	227.86	-1343.39 to 1,799.11
Drug abuse	0.82*	0.03 to 1.61	2,449.73	-992.67 to 5,892.13
Psychoses	0.91***	0.58 to 1.25	2,682.92***	1256.19 to 4,109.64
Depression	0.70***	0.36 to 1.04	1,847.64**	647.39 to 3,047.89
-Const	6.16***	5.16 to 7.16		

Notes: N = 1,124, MHSA = MHSA coverage = Mental Health and Substance Abuse coverage by insurance company
**p < .05, ** p < .01, *** p < 0.001, † approaching statistical significance*
a – Reference value omitted - Stimulant Brand Name

Analysis of Average Total Injury-Related Medical Costs in 18- to 25-Year-Olds in Comparison to Average Total Injury-Related Medical Costs in the Other Age Groups

For the purpose of understanding whether injury rate was actually higher in the 18- to 25-year-old population, thus possibly making it easier to detect non-ADHD-related outcome differences in this group, an ANOVA was performed comparing mean injury-related costs as a percentage of total medical costs among the five age groups. The results for the ANOVA indicated that mean injury-related costs as a percentage of total medical costs was different at a statistically significant level between at least one of the comparison pairs ($F = 3.46$, $p<.01$).

Post hoc pairwise comparisons using the Sidak method only showed a statistically significant difference between the 18- to 25-year-old group and the 36-to 45-year-old population ($p<.01$).

V: DISCUSSION

This study attempted to answer a question significant to adults with ADHD in the US and to those who provide care for them. Is there a connection between the type of ADHD medication that an adult with ADHD takes and general health as reflected in costs for non-ADHD-related medical services and prescriptions?

No statistically significant differences in the total-non-ADHD-related cost outcomes were found in any of the comparisons in the full population. Additional post hoc comparisons were done in the 18- to 25-year-old subpopulation and a statistically significant increase in non-ADHD-related costs was found for those taking atomoxetine (Strattera) compared to those taking brand name Adderall, generic Adderal, or brand name non-Adderall stimulants.

One possible explanation for the finding that non-ADHD-related costs in the 18- to 25-year-old age group are higher for those taking atomoxetine (Strattera) than for those taking the reference brand name Adderall could be that substance abuse, depression, and alcoholism are known predictors for prescribing atomoxetine (Strattera) versus a stimulant medication (Van Brunt et al. 2006).This is possibly because it is seen as non-addictive and thus a better choice for those patients who have already demonstrated addictive behavior to substances. The identified prevalence of alcohol use in the 18- to 25-year-old population at 1.9% is higher than the identified prevalence of alcohol use in the whole sample population at 1.4%. Similarly, the prevalence of identified drug abuse at 1.9% in the 18- to 25-year-old population is higher than the total sample population prevalence of 1.3%. Given that this group is more likely to have alcohol and substance abuse issues, it is possible that substance and alcohol abuse was underidentified, even given the substantially higher prevalence identified in this group. Underidentification of these comorbidities would lead to their being insufficiently controlled for in the

model results and possibly explain some of the additional non-ADHD-related cost for those taking atomoxetine (Strattera).

Additionally, if one posits that injury rates and costs are amenable to reduction for those adults with ADHD who are on adequate medication control, it is possible that the impact of health issues related to injuries and accidents may be easier to detect in this age group, thus making it easier to identify variation in outcomes among the five different treatment groups. Post hoc analysis of mean injury-related costs as a percentage of total medical costs compared among the five age groups, though, only showed a statistically significant difference between the 18-to 25-year olds and the 36- to 45-year-old population.

Study Limitations

Several study limitations are noted. First, using the net insurance payment for evaluation of medical costs and the average wholesale price (AWP) for approximation of drug cost is not a perfect solution although it is an appropriate choice available given the data available. Second, patients who pay for their own medication in spite of having prescription coverage due to either restrictive insurance coverage guidelines or a desire to avoid having mental health related information in their record would not be identified. Third, a significant limitation to using a commercial claims database in this case is that on-the-job and automobile injuries are frequently billed to worker's comp or automobile insurance carriers rather than to the patient's primary or secondary health insurance. Consequently, this could lead to an artificially low identification of injury prevalence and the health care costs associated with injuries among working adults. Finally, although they are a valuable resource, medical claims are intended for purposes of billing and reimbursement rather than for research and may contain coding errors. (Curtiss and Fairman 2007). Assignment of ICD-9-CM diagnosis codes can be biased by practices

intended to maximize reimbursement and by insufficient training or experience in those assigning final codes to claims. Additionally, significant secondary diagnoses (which could be either the diagnosis studied or comorbidities) can be missed when submitting the claim, given the emphasis on primary diagnoses in most reimbursement systems.

Conclusions and Recommendations

For adults aged 18-64, no statistically significant difference in total non-ADHD-related costs among the five groups studied can be found using this commercial claims database. The same holds true when comparing adults aged 18-64 who are taking brand name versus generic stimulant medication. Among 18- to 25-year-olds, post hoc analysis found higher non-ADHD-related costs for those on atomoxetine (Strattera), as compared to those on brand name Adderall, generic Adderall, or brand name non-Adderall stimulants. This study lays the groundwork for future studies in adults with ADHD that seek to compare the effectiveness of different types of medication in control of ADHD symptoms, a key element of improving the ADHD patient's quality of life. Future studies can build on these findings by using different data sources to continue to examine whether health outcomes and health care utilization are comparable among those taking different types of medication for adults diagnosed with ADHD. Future research should also examine the 18-25 year population more closely to gain a better understanding as to why their total non-ADHD-costs appear to be higher when they are taking Strattera as opposed to stimulant medications and why this appears in their age group but not in others.

APPENDIX A – DSM-IV CRITERIA FOR DIAGNOSIS OF ADHD

Diagnostic Criteria for Attention-Deficit/ Hyperactivity Disorder

A. Either (1) or (2):

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

Inattention

(a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities

(b) often has difficulty sustaining attention in tasks or play activities

(c) often does not seem to listen when spoken to directly

(d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)

(e) often has difficulty organizing tasks and activities

(f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort such as schoolwork or homework)

(g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)

(h) is often easily distracted by extraneous stimuli

(i) is often forgetful in daily activities

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

Hyperactivity

(a) often fidgets with hands or feet or squirms in seat

(b) often leaves seat in classroom or in other situations in which remaining seated is expected

(c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)

(d) often has difficulty playing or engaging in leisure activities quietly

(e) is often “on the go” or often acts as if “driven by a motor”

(f) often talks excessively

Impulsivity

(g) often blurts out answers before the questions have been completed

(h) often has difficulty awaiting turn

(i) often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive–impulsive or inattentive symptoms that caused impairment were present before age 7 years.

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

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

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

Code based on type:

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

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

314.01 Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type: if Criterion A2 is met but Criterion A1 is not met for the past 6 months.

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

APPENDIX B – LIST OF ELIXHAUSER COMORBIDITY INDICATORS ASSIGNED BY HCUP SOFTWARE

Non-Mental Health Comorbidities Merged into Combined Medical Comorbidities Indicator Variable (25)
Congestive heart failure
Valvular disease
Pulmonary circulation disease
Peripheral vascular disease
Paralysis
Other neurological disorders
Chronic pulmonary disease
Diabetes without chronic complications
Diabetes with chronic complications
Hypothyroidism
Renal failure
Liver disease
Peptic ulcer disease x bleeding
Acquired immune deficiency syndrome
Lymphoma
Metastatic cancer
Solid tumor without metastasis
Rheumatoid arthritis/ collagen vascular diseases
Coagulopathy
Obesity
Weight loss
Fluid and electrolyte disorders
Chronic blood loss anemia
Deficiency anemias
Hypertension
Mental Health Comorbidities Kept as Separate Dichotomous Comorbidity Indicators
Alcohol abuse
Drug abuse
Psychoses
Depression

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