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FACTORS ASSOCIATED WITH SUSTAINED RELEASE
PSYCHOSTIMULANT PRESCRIPTIONS FOR PEDIATRIC ADHD

BY

ROBERT MCCONEGHY

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF

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MASTER OF SCIENCE THESIS

OF

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ABSTRACT

Background: Attention Deficit Hyperactivity Disorder (ADHD) is a mental health disorder characterized by functional impairment due to symptoms of inattention, impulsivity, and hyperactivity. Psychostimulant medications effectively reduce these symptoms, however there is little evidence regarding the factors associated with use of different types of stimulant medications.

Objective: To investigate factors associated with sustained release (SR) versus immediate release (IR) stimulant prescription for pediatric ADHD.

Methodology: A cross-sectional observational study was conducted using the 2012 National Ambulatory Medical Care Survey (NAMCS), a nationally representative sample of physician office visits. Independent predictors of SR stimulant medication prescription, as compared to IR stimulant prescription, were identified from logistic regression models.

Results: Our data set contained visits representative of 105,548,504 visits with an associated age of 4-17 years old (11.39% of all visits). Of these pediatric visits, there were 7,088,227 visits (7.56%) with an ADHD diagnosis code (ICD-9: 314.00, 314.01). The majority of pediatric ADHD visits were male (n=5,155,695, 72.74%). The most frequent age groups were 7 to 11 years (n=3,374,121, 47.60%) and 12-17 years (n=46,097, 42.97%), while the 4-6 year age group was less frequent (n=668,010, 9.42%). The most frequent race was White (n=4,771,295, 67.31%), while less frequent were Black race (n=1,229,675, 17.35%) and Hispanic race (n=956,710, 13.50%). The most

frequent office region was the South (n=3,221,211, 45.44%). The most frequent pay types were private insurance (n=3,427,928, 48.36%) and Medicaid (n=2,473,735, 34.90%).

After applying our study inclusion criteria, there were 4,617,709 pediatric visits with IR or SR prescriptions. Of this visit sample, 3,431,741 had sustained release (74.35%) and 1,185,968 visits had immediate release stimulant prescriptions (25.68%). There were 1,969,116 visits with a combination of SR/IR (42.64%), which we included as SR in our modeling.

Our logistic modeling approach identified a number of non-significant sociodemographic predictors of SR prescription, relative to IR prescription. Compared with the 7-11 year old age group, the 12-17 year old group was 70% more likely to have a SR vs IR prescription (OR=1.695), while the 4-6 year old group was roughly 70% less likely to have SR than IR (OR=0.359). Relative to those with white race/ethnicity, those of black race (OR=2.183), Hispanic race (OR=2.223), and "Other" race (OR=2.717) had a non-significant but doubled likelihood of receiving an SR vs IR only prescription. Our logistic approach did not find evidence that sex or ADHD subtype were significant predictors of SR vs IR stimulant prescription. Overall, this modeling approach did not identify any significant sociodemographic predictors of SR vs IR only use

Conclusions: In our nationally representative sample of pediatric ADHD office visits, visits of adolescent age or those with comorbid anxiety disorder had a higher likelihood of a SR stimulant drug mention than an IR mention. In contrast, visits with a diagnosis of autism and those in the Western region were less likely to have SR relative to an IR stimulant prescription. We did not find evidence to support disparities in SR versus IR stimulant prescriptions in visits of Black, Hispanic, or female children. These findings documented similarities and differences in ADHD medication prescription across sociodemographic groups that may be helpful for identifying office visits with a predisposition towards SR or IR stimulant prescription and to further understand the choice of ADHD drug for childhood ADHD.

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PREFACE

The standard format was used in preparation of this thesis.

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CHAPTER 1

Background

Attention deficit hyperactivity disorder (ADHD) is defined by persistent and developmentally inappropriate problems with attention, impulsivity, and hyperactivity that cause functional life impairments.^{1,2} Children with ADHD suffer functional impairments because of symptoms such as forgetfulness, distractibility, excessive fidgeting, and disorganization.³ Numerous studies have demonstrated ADHD is effectively and safely treated by a variety of medications including stimulants like methylphenidate and amphetamine salts, or the non-stimulant atomoxetine.⁴⁻⁶

There is a national childhood ADHD prevalence of roughly 10%, which represents over five million children.^{3,7,8} There is an estimated cost burden of ADHD between \$36 and \$52 billion dollars in 2005, due to a loss of productivity in those with ADHD.⁹⁻¹⁴ The societal cost burden includes a loss in the productivity of students and workers, totaling an estimated \$3.7 in adult work costs, and increased healthcare costs due to mental health comorbidities, unintended injuries, and utilization of behavioral therapy.^{11,12,15-17} Further, relative to their non-ADHD classmates, the five million US children with ADHD are less likely to succeed in academics^{13,14} and more likely to struggle to maintain healthy friendships and familial relationships.^{9,10} For instance, children with ADHD report almost 3 times as many peer problems as those without ADHD (21.1% vs 7.3%) and are almost 10 times as likely to

have difficulties with friendships (20.6% vs 2.0%).¹² Because these chronic impairments can lead to consequences like poor grades, low self-esteem, and hampered social lives, it is understandable that those with ADHD are more likely to develop comorbidities like depression^{18,19}, anxiety²⁰, and obesity.^{11,21,22}

In 2011, the American Academy of Pediatrics (AAP) published guidelines concerning the evaluation, diagnosis, and treatment of pediatric ADHD.²³ This document highlights the strength of evidence for diagnosis of ADHD via the diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders Version V (DSM-V), the importance of evaluation of common comorbidities like anxiety and depression, and acquiring symptom information from different perspectives including parents, teachers, and other clinicians. Concerning the 4-5 year age group, the AAP suggests that behavioral therapy should be first and psychostimulant treatment methylphenidate second, though some research supports the effectiveness of medication alone.^{4,10,14} These guidelines also suggest that children 6 years or older may have ADHD medications alone, therapy alone, or a combination of both.

Regarding medication options, there is a plethora of evidence demonstrating the effectiveness of stimulants for the treatment of ADHD. Since the 1937 study of Charles Bradley, stimulants have been proven to be effective for the reduction of hyperactivity, impulsiveness, and short attention span²⁴. In his original Bradley's study of stimulants for the treatment of severe headaches from pneumoencephalograms, Bradley observed a striking

improvement in the behavior of numerous patients. Bradley's subsequent systematic trial of stimulant use for the alteration of behavior noted "remarkably improved school performance." This groundbreaking study inspired many subsequent studies of stimulants and changed the treatment of what is known today as ADHD²⁵.

Treatment of ADHD with psychostimulants, such as methylphenidate (brand name Ritalin) and mixed amphetamine salts (brand name Adderall), has been proven effective for ADHD symptom reduction.^{4,6,9,26-29} These stimulant medications affect dopamine and norepinephrine reducing inattention, impulsivity, and hyperactivity. Though side-effects such as increased heart rate and blood pressure, tics, insomnia, and agitation may be bothersome, the evidence suggests stimulants are safe for chronic use in children older than four years.^{23,29} A few studies have shown treatment benefits in meaningful endpoints like academic success.^{13,14,30} Relative to behavioral therapy, ADHD medication has been shown to be cost effective in symptom reduction and more cost-effective than behavior therapy alone.^{26,31-33} The main non-stimulant treatment for ADHD is atomoxetine. This non-stimulant may be preferable for children with ADHD and certain comorbidities, such as comorbid anxiety disorder, substance abuse disorder, and tics.^{5,34,35}

There are a variety of formulations of the stimulant medications which differ primarily in their duration of effect. Immediate release (IR) stimulants may last 3-4 hours and require multiple daily doses, whereas sustained release (SR) stimulants may last upwards of 12 hours and have a longer

duration of effect and slightly different modes of delivery, factors which may contribute to slight improvements in adherence.³⁶ For instance, lisdexamfetamine (brand name Vyvanse) is an SR stimulant pro-drug which requires lysine cleavage in the red blood cells to become the active dextroamphetamine. Thus, lisdexamfetamine has both a long duration of effect and has a reduced potential for abuse, offering a contrast with mixed amphetamine salt which is racemic and not ingested in a pro-drug form.

Stimulants have their drawbacks, however, as they may cause side-effects including increased heartrate and blood pressure, decreased appetite and trouble sleeping.³⁷ The use of IR medication may lead to uncomfortable dose peaking with increases in adverse effects, increased inconvenience of multiple daily doses, and a lower adherence rate relative to extended release stimulants³⁸. Since the introduction of SR medication formulations, such as long-acting methylphenidate (brand name Ritalin-LA) in 2002 and extended-release mixed amphetamine salts (brand name Adderall XR) in 2001, SR formulation use has increased.³⁹ This trend may be due to improved drug adherence, patient convenience, and lower peak and higher trough dose concentrations relative to IR formulations. Therefore, patients on SR medications may have more comfortable dose peaking and improved adherence.⁴⁰⁻⁴³ Suffice to say, as our understanding of ADHD has grown, so too has the number of ADHD drugs, with over twenty medications and formulations approved by the FDA for treatment of ADHD.

While prescription of these SR formulations may yield improvements in adherence, some SR formulations may be more expensive than IR formulations. Considering formulation price differences, there may be sociodemographic disparities in the prescription of these more expensive formulations. One 2013 study of Florida Medicaid claims found no racial disparity in SR medication prescriptions.³⁶ However, due to a limited and non-generalizable sample, this study was not applicable to the American population at large. Further, although numerous studies have compared the proportions of any medication use in different racial or socioeconomic groups, we have not identified any studies of factors associated with SR versus IR prescription in nationally representative data derived from medical charts versus information recall.^{4,14,41,43,44}

Our cross-sectional analysis and predictive modeling of ADHD medication prescriptions may be a useful addition to this literature. While one previous study provided useful information on the prevalence of ADHD diagnosis and medication prescription, no published NAMCS study has built a predictive model of SR treatment.⁴⁵ Furthermore, the majority of medication treatment studies in other data sources did not examine predictors of specific types of medication prescription. Finally, there are few studies in the literature of predictors SR vs IR stimulant prescription and those few studies of medication type used limited regional datasets to make predictions.^{38,43}

To address these evidence gaps, the purpose of this study was to identify predictors of SR versus IR stimulant prescription in the United States.

To do so, we conducted a cross-sectional observational study of a nationally representative survey of 2012 physician office visits. Our research question was whether or not there are sociodemographic predictors of SR versus IR stimulant prescription in the US pediatric population. Potential predictors were identified from a set of sociodemographic covariates including age, sex, pay type, office region, race, and physician specialty. This analysis was strong in its national generalizability, up-to-date data source, and use of multivariate modeling for adjustment of odds ratios. While our study had limitations due to a lack of patient-level data in the NAMCS and due to the relatively small pediatric ADHD sample present in the 2012 data, we are confident our findings will be a useful piece of evidence for prescribing patterns in the United States.

CHAPTER 2

LITERATURE REVIEW

Literature Review

Methods for Literature Search

To ensure this project targeted specific evidence gaps related to SR medication treatment disparities in childhood ADHD, a thorough literature review was conducted with the PubMed Medical Subject Heading system (MeSH) terms: ("Attention Deficit Disorder with Hyperactivity/drug therapy") and ("healthcare disparities" OR "epidemiology" OR "Delayed-Action Preparations"). To ensure our search examined only childhood ADHD (ages 4-17), the PubMed filter "Child" was utilized. We chose to search the literature from January 1987 to September 2015 because throughout this period, hundreds of studies have been published while subtle changes occurred in the DSM III-R in 1987, the DSM IV in 1994, and the current DSM-V, published in 2013. The year 1987 was an appropriate starting date for our search since that year the disorder title was changed from ADD to ADHD and there was more robust empirical validation of diagnostic criteria.

From over 10,000 study titles reviewed in the literature search, 33 articles relevant to this study of sustained release medication disparities were included (Figure 1). From 10,000 titles, studies of adults, genetics, neuroimaging, historical analyses, editorials, opinions, and commentaries

were excluded. The abstracts of approximately 500 relevant abstracts were reviewed for inclusion. After abstract review, 360 were excluded due to utilizing adult populations, performing a different type of study, or being a duplicate abstract. The full text for each included study was acquired to determine the evidence base on sustained release disparities.

While numerous studies were included on the background of ADHD prevalence, diagnosis, and treatment, many were excluded due to lack of relevance to predictors of medication prescription. Moreover, several prevalence studies and meta-analyses of these prevalence studies were examined. We excluded any prevalence studies that did not analyze predictors of medication treatment. Nevertheless, many of these articles on prevalence trends have been useful in the establishment of the burden and impact of ADHD and we include a small synopsis of this work in order to establish the proper context for our work.

Literature Review

Trends in Treatment

While studies are not in agreement about trends in ADHD diagnosis rates, there is a strong consensus that prescription medication use for ADHD has increased in recent years. In 2007, in broadly representative regional and national prescription benefit plans, Castle et al. determined that treatment prevalence increased 11.8% for children and adults in the period 2000-2005⁴⁶. They noted a particular increase in girls and adults. Also, this study found that

ER became increasingly preferred over IR from 2000-2005 and that generic use in children went down from 2000-2005. In 2012, Chai et al. found that ADHD medication use increased 46% from 2002 to 2010 and that MPH was the most prescribed medicine to adolescents (12-17)⁴⁷. Furthermore, in 2014 Visser et al. found the prevalence of medicated ADHD increased by 28% from 2007-2011⁷. Finally, Toh et al. in 2006 used the NAMCS 1993-2003 data and found an increase of 2.1% to 4.0%⁴⁵. Therefore, if we examine medication use in the NAMCS in 2012, we might see the rate of drug mentions for childhood ADHD in the range of 4% to perhaps as much as 8%, if increases are found to be consistent with previous findings. These studies are generally in agreement: ADHD medication use has become more frequent over recent years. Most of these studies did not examine predictors for specific types of medication, but were rather simple trend analyses. Therefore, another trend analysis would not target evidence gaps.

Literature Review

Predictors of Treatment

We examined the literature regarding predictive factors associated with ADHD diagnosis and treatment, including age, sex, race, insurance status, and region. In 2012, Lingenini et al. found that depression, anxiety, type of healthcare coverage, and male gender were all associated with ADHD diagnosis⁴⁸. To do so, they used the National Survey of Children's Health (NSCH), which is a population-based cross-sectional survey collected via digital-dialing of US households from 2007-2008. Their sample included

91,642 children and they found that roughly 10% of parents reported their child had received a diagnosis at some point. Like the diagnosis, medication use at any prior or current time was assessed via a survey question to parents. Lingineni et al. found that, relative to white children, Black and Hispanic children were less likely to be diagnosed (OR=0.72 and OR=0.65).

Numerous studies suggested ADHD differences in females, perhaps due to the lack of hyperactivity and impulsivity symptoms in some girls with ADHD. Froehlich et al. examined 2001-2004 NHANES data and found that boys were more likely to be diagnosed.⁴⁹ Furthermore, there may be varying rates of care in groups of lower socioeconomic status and in different racial/ethnic groups. In their 2007 study of 2001-2004 NHANES data, Froehlich et al. utilized three different logistic regression models, including one for medication treatment amongst those with ADHD by DSM-IV criteria. They found that, relative to 8-11 year olds, 12-15 year olds were more than three times likelier (AOR=3.6, 95% CI = 1.6-8.2) to take any medication in the past year. Furthermore, they found that relative to white children, African-American (AOR = 0.7, 95% CI = 0.4-1.6) and Mexican-American (AOR = 0.6, 95% CI = 0.2-2.0) children were less likely to have medication treatment. While this study does have the strength of measuring prevalence with reported symptoms, the small sample size (n=222) does not confer statistical significance to odds ratios of treatment across sociodemographic groups. Another study of the NHANES data by Merikangas et al. agreed with these findings of prevalence and rates in subgroups¹⁷. Since the NHANES dataset

only includes a survey question about any ADHD medication use in the past year, these studies did not report type of medication used, whereas our study will do so.

An earlier study in 2004 by Stevens et al had similar findings on ADHD disparities as these NHANES studies. They found that ethnic and regional differences existed in ADHD diagnosis for pediatric primary care visits.⁵⁰ Relative to whites, Hispanics were less likely to be diagnosed and African-Americans less likely to use medication. Symptomatic prevalence was higher for poor children, whilst medication use was more likely in the wealthiest children.

Another examination of race and medication use was published in 2006 by Zuvekas et al., which looked at trends in stimulant use and analyzed stimulant use in sociodemographic subgroups.⁵⁴ In their 2002 data source, they found that females, blacks and Hispanics, and uninsured children had lower proportions of stimulant use relative to respectively, boys, whites, and those on private/public insurance. Furthermore, geographically the study found slight regional differences in medication use in 2002, with the South (3.4%) and Midwest (3.0%) having more use than the Northeast (2.7%) and the West (2.2%).

While these previous studies examined diagnosis and any kind of treatment, they didn't address SR or IR stimulant prescription specifically. In 2013, Saloner et al. published a highly relevant study to predictors of sustained release ADHD medication use³⁶. Their data source was claims data

and it was limited to Florida Medicaid 96-05. The authors found that ADHD-diagnosed minorities were less likely to utilize medication (unadjusted odds anywhere from 18% less likely to 22% less likely depending on year and group comparison). Amongst those who did use medications, they found African-American and Hispanic children were not much less likely to use long-acting medications than white children (unadjusted odds from 5% to 14% less likely for African-Americans and 3 to 13% less likely for Hispanics). One limitation of this study is it does not utilize a nationally generalizable, up-to-date study population. For example, new medications/formulations were recently released, which this data did not capture (e.g. Kapvay in 2010, Quillivant XR in 2012, and Azenys XR-ODT in 2016). Furthermore, Florida Medicaid data is not necessarily indicative of the national population of American children.

Another study published in 2010 by Lang et al. primarily examined trends in medication but which specifically looked at short-acting vs long-acting ADHD medications from 1994-2003 with international pharmaceutical claims data.³⁹ They found that US medication expenditures for ADHD increased 594% from 1994-2003 largely due to price increases from expensive new treatments introduced in their study period. These analyses demonstrated that only 1% of the rise in US expenditures was due to sales volume, whereas 97% was due to price and 2% to residual. Therefore, we can see a shift towards more expensive long-acting medications in the USA before 2012.

In their 2013 study of UK data of 77 individuals aged 6-18, Gormez et al. studied the effects of switching to MPH-SR from MPH-IR.⁵¹ They found that some clinicians may consider using higher doses or an additional MPH-IR dose to augment the effects of MPH-SR. They also supported the use of specialist ADHD clinics, relative to generic service centers. This built upon the 2010 study by Thompson et al., which was a UK study that found amongst 97 patients, 32% responded poorly to the switch and in 26 of the 97 patients, SR treatment was a failure and they were switched back.⁵² These studies highlight the need for monitoring patients who switch from IR to SR medications.

Specifically regarding the superiority of SR vs IR stimulant formulations, there have been a few studies on the question. In 2006, Steele et al. conducted a randomized controlled effectiveness trial and found once-daily formulations are more effective in multiple outcome measures including remission rate⁵³. In 2009, the Canadian Paediatric Society (CPS) put out a position statement that suggests extended-release (XR) medications are preferred over short-acting medications by both families and physicians. Furthermore, these authors claim that XR preparations are expensive and more unaffordable for disadvantaged populations.⁵⁴ Along with this CPS position statement, the NICE organization from the UK published guidelines on ADHD that concluded modified-release medications are preferred over IR medications because of convenience, improving adherence, different pharmacokinetic profiles, reducing stigma, and reducing problems relating to schools storing drugs (guideline 1.5.5.4).⁵⁵ These three studies provided

sufficient evidence that there are benefits for SR stimulant formulations, relative to IR formulations. This body of work provides the crucial evidence to support the central premise of our study, which is that SR may be slightly better than IR and questioning if there are disparities in SR prescription.

In summary, this literature search identified the studies establishing the advantages of SR over IR stimulant formulations and the studies highlighting sociodemographic disparities in ADHD treatment. Therefore, since our study purpose was to examine potential predictors of healthcare disparities in ADHD medication treatment, our specific research question was whether or not there were sociodemographic predictors of SR versus IR stimulant prescription in the US pediatric population. Based upon our knowledge of previous literature, we hypothesized that there may be sociodemographic predictors of SR vs IR prescription including subgroups of age, sex, race, insurance status, and a number of other potential predictors not addressed in previous studies.

Our study had strengths to build upon this previous literature, assessing prescription patterns in a nationally representative sample and providing adjusted odds ratios for sociodemographic predictors of prescription of superior medication formulations. While potentially useful to ADHD treatment decision-makers, our study limitations must be considered including a lack of longitudinal data, a lack of utilization information, and smaller analytic sample due to the use of only a single year of data. Nevertheless, our study may provide valuable information in assessing sociodemographic disparities in ADHD medication treatment.

CHAPTER 3

METHODS

Study Design

A cross-sectional study design was used, in which exposures and outcomes are determined at the same point in time for a given population. This study design allowed a broad analysis across many different levels of variables, which will be useful for our study of pediatric ADHD treatment disparities in the United States.

Methods

Sample

This study examined 2012 pediatric ambulatory care visits with an ADHD diagnosis in the National Ambulatory Medical Care Survey (NAMCS). The NAMCS a nationally representative survey distributed by the Center for Disease Control (CDC). In the NAMCS, the basic unit of observation is the physician office visit; therefore the study population is only representative of those who visited physician offices. This data was generated by physicians recording information about office visits in a randomly assigned week on a survey form.

This data includes numerous variables including diagnoses, medication codes, procedure codes, and sociodemographic variables. Diagnoses are

indicated by the International Classification of Diseases (ICD-9) diagnostic codes. Medication codes, including those for generic and brand name drugs, do not indicate prevalent use, incident use, or drug switching, nor dosage or actual drug utilization. Sociodemographic information is encoded in categorical variables, though there may be numerous missing values including race in 32.9% of visits. The NAMCS does provide weights, strata, and cluster information so that SAS 9.3 can produce nationally representative estimates of sociodemographic information.

In the 2012 NAMCS there were a total of 76,630 unweighted visits and 928,629,953 weighted visits. There were 8,694 unweighted visits and 105,548,504 weighted visits with an age of 4-17. We applied inclusion criteria to create a study sample of pediatric ADHD visits with stimulant prescription (Figure 2). Our analytic sample was constructed as follows:

- 1) Visits with an age between 4 and 17 and with an ICD-9 code of 314.0, 314.00, or 314.01 were included as the pediatric ADHD visit population.
- 2) Medication information was identified by medication codes and drug ID codes, identified in the appendices.
 - a. Visits with Adderall XR, Ritalin LA, Focalin XR, Methylin-ER, Ritalin-SR, and Vyvanse were included in the SR group of interest.
 - b. Those with only Ritalin, Focalin, Adderall, Methylin, or Methamphetamine were included in the IR reference group.
 - c. Those with a combination of IR and SR mentions will be considered as SR, thus our model will compare "Any SR" vs. "IR Only"

- d. Those with a generic code for methylphenidate or mixed-amphetamine salt combo were included as IR.

With these pediatric ADHD stimulant visits, we conducted a cross-sectional study to determine any sociodemographic factors associated with sustained release (SR) versus immediate release (IR) stimulant prescriptions.

Methods

Descriptive Statistics

Descriptive statistics were used to characterize the study population by frequency and percentage. These analyses examined all pediatric visits with an ADHD diagnosis as well as those visits with certain types of medication prescribed like non-stimulants, SR, and IR stimulants. We used standard NAMCS nationally representative weighing procedures to calculate medication treatment in the independent variables including age group, sex, insurance status, office region, race, and physician specialty. We also included comorbidities relevant to ADHD, including obesity⁵⁶, asthma¹⁵, anxiety⁵, depression⁴⁸, or autism.⁵⁷ While these comorbidities were examined in our descriptive statistics, they were not included in our modeling approach since the research question for this study specifically targeted sociodemographic disparities.

The national weighing process in the NAMCS utilized information on the data cluster, data stratum, and patient weight for each NAMCS observation. Cluster and strata adjustments are necessary due to the complex multi-stage

sample design of the survey. These design variables in the NAMCS allow for creation of nationally representative estimates with appropriate variance estimation for surveys. A priori power analyses were not conducted since these statistical tests utilized readily available data entries.

To compare treatment proportions in population subgroups, we used basic statistical tests of difference. To test for differences in the proportion of SR stimulant used across different values of categorical variables, the Pearson Chi-square (χ^2) test or Fisher's exact test was utilized, if the assumptions for the χ^2 were not met. The question for each independent variable was whether or not proportions of that variable differed significantly for those with SR vs. those with IR. While independent variables related to diagnoses were dichotomous, for the independent variables, including race, pay type, age group, physician specialty, and office region, overall p-values for the entire variable were assessed. For the only continuous variable, age, a t-test was used to determine if SR medication prescription has a relationship with age.

For all descriptive analyses, the 2-tailed alpha level of significance was set at 0.05. All statistical tests were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Methods

Multivariate Regression Modeling

To address the evidence gap regarding the predictors of SR ADHD medication prescription, we utilized a predictive logistic regression modeling approach. This method allowed us to examine the associations between the dependent variable, SR stimulant prescription, and the predictors of interest including sex, age, racial and ethnic background, geographic region, pay type, and physician specialty. For each predictor of interest, our logistic regression model produced adjusted odds ratios comparing the relative likelihood of SR stimulant prescriptions vs. those with only IR prescriptions. We constructed both an initial multivariate model and we sequentially removed variables using an iterative, manual process to remove covariates that are not predictive of SR vs IR stimulant prescription. This reduced model was compared to the larger initial multivariate model using the AIC, c-statistic, and the Hosmer-Lemeshow test in order to assess model fit.

An initial multivariate logistic regression model was built using the first univariate associations, then assessing multi-collinearity of selected variables.⁵⁸ Univariate tests of association were conducted between the dependent variable, (i.e. type of medication prescribed [SR vs IR]), and the independent variables, potential sociodemographic predictors. A parametric assessment was conducted to assess the continuous variable "Age" for possible creation of an age category variable (see appendix for assessment). Potential predictor variables with a univariate test p-value of <0.15 were candidates for multivariate model inclusion⁵⁹. Multicollinearity was assessed for this model and all condition indices being less than 30 and variance

inflation factors being less than 8, multi-collinearity was not an issue for this data.

To refine this initial model, an iterative, manual process of backwards elimination was used to remove variables that do not contribute to the prediction of the mention of SR vs IR. Variables with a Wald p-value assessment of $p > 0.10$ were excluded and the AIC was examined – a lower AIC meaning a better fitting model. Furthermore, the c-statistic was examined for each model, with a preferable range of 0.6-0.8 for a model but 0.5 being the minimum accepted value. Goodness of fit was tested using the Hosmer-Lemeshow test, wherein a non-significant value ($p > 0.05$) shows the model to be a good fit. Using multiple model fit tests ensured our multivariate logistic regression models of SR vs IR prescription were aptly fit to the data.

Equation 1 defines the general equation of multiple logistic regression:

$$\text{Eq1: } g(x) = \ln\left(\frac{\pi(x)}{1-\pi(x)}\right) = \alpha + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p$$

Equation 2 defines the logistic regression model that was used:

Equation 2:

$$y = \alpha + \beta_1 age + \beta_2 Sex + \beta_3 race + \beta_4 Insurance + \beta_5 Specialty + \beta_6 Region + \varepsilon$$

Where y is the probability of having SR stimulant treatment, α is the intercept, and the β 's are the coefficients on the independent variables and ε is standard error. If analysis indicates that significant interactions exist between

variables, they were added to the model. To interpret our odds ratios (OR), an OR higher than 1 indicates higher odds of having SR treatment, for example an OR of 1.2 means 20% higher odds of having SR treatment.

The independent variables we investigated for inclusion in our model consist of the sociodemographic information available in the NAMCS (see appendix). The main divisions of race/ethnicity were African-American, Hispanic, Other, and White. Regarding insurance status, we examined Medicaid, Self-Pay, and other groups against Private Insurance. Age grouping via parametric assessment was considered, since clinical guidelines vary for those younger than 6 compared to 6-11 year olds and 11-17 year olds. There were numerous categories of physician specialty; however, the only values with sufficient sample size were General/Family physician, Pediatrician, Psychiatrist, and Neurologist.

CHAPTER 4

RESULTS

Our study purpose was to examine potential predictors of healthcare disparities in ADHD medication. First, we used descriptive statistical analysis to answer the question of whether there are different proportions of medication prescription in different population subgroups. Then we built a logistic regression model to assess whether there are predictors of the prescription of SR vs IR stimulants. These two analyses were targeted to build upon previous literature and shed light on ADHD treatment evidence gaps.

Results

Sample characteristics

Out of a total of 928,629,953 office visits in 2012 and 105,548,504 (11.37%) visits with an age of 4-17, we found 7,088,227 (7.56%) had one of the two diagnosis codes for ADHD (ICD-9: 314.00, 314.01). After applying our study inclusion criteria, we selected a total of 4,617,709 (65.15%) pediatric visits for our study of stimulant medication prescription. The majority of selected visits mentioned sustained release (SR) stimulant (n=3,431,741, 74.32%) while the minority mentioned only immediate release (IR) stimulant (n=1,185,968, 25.68%). There were 2,268,862 visits (32.01%), with a combination of SR/IR which we included as "SR" in our analyses.

Regarding medications taken in the general childhood ADHD population (n=7,088,227), we found that 5,475,854 visits (77.25%) had a mention of any ADHD drug (stimulants or non-stimulants) (Table 1). SR stimulants were prescribed for 3,886,395 visits (54.83%), while IR stimulants were prescribed for 3,904,438 visits (55.08 %), and 2,540,260 had codes for both SR and IR stimulants (35.84 %). The most common drugs included methylphenidate extended-release (brand name Concerta, n=1,551,329, 21.89%), lisdexamfetamine (n=1,395,967, 19.69%), and dexamethylphenidate (n=786,221, 11.09%). Methylphenidate of any sort was prescribed in approximately one third of pediatric ADHD visits (n=2,444,725 (34.49%). The brand version Adderall was frequently prescribed (n=434,082, 6.12%), as was the generic code mixed amphetamine salts (n=781,624, 11.03%). A small minority of visits had a mention of a non-stimulant medication for ADHD (n=858,145, 12.11%), including mentions of atomoxetine (n=178,195, 2.51%), guanfacine (n=343,206, 4.84%), and clonidine (n=385,038, 5.43%).

Results

Demographics of SR and IR Medication Groups

To examine the SR or IR stimulant prescription study population that was used in the logistic model, we performed chi-square tests between each of the independent variables and our dependent variable, SR prescription (relative to IR only prescription). We found statistically significant associations between SR prescription and pay type, office region, anxiety, and autism (Table 2). The logistic model study sample, 421 unweighted visits, comprised

of those visits with either SR or IR medication. Of these 421 visits, 313 had SR prescription representing 3,431,741 weighted visits (74.35%). In this sample, there was roughly a 3:1 ratio of males to females (2,508,268 vs. 923,473) and males had a non-significantly higher rate of SR prescription (76.46% vs. 69.05%, $p=0.23$). There was also a non-significant difference between the 4-6 age group ($n=163,120$, 54.92%) and the 7-11 age group ($n=1,744,109$, 73.50%) and the 12-17 group ($n=1,524,512$, 78.27%, $p=0.09$). Relative to white children, who had the lowest rate of SR prescription ($n=2,220,275$, 71.11%), children with a race of Black ($n=669,357$, 80.59%) and Hispanic race ($n=498,270$, 80.70%) and "Other" race ($n=43,838$, 92.62%) had slightly higher proportions of SR prescription.

Regarding payment type, the few self-pay visits had a significantly lower rate of SR prescription ($n=105,146$, 59.24%), whereas the private insurance ($n=1,834,308$, 79.75%) and Medicaid ($n=1,227,480$, 77.93%, $p=0.01$). populations had significantly higher proportions of SR prescription. The Southern region had significantly more SR prescriptions ($n=1,697,891$, 80.94%) whereas the Midwestern ($n=850,702$, 71.54%) and Northeastern ($n=400,037$, 76.22%) regions had lower rates and the Western region had the lowest rate of prescriptions ($n=483,111$, 59.95%, $p=0.05$). Finally, there was a significantly larger proportion of SR prescription in those with a comorbid anxiety disorder ($n=154,062$, 90.34%, $p=0.01$) than those without anxiety. Furthermore, there was a significantly low rate of SR prescription in the very few cases of comorbid ADHD and autism ($n=805$, 3.22%).

Results

Multivariate Logistic Regression

To begin our logistic regression, we performed univariate logistic regression between presence of the dependent variable (SR vs IR only) and the independent variables, including sex, age group, race, pay type, office region, and physician specialty (Table 3). We found five significant univariate predictors of SR prescription relative to IR prescription, including age group, race, office region, payment type, and physician specialty. Significance was determined by the Wald Chi-square P-value threshold of $P=0.15$, considering individual levels of categorical variables. Regarding age, we conducted a parametric assessment and decided to treat this variable as a categorical variable in three groups (see Appendix D for parametric assessment).

Once we determined the univariate predictors to include, we ran an initial multivariate logistic regression model to attempt to predict SR vs. IR (Table 4). Examining the adjusted odds ratios and their 95% confidence limits, we see no covariate with confidence limits not including the value 1. This indicates that amongst these sociodemographic variables in the 421 unweighted visit sample in the 2012 NAMCS, there are perhaps only non-significant predictors to assess. For example, regarding age grouping, we see that when compared to those aged 7-11, those 12-17 are 1.69 times more likely to have SR prescription (versus IR) and (OR=1.691, 95% CL: [0.795, 3.595]) and those aged 4-6 are almost 3 times less likely to receive SR versus IR (OR=0.359, [0.131, 0.985]). Relative to visits with a white race/ethnicity,

those with Black race (OR=2.183, [0.777, 6.134]), Hispanic race (OR=2.223, [0.457, 10.819]), and "Other" race (OR=2.717, [0.397, 18.611]) are all non-significantly more likely to have SR versus IR only prescription. Relative to visits with a general or family practitioner, those with pediatricians (OR=1.725, [0.644, 4.618]), psychiatrists (OR=1.773, [0.590, 5.328]), and neurologists (OR=1.183, [0.397, 3.527]) were all non-significantly more likely to prescribe SR vs IR only. Relative to the Northeast region, the Midwest (OR=0.794, [0.317, 1.991]) and the West (OR=0.684, [0.197, 2.370]) were less likely to prescribe SR versus IR while the South (OR=1.351, [0.507, 3.597]) was more likely to prescribe SR versus IR. Finally, relative to those with private insurance, visits with Medicaid/CHIP (OR=0.823, [0.335, 2.020]), Self-Pay (OR=0.286, [0.060, 1.372]), and "Other" payment (OR=0.598, [0.115, 3.107]) were all less likely to prescribe SR versus IR stimulants.

Regarding model fit, since proc surveylogistic does not have the ability to conduct the Hosmer-Lemeshow test, we examined the AIC, the C-statistic, and we constructed an identical initial model with proc logistic. The survey methods and non-survey methods produce the same odds ratio point estimates for predictors, however the survey methods produce a wider confidence interval for these estimates. We then tested the non-survey model fit with a Hosmer-Lemeshow goodness of fit test and found a properly specified initial model ($p=0.1954$) (see Appendix E).

When attempting to construct a reduced multivariate model that would have improved model fit, we were unable to exclude any of these four

categorical variables without worsening model fit. First, we manually selected region to remove based upon its p-values being non-significant, however we saw a decreased C-statistic from 0.663 to 0.648, an increased AIC from 4075966.2 to 4116137.9, and saw non-significant Hosmer-Lemeshow tests for both models. This indicates that this model is not improved via the removal of region. Similar analyses were conducted after cutting each of the other variables, and in each case the C-statistic and AIC worsened while Hosmer-Lemeshow remained non-significant. Therefore, the initial model is the best and we do not present any final models here.

Results

Sensitivity Analysis

Since our model counted generic drug codes, including "Methylphenidate" and "Amphetamine Salt Combo," as IR drugs and not SR drugs, we conducted a basic descriptive analysis of generic drug codes. If generic drugs are not counted as IR drugs, but rather excluded altogether, then the count of IR drug codes decreases from 314 (73.67%) to 128 (29.52%). The two generic methylphenidate codes (n=29, 7.67% and n=193, 46.41%) and the Adderall generic code (n=64, 14.15%) are present in the majority of ADHD visits. Therefore, if these codes were not included in our model, we would see a large reduction in sample size. In the future, a full sensitivity analysis of the logistic modeling will be conducted to assess the effect of this medication coding decision.

CHAPTER 5

DISCUSSION

Attention deficit hyperactivity disorder (ADHD) is a highly prevalent mental health disorder in the United States and billions of dollars are spent on ADHD treatments each year. Our study provides an important piece of evidence which targets the paucity of information regarding the predictors of prescription of sustained release (SR) versus immediate release (IR) stimulants. In the current study, we have identified non-significant predictors of SR vs IR prescription, including race, region, age group, physician specialty, and payment type. While the 95% confidence limits for these adjusted odds-ratios for all of these covariates included 1, we nevertheless can use these results to state that there is no stand-out disparity in the prescription of SR vs IR stimulants for pediatric ADHD in the United States.

After building our logistic models, we found that age group and race were important predictors of SR prescription in office visits. The predictive relationship between older age group and SR vs IR only prescription may arise from the benefits of SR stimulants, including reduced stigma at school, less potential for misuse, slightly improved adherence, or from the prioritization of avoiding side effects such as agitation and anxiety. Regarding race, it is interesting to note that while the odds of receiving SR vs IR were over twice as great in Black, Hispanic, and Other race when compared to White race, there

is a chance these odds are 1. Further study with multiple years of the NAMCS dataset may provide a larger sample to reduce the variance of the 2012 data.

Furthermore, in this initial multivariate model, we found that physician specialty, payment type, and office region were non-significant predictors of SR vs IR only. While pediatricians and psychiatrists may be 1.7 times more likely to prescribe SR vs IR only, it is also possible these values are close to 1. Further, though private insurance is more likely to prescribe SR vs IR only than all of the other payment types, once again there are non-significant intervals for Medicaid, Self-Pay, and Other. Lastly, though the South may be most likely to prescribe SR vs IR only, and the Midwest and West the least likely to prescribe SR vs IR only, these odds ratios are fairly close to 1 as well. In summation, though our models did not necessarily support the argument that SR stimulants are prescribed differently in varying sociodemographic groups, numerous non-significant odds-ratios were identified which may point towards a measurement of disparity if a larger sample size was used to build the model.

Due to these negative findings, we were unable to confirm many previously studied disparities in ADHD medication prescription. This may be indicative of improvement in prescribing patterns and equal access for those in minority groups. Furthermore, since the sampling frame for our study is shifted to 2012, it is possible that new diagnostic criteria, medication options, or increased awareness may be different from earlier study sample frames. Lastly, covariates that were important in previous studies, such as sex and

ADHD subtype, were not found to be significantly associated with SR vs IR only prescription. Therefore, though we did not find stark evidence of disparities in SR prescription, these null findings are a useful piece of evidence and may encourage further consideration of ADHD healthcare disparities.

Our study brings useful evidence to the scholarly discussion of SR vs IR stimulant prescription. While other studies have conducted somewhat similar analyses of SR vs IR, our study was the only nationally representative comparison of IR and SR medication prescription with logistic modeling approaches. Though Lingenini et al. had a relevant comparison of IR and SR, their dataset was from Florida insurance claims alone. Furthermore, while Toh et al. studied stimulant prescriptions in the NAMCS, they did not use the most recent data set and their statistical analysis was limited to descriptive statistics. Therefore, our study provides a set of nationally representative non-significant predictors which may guide ADHD decision-making. This may aid in optimizing care, highlighting differences in type of medication prescription in different sociodemographic groups, and examining how to reduce mental healthcare disparities in the United States pediatric population.

Combining the findings of our study and previous studies, there still remains an evidence gap regarding national trends in ADHD medication use. We could expand the current analysis of 2012 SR vs IR prescription by comparing non-stimulants to stimulants and comparing these with visits with no drug use. Furthermore, one might utilize a more recent year than 2012, multiple years of data, or a data source that contains patient-level longitudinal

data. Finally, one could expand the current analyses by incorporating multiple years of the NAMCS that pre-date 2012. These future analyses would all be complementary to the present study with some of its limitations.

Discussion

Limitations

There are a few limitations to this study. First, cross-sectional study designs are not able to follow patients over time, thus we do not have indications of incident vs prevalent use or a change in medication status. Despite this limitation, our study design examined a large, nationally representative data set to draw conclusions about predictors of current medication status in office visits.

One potential issue with survey data and medication coding, however, is that a survey of ADHD medication prescriptions may be prone to misclassification errors. In filling out a survey, a physician may mistakenly classify a prescription of an SR stimulant like Adderall XR as simply Adderall, which we would then reduce the magnitude any potential differences in the two groups. This misclassification is one example of the fallibility of physician reporting in surveys.

Another medication coding issue is the assumption in our model that generic drugs represent IR prescriptions, not SR prescriptions, though generics could potentially refer to either an IR or SR formulation. To examine the frequency of these generic drugs, we conducted a descriptive statistical

analysis and found that generic codes are present in over 60% (n=286) of our study sample visits. Though we assume these 286 visits all have IR prescriptions, it is possible some fraction was actually referring to SR prescriptions. To address this uncertainty, future analyses should conduct a full sensitivity analysis by producing logistic model with verified IR and SR codes via brand-name drugs.

Our current results will be generalizable only to the American pediatric population that visited physicians' offices in 2012. Therefore, this data is not necessarily representative of the American pediatric population at large, since different sociodemographic groups may have differing likelihoods to visit a physician's office. Our estimates of prevalence and drug utilization may have been lower than the true population levels, since previous studies have demonstrated lower estimates in ICD-9 based studies. Prescription of ADHD medication was measured by drug codes in a cross-sectional study design, which could not take into account adherence, persistence, or differentiate between prevalent and incident medication use. Finally, some confounding variables were not present in our data set, including socio-economic status, severity of ADHD symptoms, or previous medication therapy. Therefore, our logistic model could not adjust for these unmeasured confounders.

Despite these limitations, our dataset and methods allowed us to target existing evidence gaps and to expand the evidence base for decision-makers. Since few studies have identified predictors for SR stimulant prescriptions, and none in a nationally representative dataset, our analyses may provide useful

evidence about prescribing patterns for pediatric ADHD. Specifically, we have shown that there is not stark evidence for sociodemographic disparities in the prescription of SR vs IR stimulants for ADHD in the United States in 2012. While our evidence may point towards some disparities, due to a small sample size and perhaps high variance data, we were unable to find significant predictors of SR vs IR prescription use.

CHAPTER 6

CONCLUSION

In this 2012 sample of physician office visits, we selected a study population of 4,617,709 pediatric ADHD visits with prescriptions of SR or IR stimulant. After conducting a logistic predictive model, we did not find significant sociodemographic predictors of SR vs IR prescription. First, we did not find that subtype of ADHD or sex were significant univariate predictors of SR vs IR prescription. Nevertheless, relative to 7-11 year olds, we found a non-significantly higher likelihood of SR vs IR stimulant prescription in those aged 12-17 (OR=1.691, 95% CL: [0.795, 3.595]) and a lower likelihood in those aged 4-6 years old (OR=0.359, [0.131, 0.985]). Non-white race non-significantly increased likelihood of SR vs IR prescription by a factor of two, while those without private insurance were non-significantly less likely to have SR vs IR. These non-significant odds ratios may have been due to the changing patterns of treatment or to the varying methods to measure ADHD treatment.

These analyses did not identify any strong sociodemographic predictors for SR versus IR stimulant drug prescription. This is a positive and noteworthy result especially when considering this study utilized a recent year of data that was nationally representative. While many other studies found disparities in sociodemographics, some were in older data sources and some were not nationally representative. Therefore, our findings may be helpful for assessing

the current state of American ADHD treatment. With this knowledge, practitioners and policy-makers may move forward with slightly more detailed evidence to guide future ADHD decision-making.

Table 1. Characteristics of Pediatric ADHD Visit Population

Characteristic	Frequency	Weighted Frequency	Percent
All Pediatric ADHD Visits	711	7,088,227	100.00
Female	190	1,932,532	27.26
Male	521	5,155,695	72.74
4 to 6 years old	68	668,010	9.42
7 to 11 years old	335	3,374,121	47.60
12 to 17 years old	308	3,046,097	42.97
Private Insurance	325	3,427,928	48.36
Medicaid/CHIP	272	2,473,735	34.90
Self Pay	36	321,547	4.54
Other Payment Type	23	249,713	3.52
White Race	486	4,771,295	67.31
Black Race	120	1,229,675	17.35
Hispanic Race	78	956,710	13.50
Other Race	27	130,547	1.84
Northeast Region	87	912,679	12.88
Midwest Region	200	1,786,761	25.21
South Region	291	3,221,211	45.44
West Region	133	1,167,575	16.47
General and Family Practitioner	91	1,133,772	16.00
Pediatrician	299	3,715,065	52.41
Psychiatrist	277	1,730,501	24.41
Neurologist	32	393,403	5.55
ADHD Primarily Inattentive	132	1,511,043	21.32
ADHD Combined Type	579	5,577,184	78.68
Depression	73	664,730	9.38
Anxiety	62	348,965	4.92
Autism	9	80,894	1.14
Asthma	51	601,921	8.49
Obesity	20	249,534	3.52
Any ADHD Drug	538	5,475,854	77.25
Combination SR/IR	250	2,540,260	35.84
Immediate Release	379	3,904,438	55.08
Adderall	44	434,082	6.12
Adderall Generic	81	781,624	11.03
Methylphenidate	234	2,444,725	34.49
Dextrostat	4	27,753	0.39
Dexmethylphenidate	73	786,221	11.09
Sustained Release	375	3,886,395	54.83
Adderall XR	36	342,147	4.83

Vyvanse	134	1,395,967	19.69
Daytrana	11	95,483	1.35
Ritalin SR	2	40,731	0.57
Ritalin LA	1	3,003	0.04
Metadate CD	7	80,956	1.14
Methylin ER	3	22,866	0.32
Concerta	157	1,551,329	21.89
Focalin XR	30	387,330	5.46
Non-stimulants	117	858,145	12.11
Guanfacine	44	343,206	4.84
Clonidine	59	385,038	5.43
Atomoxetine	20	178,195	2.51

Table 1. Characteristics of Pediatric ADHD Visit Population. This sample of ADHD visits includes those visits with patients aged 4-17 and with ICD-9 diagnosis codes used for ADHD: 31400 and 31401.

Acronyms Used: CHIP= Children's Health Insurance Program; SR = sustained release; IR=immediate release; ADHD= Attention Deficit Hyperactivity Disorder; LA=long acting; ER=extended release; XR=extended release;

Table 2. Comparison of Characteristics of Visits with Sustained Release versus Immediate Release Stimulants

Demographic Group	Sample (IR and/or SR)	Freq of SR Rx	Wtd Freq of SR Rx	% SR Rx	Pr > ChiSq
Study Sample	421	313	3,431,741	74.35	
Sex					0.23
Female	119	83	923,473	69.05	
Male	302	230	2,508,268	76.46	
Age Group					0.09
4 to 6	31	19	163,120	54.92	
7 to 11	212	152	1,744,109	73.50	
12 to 17	178	142	1,524,512	78.27	
Pay Type					0.01
Private Insurance	205	161	1,834,308	79.75	
Medicaid/CHIP	153	116	1,227,480	77.93	
Self Pay	20	11	105,146	59.24	
Other	9	5	92,915	67.84	
Race / Ethnicity					0.30
White	292	207	2,220,275	71.11	
Black	70	56	669,357	80.59	
Hispanic	48	41	498,270	80.70	
Other	11	9	43,838	92.62	
Office Region					0.05
Northeast	53	39	400,037	76.22	
Midwest	127	94	850,702	71.54	
South	168	134	1,697,891	80.94	
West	73	46	483,111	59.95	
ADHD Subtype					0.68
ADHD PI	77	54	697,115	72.19	
ADHD CT	344	259	2,734,626	74.88	
Physician Specialty					0.41
General and Family Practice	62	40	556,497	65.83	
Pediatrics	193	144	1,929,855	75.38	
Psychiatry	134	104	684,297	78.51	
Neurology	23	17	184,340	75.03	
Comorbidities					
Depression	38	31	288,112	80.03	0.55
Anxiety	26	21	154,062	90.34	0.01
Autism	4	1	805	3.22	<.0001
Asthma	29	21	306,956	77.05	0.75
Obesity	10	8	140,910	71.25	0.86

Table 2. Comparison of Characteristics of Visits with Sustained Release versus Immediate Release Stimulants. This study population includes those with either an IR stimulant or SR stimulant drug prescription, combinations were included as SR. The chi-square test was used to compare proportions across groups. These study subgroup estimates are nationally representative, calculated in SAS 9.3 via proc surveyfreq.

Acronyms Used: CHIP= Children's Health Insurance Program; SR = sustained release; IR=immediate release; ADHD= Attention Deficit Hyperactivity Disorder; Rx=prescription; PI=primarily inattentive; CT=combined type.

Table 3. Univariate Logistic Regression Predicting Sustained Release Prescription with Potential Sociodemographic Predictors

Analysis of Maximum Likelihood Estimates				Odds Ratio Estimates		
Parameter	Estimate	Wald Chi-Square	Pr > ChiSq	Point Estimate	95% Wald Confidence Limits	
Sex Female (vs Male)	0.3758	1.2146	0.2704	1.456	0.746	2.841
Age 4-6 (vs 7-11)	-0.8233	2.7648	0.0964	0.439	0.166	1.159
Age 12-17 (vs 7-11)	0.2613	0.6100	0.4348	1.299	0.674	2.502
Race (ref=White)	--	--	--	--	--	--
Race Black	0.5231	1.2173	0.2699	1.687	0.666	4.273
Race Hispanic	0.5301	1.0986	0.2946	1.699	0.631	4.579
Race Other	1.6293	3.4251	0.0642	5.1	0.908	28.637
Pay type (ref=Private Insurance)	--	--	--	--	--	--
Pay type Medicaid/CHIP	-0.1089	0.0822	0.7743	0.897	0.426	1.888
Pay type Other	-0.6242	0.4917	0.4832	0.536	0.094	3.066
Pay type Self	-0.9967	1.8156	0.1778	0.369	0.087	1.573
Physician Specialty (ref=Gen/Fam)	--	--	--	--	--	--
Pediatrics	0.4630	0.9959	0.3183	1.589	0.640	3.945
Psychiatry	0.6396	1.8444	0.1744	1.896	0.753	4.772
Neurology	0.4445	1.0774	0.2993	1.560	0.674	3.611
Region (ref=Northeast)	--	--	--	--	--	--
Region Midwest	-0.243	0.2645	0.607	0.784	0.311	1.98
Region South	0.2814	0.3618	0.5475	1.325	0.53	3.314
Region West	-0.761	2.1498	0.1426	0.467	0.169	1.292
ADHD CT (vs ADHD PI)	0.1383	0.1566	0.6923	1.148	0.579	2.277
Anxiety Disorder	1.2044	5.5133	0.0189	3.335	1.22	9.113
Asthma	0.162	0.0764	0.7823	1.176	0.373	3.71
Depression	0.3509	0.3627	0.547	1.42	0.453	4.45
Obesity	-0.1622	0.0292	0.8643	0.85	0.132	5.464

Table 3. Univariate Logistic Regression Predicting Sustained Release Prescription with Potential Sociodemographic Predictors. We assessed the univariate association between demographic characteristics of visits with SR drug prescriptions, relative to IR only. The reference group for comorbidities was those who did not have that comorbidity. For instance, the odds for SR prescription for those with anxiety disorder were compared to the odds of those without anxiety disorder.

Acronyms Used: CHIP= Children's Health Insurance Program; SR = sustained release; IR=immediate release; ADHD= Attention Deficit Hyperactivity Disorder; Gen/Fam= General and Family Practitioner; PI=primarily inattentive; CT=combined type.

Table 4. Initial Multivariate Logistic Model of Sustained Release vs. Immediate Release Stimulant Prescription

Analysis of Maximum Likelihood Estimates					Odds Ratio Estimates		
Parameter	Freq in SR	Estimate	Wald Chi- Square	Pr > Chi Sq	Point Estimate	95% Wald C.L.	
Intercept		0.2794	0.2033	0.6521			
4-6 (vs 7-11)	212	-1.0246	3.9550	0.0467	0.359	0.131	0.985
12-17 (vs 7-11)	178	0.5253	1.8641	0.1721	1.691	0.795	3.595
RACE White	292	--	--	--	--	--	--
RACE Black	70	0.7809	2.1952	0.1384	2.183	0.777	6.134
RACE Hispanic	48	0.7990	0.9794	0.3224	2.223	0.457	10.81
RACE Other	11	0.9994	1.0360	0.3087	2.717	0.397	9
REGION Northeast (ref)	53	--	--	--	--	--	18.61
REGION Midwest	127	-0.2304	0.2415	0.6231	0.794	0.317	1
REGION South	168	0.3006	0.3617	0.5475	1.351	0.507	
REGION West		-0.3801	0.3592	0.5489	0.684	0.197	
Pay type (ref=Private Ins)	161	--	--	--	--	--	
Medicaid/CHIP	116	-0.1949	0.1810	0.6705	0.823	0.335	
Pay type Self	11	-1.2508	2.4469	0.1178	0.286	0.060	
Pay type Other	5	-0.5144	0.3743	0.5407	0.598	0.115	
Physician Specialty (ref=Gen/Fam)	40	--	--	--	--	--	
Pediatrics	144	0.5451	1.1769	0.2780	1.725	0.644	
Psychiatry	104	0.5727	1.0408	0.3076	1.773	0.590	
Neurology	17	0.1678	0.0906	0.7634	1.183	0.397	

Table 4. Initial Multivariate Logistic Model of Sustained Release vs. Immediate Release Stimulant Prescription. A multivariate logistic regression model was constructed using covariates with a univariate association to SR prescription (relative to IR only). These study subgroup estimates are nationally representative, calculated in SAS 9.3 via proc surveylogistic.

Acronyms Used: CHIP= Children's Health Insurance Program; SR = sustained release; IR=immediate release; ADHD= Attention Deficit Hyperactivity Disorder; Gen/Fam= General and Family Practitioner; Freq=Frequency;

Figure 1. Literature Search Overview

Figure 1. Literature Search Overview. We conducted a literature search with the PubMed MeSH system to identify important articles related to stimulant use for pediatric ADHD. Our literature search aimed to answer the question of whether or not SR drugs are less likely to be used in certain subgroups, relative to IR drugs. After removal of irrelevant articles, we found 33 studies in the literature which were relevant to our question about predictors of sustained release stimulant use.

PubMed Search Terms: ("Attention Deficit Disorder with Hyperactivity/drug therapy") and ("healthcare disparities" OR "epidemiology" OR "Delayed-Action Preparations")

Figure 2. Study Sample Selection Flowchart

Figure 2. Study Sample Selection Flowchart. To select visits for our study of predictors of pediatric SR prescription in 2012, we first included pediatric and ADHD visits. Next, we included visits with stimulant prescription, exclusive of those with concurrent non-stimulant drug usage. This left us with two subgroups of ADHD visits to compare in our logistic regression modeling.

Appendix A: Variables of interest and codes in the 2012 NAMCS

Variable Title	NAMCS Variable	Possible Values	Notes
Diagnosis Code ^{1, 2} for ADHD (or comorbidities)	DIAG1-DIAG3	314.00, 314.01	.00=ADD no H, thus IA .01= ADD w H, thus PH or CT
Drug Entry Name / Generic Name Code ³	MED1-MED10	00001-99227	May be generic name or drug entry name
Drug Entry Name / Generic Name Code	DRUGID1-DRUGID10	d00000	Is generic in all cases and value starts with "d"
Type of Payment	PAYTYPER	1 Private Insurance 3 Medicaid/CHIP 5 self-pay 7 Other	
Sex	SEX	1, 2	1=Female 2=Male
Race	RACERETH	1, 2, 3, 4	White, Black, Hispanic, Other (IMPUTED)
Age	AGE	000-099	000= <1 100= >100
Geographic Region	REGIONOFF	1= NE, 2= MW 3=S, 4=W	
Weight Variables	PATWT CSTRATM CPSUM		Weight, Stratum, and Cluster variables

1. 314.00, denotes "Attention deficit disorder without mention of hyperactivity"; 314.01 denotes "Attention deficit disorder with hyperactivity".

2. For full list of comorbidities, see Appendix C.

3. Drug utilization information is captured via generic drug mentions in DRUGID1 and also the MED1 variable. For a comprehensive list of medication variables in the NAMCS, see the table below.

Appendix B. Drug Codes for Psychostimulant and Non-stimulant ADHD Medications in the 2012 NAMCS

Brand Name ¹	Generic Name ^{1,2}
Amphetamine Psychostimulants	
'95016'='ADDERALL'	'03279'='AMPHETAMINE SALT COMBO' 'd04035'='AMPHETAMINE-DEXTROAMPHETAMINE' '10389'='DEXTROAMPHETAMINE/AMPHETAMINE'
	'd00803'='AMPHETAMINE' '01660'='AMPHETAMINE'
'01281'='ADDERALL XR'	Amphetamine, dextroamphetamine mixed salts
'07406'='VYVANSE'	'd06663'='LISDEXAMFETAMINE'
Methylphenidate Psychostimulants	
'26760'='RITALIN'	'19175'='METHYLPHENIDATE' 'd00900'='METHYLPHENIDATE'
'02271'='RITALIN LA'	MPH HCl E-R capsules
'01234'='RITALIN-SR'	MPH HCl
'00233'='CONCERTA'	MPH HCl E-R tablets
'06172'='DAYTRANA'	Methylphenidate transdermal
'01249'='METADATE CD'	MPH HCl E-R capsules
'02018'='FOCALIN'	'09384'='DEXMETHYLPHENIDATE' 'd04777'='DEXMETHYLPHENIDATE'
'06004'='FOCALIN XR'	MPH HCl E-R capsules
Non-Stimulant Medications	
'03080'='STRATTERA'	'd04827'='ATOMOXETINE' '03237'='ATOMOXETINE HCL'
'09396'='INTUNIV (ER) '30777'='TENEX'' (IR)	'd00717'='GUANFACINE' '97089'='GUANFACINE'
'05895'='CATAPRES' '12129'='KAPVAY'	'06985'='CLONIDINE'

¹Med Cod variable includes brand names and generics. MEDCOD1-8 has values 00000-99999. Note: Med Cod values do NOT have a lower-case "d".

²Drug ID is the generic coding variable. DRUGID1-8 has values in the range: d00000-d99999. Note: DrugID values do have a lower-case "d".

Appendix C. Diagnosis Variables and Codes in NAMCS

Diagnosis	Variable Names	Variable Values (DIAG1-DIAG3) (ICD-9)	Notes
ADHD	DIAG	31400, 31401	00=predom IA 01= PH or CT
Depression ^{18,19}	DIAG DEPRN	'29620','29621','29622','29623','29624', '29625','29626', '29630','29631','29632','29633','29634', '29635','29636', '2980', '3004-', '3091','311'	If DEPRN = 2 then Depression=Y (From a specific survey question screening)
Asthma	DIAG ASTHMA	49390, 49392, 49391	If ASTHMA = 2 then Asthma=Y
Obesity	DIAG OBESITY	2780-, 27800, 27801	If OBESITY = 2 then Obesity=Y
Anxiety ²⁰	DIAG	'30000','30001','30002','30009','30020', '30021','30022','30023', '30029','3003-', '308-' '30924','30928','30981'	
Autism	DIAG	29900 29901	

Appendix D. Parametric Assessment of Age Variable vs. SR Stimulant Code

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	0.1969	0.4473	0.1937	0.6598
AGEN	2	1	0.8233	0.4951	2.7648	0.0964
AGEN	3	1	1.0845	0.5099	4.5240	0.0334

Note: AGEN=1 indicates age 4-6, AGEN=2 indicates age 7-11, AGEN=3 indicates age 12-17. Since the beta estimates for the three age categories are 0, 0.82, and 1.08, we are not confident that there is a parametric relationship with age and SR medication code.

Appendix E. Hosmer-Lemeshow Goodness of Fit Test

Since proc surveylogistic cannot perform a Hosmer-Lemeshow test and is needed to produce nationally representative estimates for survey data, an identical model in proc logistic was constructed so that a test could be performed. Hosmer-Lemeshow tests are presented below for both the initial and reduced multivariate models.

Initial Multivariate Models (Table 4) GOF:

Hosmer and Lemeshow Goodness-of-Fit Test		
Chi-Square	DF	Pr > ChiSq
11.1121	8	0.1954

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