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# THE OFF-LABEL USE OF ATYPICAL ANTIPSYCHOTICS AND ITS IMPACT ON ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD)

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# THE OFF-LABEL USE OF ATYPICAL ANTIPSYCHOTICS AND ITS IMPACT ON ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD)

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DISSERTATION

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Pharmacy at the
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By
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Lexington, Kentucky

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2014

ABSTRACT OF DISSERTATION

THE OFF-LABEL USE OF ATYPICAL ANTIPSYCHOTICS AND
ITS IMPACT ON ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD)

Atypical antipsychotics (AAPs) (also known as second-generation antipsychotics) are the US Food and Drug Administration (FDA) approved medications for schizophrenia, bipolar I disorder, depression and autism. Compared to the typical antipsychotics, AAPs were marketed as reducing adverse side effects such as extrapyramidal symptoms. This resulted in extensive use of AAPs for not only the FDA approved indications but also other conditions that are not approved. However, several post-marketing clinical trials evaluated the use of AAPs and reported serious adverse side effects, including metabolic syndrome, cardiovascular events, or death.

The extensive use of AAPs by pediatrics is an important policy problem that imposes serious concerns on public health and economy in the US. A large proportion of total pediatric AAP use is off-label in which the safety and effectiveness are not yet established. Moreover, among the off-label conditions for which AAPs were used, ADHD was the most common primary mental diagnosis.

From public health perspective, the risk of type II diabetes in pediatric AAP users was estimated. A retrospective cohort study was conducted and a twice higher risk of developing type II diabetes was estimated for AAP users compared to non-users in pediatrics.

From economic efficiency perspective, the cost-effectiveness of AAPs compared to other ADHD medications in pediatric ADHD patients was estimated. Among non-stimulant ADHD medication treatment strategies, AAPs resulted in the lower expected health outcome than other ADHD medications. Also, AAPs were not a favored choice with respect to cost-effectiveness. A comparative effectiveness study that compares resource utilization and costs between atypical antipsychotic (AAP) users and non-AAP users in ADHD revealed that AAP users were likely to visit a healthcare facility for outpatient and inpatient services more frequently than non-AAP users. Total health care costs were significantly higher for AAP users with additional costs of $1,393 (2012 dollars) during six months and $2,784 (2012 dollars) during a year after initiating the AAP treatment.

KEYWORDS: Atypical antipsychotics (AAPs), Attention-deficit/hyperactivity disorder (ADHD), Type II diabetes (T2DM), Cost-effectiveness, Comparative effectiveness

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May 2, 2014

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Date

Dedicated to mom, dad, three sisters, two cats and

Eric Nybo, my life companion.

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### A. Introduction

During the current transition to national healthcare reform, much more attention is being paid to how the health care system is implemented than ever before. While it is well known that health care reform will affect the number of individuals covered by insurance, less is known about the clinical and economic impacts of the Patient Protection and Affordable Care Act (PPACA). The PPACA addresses these with titles of: 1) "Improving the quality and efficiency of health care," and 2) "Prevention of chronic disease and improving public health. " As described in the book *Tracking Medicine*, written by John Wennberg, the U.S. health care delivery system shows unwarranted variation that cannot be explained based on prevalence of illness, medical evidence, or patient preference.[1] Wennberg argues that undisciplined growth in health care and spending has contributed to the overuse of health care resources.

Antipsychotic medications have long been used for treatment of mental disorders including psychosis, schizophrenia and bipolar disorder. These medications can be broadly categorized into two classes: (1) conventional antipsychotics, also known as first generation antipsychotics or typical antipsychotics, which were discovered in 1950s.[2] (2) Atypical antipsychotics (AAPs) (also known as second-generation antipsychotics) were introduced during 1990s. Compared to the conventional antipsychotics, AAPs were marketed as reducing adverse side effects such as

extrapyramidal symptoms. This resulted in extensive use of AAPs for not only the U.S. Food and Drug Administration (FDA) approved indications but also other conditions that are not approved. However, several post-marketing clinical trials evaluated the use of AAPs and reported serious adverse side effects, including metabolic syndrome, cardiovascular events, or death.[3-5] Also, controversy exists over whether the unapproved use of AAPs is justified in terms of effectiveness and safety.[6-9] Nevertheless, AAPs are one of the top-selling classes of pharmaceuticals in the US. In fact, antipsychotic medications generated about $18.2 billion total revenue in 2011, with three individual AAP agents accounting for 65% of the total revenue.[10]

This chapter is intended to review current issues related with unapproved use of AAPs, specifically focusing on thier use in attention-deficit/hyperactivity disorder (ADHD) children and adolescents. I start by providing general information about ADHD such as symptoms, diagnostic process and prevalence, followed by ADHD treatment options and costs of illness. Then, I motivate the study rationale for why AAP use in ADHD is important from a public health perspective, as well as a social efficiency perspective. Next, we give a systematic review of AAP use in the young population and the associated clinical side effects. Lastly, with commentary about the systematic review, future areas of research will be suggested.

**B. ADHD symptoms, diagnosis, and prevalence**

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood, characterized by having trouble paying

attention, not being able to control impulsive behaviors, or being overly active.[11] Those with ADHD may experience academic underachievement, troublesome interpersonal relationship development, and low self-esteem. Core ADHD symptoms can be divided by two dimensions based on psychometric properties. One is the inattention dimension that includes symptoms such as making careless mistakes, having difficulty sustaining attention, or being easily distracted. The other is hyperactivity-impulsivity dimension that is characterized by symptoms such as being unable to stay seated, having difficulty engaging in leisure activities quietly, or interrupting/intruding on others. ADHD diagnosis is made when at least six or more core symptoms are present in either or both of dimensions. Core symptoms of ADHD adapted from the DSM-IV-TR are shown in Table 1. 1.

The prevalence of ADHD has been increased from 7.8% to 9.5 % during 2003-2007, according to the Center for Disease Control (CDC) in 2010.[12] The increase in prevalence can occur when the incidence increases. Some of the increase is due to the way of patients are diagnosed or detected. Also, it is likely that the observed increase in prevalence is explained by, in part, by the increased recognition of the condition. In fact, the CDC report shows that twelve states had significant increases in the number of diagnosed ADHD cases and this suggests that state policy or practice changes, such as widespread behavioral health screening, could have resulted in the increased prevalence rate. Furthermore, the diagnostic and treatment scope for ADHD has expanded as recent clinical practice guidelines for ADHD, published by the American Academy of

Pediatrics, expanded the age range of the recommendations from 6-12 years of age to 4-18 years of age.[11]

**C. Treatment options for ADHD**

Treatment options for ADHD include medication therapy and behavior therapy. According to the ADHD clinical practice guideline, only behavioral therapy is recommended for preschool-aged children (4-5 years of age) as the first line treatment. For school-aged children and adolescents (6-18 years of age), the combination of medication and behavioral therapies is preferred. Medication therapy usually initiates with stimulants such as amphetamine derivatives (e.g., Adderall), which are FDA-approved medications for ADHD. Selective norepinephrine reuptake inhibitor (atomoxetine) and selective $\alpha_2$-adrenergic agonists (clonidine, guanfacine) are also FDA-approved medications for ADHD management and are often considered as alternatives or adjunctive therapy with stimulants. FDA-approved medications including their generic and brand names are shown in Table 1. 2.

Typical behavioral therapy includes parent-training programs in which the parents or caregivers of children with ADHD are educated with skills to manage behavioral symptoms of their child. As another strategy, changing the physical environment, such as the classroom, is also considered and recommended because it could reduce stimuli that trigger behavioral symptoms. Although it has been shown effective for ADHD management, behavioral therapy requires a high level of family involvement and it might not be easily accessible for some patients.

**D. Cost of illness**

The ADHD patients experience substantial difficulties in many areas of their lives, including academic underachievement, and impaired social functioning, which may impact them the rest of their lives. For example, poorer social functioning among ADHD patients was observed in several studies, which report that those with ADHD have fewer close friends and are more frequently rejected by peers, compared to those without ADHD.[15-17] More importantly, according to the findings of Bagwell et al., these problems are persistent from childhood to adolescence.[15] They retrospectively followed adolescents based on their ADHD history and found that impairments in peer relations during adolescence were highly predicted by childhood ADHD.

ADHD also affects families and caregivers in a form of emotional distress or the loss of work productivity, due to excessive care-giving effort required by ADHD patients.[14,18] Swensen et al., estimated medical care costs and costs associated with work loss accrued to the family members of ADHD patients.[14] They reported that ADHD family members had a higher rate of mental disorders compared to their matched controls. The prevalence of depression was more than twofold higher in the ADHD family members (9% vs. 4%). They also showed that having an ADHD patient in the family was associated with higher medical expenses for other family members, as well as higher indirect costs generated from work absenteeism.

**E. Atypical antipsychotics and ADHD**

Economic burden of ADHD could vary significantly depending on the choice of treatment regimen and how well the patient responds to the therapy. For example, although the symptoms are successfully managed with stimulants in most ADHD patients for the short term (6-10 weeks),[19-21] an alternative medication regimen is often considered due to the adverse side effects, tolerance development or lack of symptom improvement. While atomoxetine, clonidine or guanfacine are recommended as the alternative to stimulants, a growing number of ADHD children are prescribed with AAPs.[8,22,23] The AAP use is concerning because they are not approved for ADHD management by FDA nor recommended by ADHD practice guidelines.

Atypical antipsychotics (AAPs, or second-generation antipsychotics) are a relatively new class of antipsychotic medications. Frequently used AAPs are: olanzapine, risperidone, quetiapine, ziprasidone, paliperidone, and aripiprazole. Atypical antipsychotics are thought to block dopamine receptors as their mechanism of action, except aripiprazole. Aripiprazole does not block the dopamine receptor but acts as a partial agonist and reduces the receptor activation by competing with dopamine or other full agonists. Atypical antipsychotics are FDA-approved for the treatment of schizophrenia and bipolar mania, and a few have also been approved for autism spectrum disorders and major depression. FDA-approved indications for AAPs and their generic/brand names are shown in Table 1. 3.

The use of AAPs in children and adolescents with ADHD in practice is potentially important from the public health standpoint, as well as economic efficiency standpoint.

*Public Health Perspectives*

From the public health standpoint, AAP associated adverse side effects could impose a considerable health care burden on a number of children and adolescents. There are serious adverse side effects reported in AAP users, including obesity, metabolic syndrome, cardiovascular events, Type II diabetes, and increased mortality. In spite of the severe health risks, ADHD has been reported as one of the most frequent conditions for which children and adolescents were prescribed AAPs.[8,22,23] Pathak et al. examined the dispensing pattern of AAPs using a state Medicaid claims data and reported that ADHD was the most common condition for children and adolescents to be prescribed with AAPs from 2001 to 2005.[8] Also, Cooper et al. reported the same finding from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey.[22]

In addition to the clinical impact associated with adverse side effects of AAPs, ADHD patients taking AAPs are at risk of experiencing drug-drug interactions. More specifically, medication therapy in ADHD usually initiates with stimulants and the initial stimulant therapy is later augmented with AAPs, or switched to AAPs.[24] Therefore, the drug-drug interaction could occur between stimulants and AAPs as they have opposing mechanisms of action, such that stimulants increase dopamine level and

AAPs blocks dopamine receptor activation. For this reason, the concurrent use of the two medications could potentially mask the underlying chemical imbalance. Moreover, several studies have reported that not only concurrent use, but switching from one medication to the other also caused movement disorders such as dyskinesia or extra-pyramidal symptoms.[25,26]

*Economic Efficiency Perspective*

From the economic efficiency standpoint, AAP use in ADHD is concerning because a large number of AAPs are possibly misused in the ADHD population. Unlike most other mental disorders for which medication therapy is the only treatment option, the ADHD clinical practice guideline recommends behavioral therapy accompanied by FDA-approved medications.[11] Also, it is recommended that prescribers carefully consider benefit and harm and make sure the use of medication is beneficial. However, it is not clear whether the use of AAPs in ADHD for symptom control outweighs the potential harm, because the evidence is limited. Nevertheless, a recent study conducted by Sikirica et al., shows that approximately one in eight ADHD patients who initiated medication therapy with a stimulant were prescribed AAPs before trying other FDA-approved medications.[24] Sikirica et al., also estimated resource utilization and costs of stimulant-treated ADHD children who switched to or augmented their stimulant treatment with atypical antipsychotics compared with non-antipsychotic medications. Using samples matched based on propensity to receive an AAP, they found that the AAP cohort had higher mean all-cause and mental health-related costs compared to the

non-AAP cohort ($7,407 vs. $5,072; $5,402 vs. $3,054, respectively in 2012 US $; all P<0.001). Therefore, if AAPs are misused for ADHD, the economic impact for society will be substantial considering the high costs involved in AAP use and the number of individuals affected. [8,22,23]

**F. Systematic review of adverse side effects associated with AAP use in children and adolescents.**

The effectiveness and safety of AAPs are not yet established in children and adolescents. Prior studies about AAP-related adverse side effects in children and adolescents are not ADHD-specific. Also, the study design, patient inclusion criteria, and methodological approaches to control for confounding vary among studies. Although there are more studies about increased mortality in the elderly population[27] or the increased risk of diabetes/cardiovascular disease in adults,[28-30] fewer studies exist in children and adolescents to evaluate those risks. A majority of studies that are focused on AAP adverse effects in children and adolescents examined weight gain. Key findings of selected studies about three major AAP- related side effects, namely weight gain, Type II diabetes, and cardiovascular event, are summarized in this section.

This literature review is based on the literature from Medline search, with the Mesh terms of: "child", "adolescent", "metabolic syndrome X", "diabetes mellitus", "dyslipidemia", "cardiovascular disease", "hypertension", "hyperglycemia", "overweight", "obesity", and "weight gain". Also, the search was restricted to the Mesh major topic of "antipsychotic agents/adverse effects", in order to retrieve articles where

the adverse effects are the major focus of the article. All retrieved articles were further culled by excluding non-English written articles, letters, news and adult population based studies.[i] (Figure 1.1) The search was conducted on April 25, 2013.

It should be noted that the search terms that were used in this study may not capture articles that reported adverse side effects as a secondary outcome. We sought to search the studies that focused mainly on adverse side effects of AAPs. However, our search terms potentially miss some of the randomized controlled trials in which drug effectiveness is the primary outcome, while side effects are reported as well.

*Weight Gain*

Findings from prior studies are consistent in indicating that children and adolescents who used AAPs are likely to gain weight. From the Medline search, two review articles and nine primary studies that specifically focused on AAP-induced weight gain in children and adolescents were identified. Both review articles observed significant weight gain related with the AAP use in younger population. [31,32] Original articles about weight gain associated with AAPs are summarized in Table 1. 4. The average weight gain among AAP users was 7.45 kg (± 2.33) in 6 months if it is assumed that the rate of weight gain is consistent over time.[33-40] Interestingly, the rate of weight gain differs by agent according to studies conducted by Fleischhaker et al., which compared clozapine, olanzapine and risperidone in the follow-ups of 6 weeks and 45

[i] In the Mesh database, "adolescent" refers to a person 13 to 18 years of age. Some papers target adult population and include study subjects who are age 18 or greater. However, since they include those with age 18, the paper will include the Mesh term of "adolescent" in addition to "adult". Such papers were excluded because those are mainly adult population based.

weeks.[36,37]. The average weight gain at the 6 week follow up was the highest in olanzapine (4.6kg) followed by risperidone (2.8kg) and clozapine (2.5kg). At the 45-week follow up, olanzapine still showed the highest weight gain (16.2kg) but followed by clozapine (9.5kg) and risperidone (7.2kg). That is, having olanzapine is associated with the fastest weight gain throughout the study period (45 weeks), risperidone showed faster weight gain than clozapine in the short term (6 weeks), but clozapine became faster in the longer term (45 weeks). Correll et al., also examined agent-specific weight gains using olanzapine, quetiapine, risperidone, and aripiprazole, compared with a non-user group.[40] In their study, olanzapine was associated with the highest weight gain, which is consistent with the finding of Fleischhaker et al. In addition to the studies focusing on children and adolescents, there were three articles that studied age-dependent effects.[41-43] All three articles concluded that the change in weight was significantly larger in children and adolescents, compared to adult patients.

*Type II Diabetes*

There were few clinical studies that examined the association between AAP use and type II diabetes in children and adolescents. (Table 1. 5.)[ii] Panagiotopoulos et al., conducted a cross-sectional study using laboratory test results to identify type II diabetes patients and found a significantly higher rate of type II diabetes among the

[ii] Because the systematic review search was conducted in April 2013, a retrospective cohort study published by Bobo et al. in October 2013 was not included in this report. Bobo et al. reported the three times higher risk of type II diabetes among antipsychotic users compared to other psychotropic medication users in children and youth 6 to 24 years of age.

AAP user group, compared to the non-user group.[44] However, they did not account for any confounders in the analysis and it is possible that the higher prevalence of type II diabetes among the AAP user group is not necessarily associated with AAP use. McIntyre et al. used a state Medicaid database and adjusted for age, sex and ethnicity in their retrospective cohort study.[45] They reported a statistically significant impact of multiple AAP use on type II diabetes that was identified using ICD-9-CM (OR: 2.36; 95% CI: 1.13-4.92). However, their current user design could have overestimated the impact of AAP on the probability of Type II diabetes development. Current user design is a study design where the subjects are identified on the basis of current exposure, without tracking the past exposure. The current user design could introduce bias since the disease risk factors that may be altered by the study drug cannot be controlled. Andrade et al., on the other hand, used a new user design and matched samples using propensity scores in order to adjust for possible selection bias on AAP use.[46] They conducted a retrospective cohort study and compared the AAP new users to non-users, as well as to antidepressant users (active comparator). While AAP users were more likely to develop Type II diabetes compared to non-users in unadjusted analysis (IRR: 4.24; 95% CI: 1.95-8.72), when the two groups were matched using propensity scores, the impact of AAP became not significant (IRR: 4.47; 95% CI: 0.23-263.82). Also, when they compared AAP users to antidepressant users, the likelihood of Type II diabetes development was not significantly different either in unadjusted analysis or propensity score matching analysis.

There were two studies that did not specifically focus on children/adolescents but looked at the age-stratified relationship.[32,47] One of the studies analyzed the US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) and they reported that in the 0-17 years of age group, a 95% likelihood of diabetes-related adverse events (DRAEs) occurred at least two times more frequently than expected.[47] The other study that examined the age-dependent relationship used the current user study design and found that the association between diabetes and AAPs use was stronger in younger patients.[32] For patients aged 0-24 years, the impact of clozapine, olanzapine and risperidone was strongest among all of the age groups (clozapine OR 20.4; 95% CI: 7.5-54.9, olanzapine OR 8.2; 95% CI:4.4-15.4, risperidone OR 6.1; 95% CI: 3.8-9.7).

*Cardiovascular Events*

From the Medline search, one article was identified for cardiovascular events associated with AAP use in children and adolescents. McIntyre et al. conducted a retrospective cohort study and examined AAP-related cardiovascular events in children and adolescents at two levels of comparison in a Medicaid population: the primary comparison was performed between AAP users and non-users and secondary comparison was performed between single AAP users and multiple AAP users. Cardiovascular events included ischemic/pulmonary heart disease, arrhythmias and cardiomegaly.[45] The paper reported that the odds of having a cardiovascular event was significantly higher for multiple AAPs users than single AAP users.

**G. Need for evidences from well-designed research**

Observational studies are useful in examining drug associated side-effects that require a long-term follow-up. Although there are prior studies providing the evidence of risks associated with AAPs, the number of studies that attempt to control for confounding is still limited.

The observed variation in findings in the literature is likely due to different methods used to avoid confounding and bias. In other words, each study included different confounders in their analyses and therefore, the impact of AAP use would have been adjusted differently depending on the strength of correlation between the AAP use and other confounders. Also, different study designs and methodological approaches can result in different conclusions. Andrade et al. conducted both adjusting and matching analysis. In result, the AAP use was shown to have a significant impact on diabetes development when using the adjusting method, but the association was not significant in the propensity score matching analysis. The estimates from the two methods could be different if a selection bias is present in the study design. More specifically, adjusting controls for other confounders that are associated with treatment and also with the outcome so that the estimate of treatment reflects the independent impact of AAP. However, matching attempts to control for potential selection bias in which the treatment group has a differential impact on the outcome regardless of the treatment, by selecting samples that are only different in treatment, but otherwise similar to each other.

However, analytical method is not the only explanation for the different conclusions. Criteria for identifying AAP users could have impacted the findings as well. For example, McIntyre et al. reported a statistically significant impact of AAP on Type II diabetes using current user design, but this could make the interpretation of the result arguable whether the observation of current users yields the unique impact of AAP on the probability of Type II diabetes development. Because non-randomized studies often lack detailed historical data on pretreatment information, it is more credible to restrict the treatment group to new users so that the estimate is more internally valid.

**H. Areas of future research**

Although it is not specific to the ADHD population, prior studies have warned to be cautious about using AAPs in children and adolescents due to their adverse effects. Due to potentially important implications in public health as well as efficient resource allocation, the use of AAPs in the ADHD population needs to be assessed with a multidisciplinary approach that examines how the exposure to atypical antipsychotics clinically affects the young population, and what the economic consequences of the treatment are. Therefore, my dissertation research will address underlying problems about AAP utilization, and its implication to ADHD children and adolescents. In chapter 1, detailed backgrounds about ADHD and issues related with AAPs were provided from literature review. Then, in chapter 2, the national utilization trend of AAPs, off-label practice, and use in ADHD is examined. The chapter further inspects the trend by payer source, and regional variations in the US. In chapter 3, as one of the potential adverse

effects, the risk of Type II diabetes in pediatric AAP users is estimated. Combined with chapter 2, the findings of this chapter will suggest the magnitude of risk that is imposed on the pediatric population in the U.S. While chapters 2 and 3 focus more on AAP utilization in general and assess the potential impact on ADHD, following chapters restrict the population specifically to ADHD patients and look into the impact of the drug on the ADHD specific patient level. Chapter 4 estimates the cost-effectiveness of AAPs in ADHD from literature review. Then, chapter 5 presents an original study that compares resource utilization and costs between atypical antipsychotic (AAP) users and non-AAP users in ADHD.

Table 1. 1. Core symptoms of ADHD adapted from DSM-IV-TR

| Inattention Dimension | Hyperactivity-Impulsivity Dimension | |
|---|---|---|
| | Hyperactivity | Impulsivity |
| Careless mistakes | Fidgety | Blurts answers before questions |
| Difficulty sustaining attention | Unable to stay seated | Difficulty awaiting turn |
| Seems not to listen | Moves excessively (restless) | Interrupts/intrudes on others |
| Fails to finish tasks | Difficulty engaging in leisure activities quietly | |
| Difficulty organizing | "On the go" | |
| Avoid tasks that require sustained attention | Talks excessively | |
| Loses things | | |
| Easily distracted | | |
| Forgetful | | |

Source: Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics 2011;128:1007-22.

Table 1. 2. FDA-approved ADHD medications

| Medication | Brand name | Route | Generic form available |
|---|---|---|---|
| Mixed amphetamine salts | Adderall | Oral | √ |
| | Adderall XR | Oral | √ |
| Dextramphetamine | Dexedrine/Dextrostat | Oral | √ |
| | Dexedrine Spansule | Oral | √ |
| Lisdexamfetamine | Vyvanse | Oral | |
| Methylphenidate | Concerta | Oral | |
| | Methy ER | Oral | |
| | Methylin | Oral | |
| | Daytrana | Transdermal | |
| | Ritalin | Oral | √ |
| | Ritalin LA | Oral | |
| | Ritalin SR | Oral | √ |
| | Metadate CD | Oral | |
| Dexmethylphenidate | Focalin | Oral | √ |
| | Focalin XR | Oral | |
| Atomoxetine | Strattera | Oral | |
| Extended-release guanfacine | Intuniv | Oral | |
| Extended-release clinidine | Kapvay | Oral | |

Table 1. 3. Atypical antipsychotics and FDA-approved indications

| Medication | FDA indication | Brand | Generic form available |
|---|---|---|---|
| Aripiprazole | Schizophrenia, bipolar I disorder, adjunctive to majore depression | Abilify | |
| Asenapine Maleate | Schizophrenia, bipolar mania | Saphris | |
| Clozapine | Treatment-resistant schizophrenia | Clozaril | √ |
| Iloperidone | Schizophrenia | Fanapt | |
| Lurasidone | Schizophrenia | Latuda | |
| Olanzapine | Schizophrenia | Zyprexa<br>Zyprexa relprevv<br>Zyprexa zydis | |
| Olanzapine/Fluoxetine | Depressive episodes associated with bipolar I disorder, treatment resistant depression | Symbyax | |
| Paliperidone | Schizophrenia | Invega<br>Invega sustenna | |
| Quetiapine | Schizophrenia, bipolar mania, bipolar depression | Seroquel<br>Seroquel XR | √ |
| Risperidone | Schizophrenia, bipolar I disorder, autism | Risperdal<br>Risperdal consta | √ |
| Ziprasidone | Schizophrenia, bipolar I disordermajore depression | Geodon | √ |

Table 1. 4. Articles about AAP associated weight gain

| Reference | Study design | AAP | Follow up | Weight change in AAP group | Weight change in comparison group | Comments |
|---|---|---|---|---|---|---|
| Hellings et al. (1998) | Cohort study | Risperidone | 50 wks | 8.3kg (±5.7kg) | No comparison | All study subjects were mental retardation and autism patients. |
| Kelly et al. (1998) | Cohort study | Risperidone | 6 mons | 8.64 (±6.96kg) | 1.Conventional antipsychotics: 3.03kg (6.82kg) 2. No AAP: -1.04kg(±4.55kg) | Gains in body weight did not correlate with dose, nor concomitant use of stimulant or lithium |
| de Hoogd et al. (2012) | Cohort study | Not specific | 6.6 mons | change in weight z-score, 0.42 | No comparison | In a cross-sectional study, AAP users had higher BMI z-score than non-users. |
| Fleischhake et al. (2007) | Cohort study | Clozapine, olanzapine, and risperidone | 6 wks | olanzapine, 4.6kg(±1.9kg) risperidone, 2.8kg(±1.3kg) clozapine, 2.5kg(±2.9kg) | No comparison | Weight gain: Olanzapine>risperidone>clozapine |
| Fleischhake et al. (2008) | Cohort study | Clozapine, olanzapine, and risperidone | 45 wks | olanzapine, 16.2kg(±8.8kg) risperidone, 9.5kg(±10.4kg) clozapine, 7.2kg(±5.3kg) | No comparison | Weight gain: Olanzapine>clozapine>risperidone |

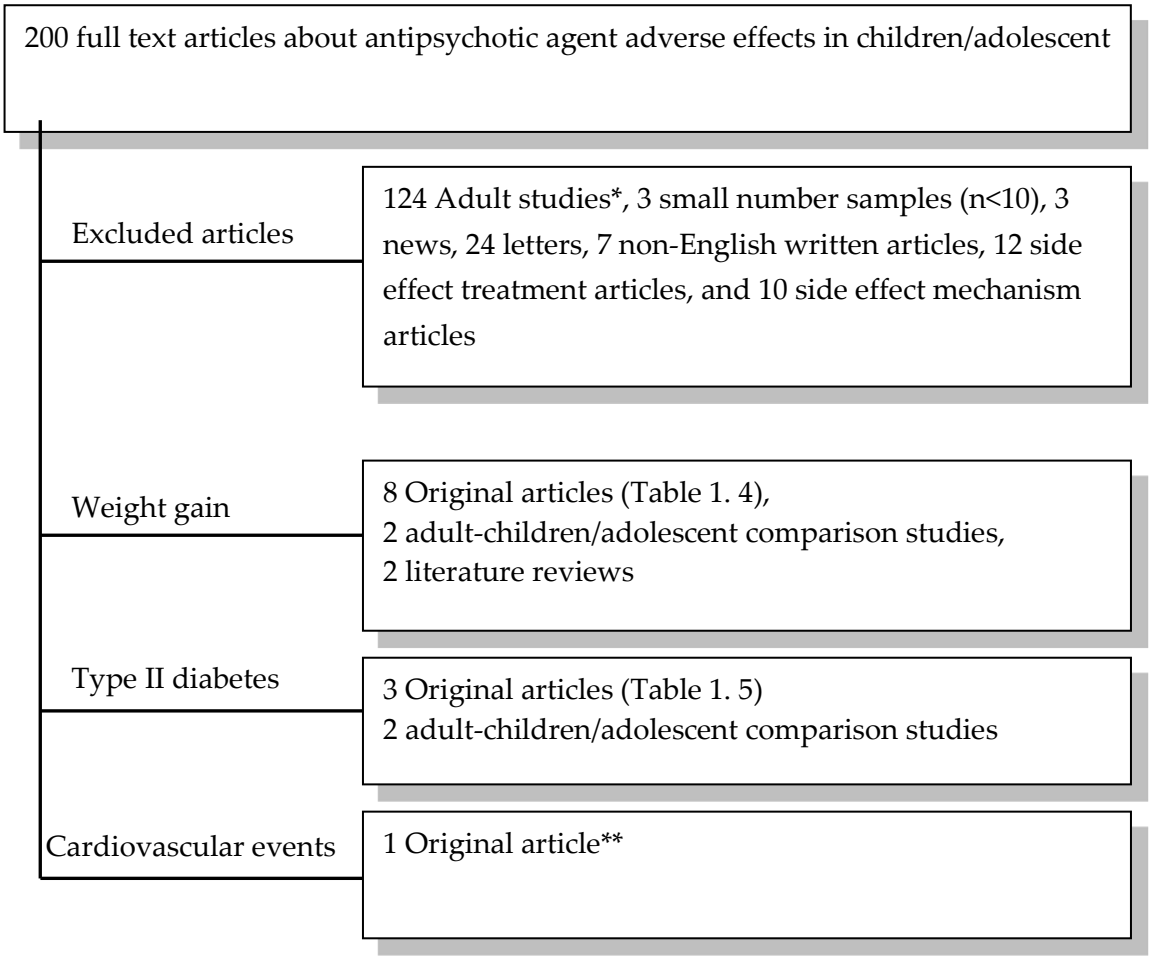
Table 1. 4-contd. Articles about AAP associated weight gain

| Reference | Study design | AAP | Follow up | Weight change in AAP group | Weight change in comparison group | Comments |
|---|---|---|---|---|---|---|
| Martin et al. (2000) | Cohort study | Risperidone | 6 mons | 7.0kg(±5.2kg) | No AAP: 0.1kg(±6.1kg) | |
| Moreno et al. (2010) | Cohort study | Not specific | 3 mons | 5.5kg(±4.8kg) | No comparison | The average BMI z-score was increased by 0.6 in AAP users |
| Correll et al. (2009) | Cohort study | Olanzapine, quetiapine, risperidone, aripiprazole | 10.8 wks | olanzapine, 8.5kg quetiapine, 6.1kg risperiodne, 5.3kg aripiprazole, 4.4kg | No AAP: 0.2kg | Weight gain: olanzapine>quetiapine>risperidone> aripiprazole |

Table 1. 5. Articles about AAP associated Type II diabetes

| Reference | Study design | AAP | Measurement | Confounder | Result |
|---|---|---|---|---|---|
| Panagiotopoulos et al. (2009) | Cross-sectional study | Not specific | Fasting glucose level | No confounders adjusted | Significantly higher IFG/Type 2 diabetes in AAP users than non-users (21.5% vs. 7.5%) |
| McIntyre et al. (2008) | Retrospective cohort study | Aripiprazole, olanzapine, ziprasidone, risperidone, quetiapine | ICD-9-CM | Age, sex, ethnicity | Significant in those exposed to multiple antipsychotics (OR, 2.36; 95% CI 1.13-4.92) |
| Andrade et al. (2011) | Retrospective cohort study | Not specific | ICD-9-CM or pharmacy fill or lab test | Age, sex, mental condition, oral corticosteroid, ambulatory care visits, other medications | In propensity score matched sample, the incidence rate ratio was not significantly different between AAP users and 2 comparison groups (non-users and antidepressant users). |

Figure 1. 1. Flowchart of review article selection




* In the Mesh database, "adolescent" refers to a person 13 to 18 years of age. Some papers target adult population and include study subjects who are age 18 or greater. However, since they include those with age 18, the paper will include the Mesh term of "adolescent" in addition to "adult". Such papers were excluded because those are mainly adult population based.

** The article about the risk of cardiovascular events also reported about Type II diabetes, and it appears twice in the figure.

## Chapter 2: National trends in atypical antipsychotics in children and adolescents

### A. Background

As a result of the intense marketing campaigns promoting atypical antipsychotics (AAPs) as a safer alternative (i.e., reducing the risk of side effects like extrapyramidal symptoms) to conventional antipsychotics, and despite the safety concerns (i.e., metabolic syndrome, cardiovascular events, or death)[3-5] raised by post-marketing studies in adults, AAP use has increased not only for indications approved by the US Food and Drug Administration (FDA) but also for other conditions.[48] In children and adolescents in the US, AAPs are probably among the most increasingly used classes of prescription drugs.[49,50] In a study using data from three Medicaid programs and one private managed care organization in the U.S., the total AAPs use for children and adolescents increased 1.5- to 3-fold between 1996 and 2001.[50] Also, medical office visits including antipsychotic medications for youth patients increased 5-fold between 1993 and 2002.[51] However, to the best of our knowledge, previous trend analyses for the pediatric AAP use have not been updated for more recent years. Also, it would be essential to understand the current trend of pediatric AAP use and characteristics before discussing the clinical/economic benefits and costs. Therefore, the purpose of this chapter is to (1) examine the historic trend of AAP use in the US among 4- to 18- year-old patients, (2) assess the characteristics of AAP use by identifying primary mental disorders and frequently used AAP agents, and (3) estimate the strength of independent

association of patient/provider characteristics with AAP prescription among pediatric (4- to 18- year-old patients) ADHD visits.

**B. Materials and methods**

*Data source*

Data sources for this study were the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS). The NAMCS and NHAMCS are national surveys that collect data on outpatient visits to non-federal employed, office-based physicians who are primarily engaged in direct patient care and outpatient departments of non-institutional general and short-stay hospitals. We intended to estimate the national trend of non-emergent visits that are relevant to an AAP prescription. For this reason, we did not analyze data collected from hospital emergency departments and ambulatory surgery centers.

In the NAMCS/NHAMCS data, each visit has information about patient socio-demographics, physician characteristics, diagnoses, and prescription drugs. Up to three diagnoses were recorded per visit using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). The maximum number of drugs that could be recorded per visit was six during 1995-2002, and it increased to eight in 2003. Following the National Center for Health Statistics recommendation,[52] we included only six first-listed drugs in most of years (between 1995 and 2010) to avoid overestimating the

prescribing rate that may be affected by the change in the number of drugs was recorded. However, five drugs were included in the analysis for the years of 1993 and 1994.[iii]

The data from 1993 to 2010 were used to compute the annual average rate of pediatric AAP visits. The data from 2007 to 2010 were combined and analyzed to assess the characteristics of pediatric AAP visits (i.e., primary mental disorders and frequently used AAP agents) and to identify predictors of AAP use in pediatric ADHD visits. Sample weights were applied in all analyses using Stata statistical software, version 12.

*Definition of an AAP visit*

An outpatient visit was regarded as an AAP visit if one or more following medications are present: risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine, and iloperiodone. For 1993-2005, the National Center for Health Statistics (NCHS) provided generic codes were used to identify AAPs. Then, beginning in 2006, NAMCS/NHAMCS changed the drug identification method by implementing Multum codes. Also, AAP visit rates for FDA approved indications were estimated. I defined an AAP visit for FDA approved indication as an AAP visit with a record of one or more indications that are approved by FDA for any age group at a given study year. Even if a pediatric patient was prescribed an AAP with an indication that is only approved for adults, I still considered that as the AAP use for a FDA

[iii] The years of 1993 and 1994 had up to five drugs that could be entered. Although the National Center for Health Statistics recommends using the consistent number of drugs throughout the study period when performing trend analyses, we considered that the contribution of these two years to the overall trend analysis was minimal and that including five drugs in 1993-1994 and six drugs in 1995-2010 in the analyses would not result in overestimation of an actual increase in prescribing an AAP during 1995-2010.

approved indication. During 1993-2010, AAPs were approved by FDA for four conditions[iv]; (1) schizophrenia (ICD-9-CM, 295), (2) bipolar disorder (ICD-9-CM, 296.0; 296.1; 296.4-296.8), (3) depression (ICD-9-CM, 296.2; 296.3; 300.4; 311.X), and (4) autism (ICD-9-CM; 299.0). Figure 2. 1 depicts FDA approved indications for each AAP agent throughout the study period.

*National trend of AAP visit (1993-2010)*

As the first objective of the study, we examined the national trend of AAP visits by calculating average AAP visit rates among 4- to 18- year-old patients for each survey year between 1993 and 2010.

Based on the major events occurred related to AAP use during the period, I combined survey years and formed three phases in a way that a new phase began when additional indication was approved by FDA for AAP use. For each phase, the average visit rate with 95% confidence interval (CI) was calculated. Then, we explored whether there were newly available AAP agents or additional FDA warnings during each phase.

*Mental diagnoses related with AAP visit (2007-2010 combined)*

We used three recorded diagnoses of AAP visits to examine (1) whether there was any mental diagnosis (ICD-9-CM, 290.XX-310.XX) in the visit, (2) if one or more mental diagnoses were present, whether there was any diagnosis for the FDA approved

[iv] Olanzapine was approved for the manifestations of psychoses (ICD-9-CM; 290.XX-299.XX) between 1996 and 2000. In 2000, the FDA changed the approval for olanzapine to schizophrenia and bipolar disorder.

indication (as defined above), and (3) if there were one or more mental diagnoses but none of FDA approved indications, what was the first-listed mental diagnosis in the visit. For the mental health visits without an FDA approved indication, the first-listed mental diagnosis was classified into following categories: (1) psychoses with origin specific to childhood ("psychoses" hereafter, ICD-9CM, 299.X), (2) disturbances (ICD-9CM, 312.XX; 313), (3) neurotic disorders (ICD-9CM, 300.0X; 300.1X, 300.2X, 300.3; 300.5; 300.8X; 300.9) and (4) other mental disorders (ICD-9-CM, other codes between 290.XX-310.XX).

*Factors associated with an AAP prescription in pediatric ADHD visits (2007-2010 combined)*

The data from 2007 to 2010 were combined and analyzed to estimate independent associations of patient demographic/socioeconomic characteristics (age, sex, race, region of residence, household income/education level based on ZIP code, and payer source), physician characteristics (provider type, metropolitan statistical area located), and patients' health information (presence of hyperactivity[v], number of non-AAP drugs, other comorbidities) with an AAP prescription among pediatric ADHD visits. A logistic regression model was developed including these covariates[vi] and odds ratios with associated 95% confidence intervals were estimated.

Among 4- to- 18-year-old ADHD patient visits during 2007-2010, 4 percent had missing observations for variables that were based on patient ZIP code, such as median

[v] There are two ICD-9-CM codes for ADHD: attention deficit disorder without hyperactivity (314.00) and attention deficit disorder with hyperactivity (314.01)

[vi] Covariates were included in the logistic regression model regardless of its statistical significance. That is, even if a covariate was not significant at 5% significance level, it was still controlled in the model.

household income and percent of Bachelor's degree or higher. These missing observations were not included in the analysis. However, I used imputed data for observations missing a race variable. There were 29 percent missing observations for the race variable during 2007-2010 and I used NAMCS/NHAMCS provided imputation values for those missing observations. The method used by NAMCS/NHAMCS for 2007 and 2008 data to impute the race value was based on the patient's locality (ZIP code or state/county of residence), physician locality, specialty, or 3-digit ICD-9-CM code for primary diagnosis. If all failed to assign the race value, the imputation was done based on a randomly selected record. For 2009 and 2010 data, race was imputed using a model-based, single, sequential regression imputation method. The model for imputing race is described in more detail in the 2009-2010 NAMCS/NHAMCS Public Use Data File Documentation.[53]

**C. Results**

*National trend of AAP use*

From 1993 to 2010, the overall AAP use showed an increasing pattern. (Figure 2. 2) When risperidone became first available in 1993, NAMCS/NHAMCS did not have a sample visit indicating a pediatric AAP use, as well as in 1994. Starting from 1995, the rate of AAP prescription increased gradually until 1999. Between 1999 and 2000, the average AAP visit rate increased more than twice from 0.4 per 100 visits to 0.9 per 100 visits. Then, the increased rate maintained at a stable level until 2002. Then, the average

rate increased twice again from 2002 to 2003 (from 0.8 per 100 visits to 1.6 per 100 visits), after which average visit rates showed a more fluctuating pattern.

Based on FDA approvals for additional AAP indication, I combined survey years and formed three phases: (1) phase I for the 1993-1999 period, (2) phase II for the 2000-2002 period, and (3) phase III for the 2003-2010 period. More specifically, each phase begins with a newly approved indication for AAP use. It was observed that the average visit rates between these phases were statistically different at 5% significance level. During phase I, the average AAP visit rate was 0.15 per 100 visits (95% CI, 0.1-0.21 per 100 visits). Three AAP agents were available in the market with two FDA approved indications during the period. Then, the average AAP visit rate increased significantly to 0.81 per 1000 visits (95% CI, 0.54-1.21 per 100 visits) in phase II. During the period, two additional AAP agents became available (total five agents available in the market). Also, olanzapine was first approved for bipolar disorder in 2000 and it remained as the only AAP agent approved for the indication until 2002. In phase III, the average AAP visit rate was 1.59 per 100 visits (95% CI 1.37-1.83). During phase III, three new AAP agents became available (total eight agents available in the market) and the FDA approved AAPs for more indications including depression and autism. Moreover, the pediatric AAP use was first approved during this period.[vii]

[vii] Readers should be reminded that I did not restrict the definition of FDA approved AAP indication into specific age group (i.e., even if a pediatric patient was prescribed an AAP with an indication that is only approved for adults, I still considered that as the AAP use for FDA approved indication). I identified additionally approved indications age-specifically (adult and pediatric) only for the purpose of exploring events occurred during each phase.

Throughout the study period, a majority of AAP visits did not include a diagnosis for FDA approved indications (referred to as "off-indication" in the Figure 2. 2). The off-indication visits accounted for approximately 86 percent of pediatric AAP visits during 1995-2003 and 71 percent during 2004-2010. A statistically significant increase for FDA approved AAP use was observed between 2003 and 2004, when three AAP agents including aripiprazole, quetiapine, and ziprasidone were approved for bipolar disorder in addition to their previously approved indication, schizophrenia.

*Mental diagnoses related with AAP visit*

The estimated number of total outpatient AAP visits among 4- to 18- year-old patients during 2007-2010 was 8,380,436 (weighted count) which accounted for approximately 2 percent of total pediatric outpatient visits in the U.S.. Of those, 34% visits included one or more diagnoses of FDA approved indications. (Figure 2. 3) Within this group, a majority of visits had diagnoses of bipolar disorder or depression (16% or 14% of total pediatric AAP visits, respectively), followed by autism and schizophrenia (5% or 1% of total pediatric AAP visits, respectively). Approximately 2% of total pediatric AAP visits had two of more diagnoses of FDA approved indications.

Among the pediatric AAP visits without any FDA approved indications, ADHD was the most common primary mental diagnosis (24% of total pediatric AAP visits), followed by psychoses (14% of total pediatric AAP visits). Disturbances and neurotic disorders took up about 5% of total pediatric AAP visits respectively. Approximately 15% of total pediatric AAP visits did not include any mental disorder diagnosis.

*Frequently prescribed atypical antipsychotics*

Of the 8,380,436 total pediatric AAP visits, a majority of visits prescribed risperidone, aripiprazole or quetiapine (35%, 32%, or 18% of total pediatric AAP visits) (Figure 2. 4). A smaller proportion of visits prescribed ziprasidone, olanzapine, or paliperidone (6%, 5%, or 1% of total pediatric AAP visits). Approximately 3% of total pediatric AAP visits prescribed two or more AAPs.

*Factors associated with an AAP prescription in pediatric ADHD visits*

During 2007-2010, the total number of pediatric ADHD visits was estimated to be 31,501,209. Of those, 12% included one or more AAP prescriptions (weighted count: 3,763,296). Baseline characteristics of pediatric ADHD visits are summarized in Table 2. 1. Between AAP visits and non-AAP visits, patient demographics and health care provider characteristics were not statistically significantly different. However, significantly larger proportion of AAP visits had Medicaid as the primary source of payment. In terms of ADHD characteristics, AAP visits were more likely to have attention deficit disorder with hyperactivity compared to those without hyperactivity. Also, AAP visits had more drugs (other than AAPs) prescribed compared to non-AAP visits. Baseline comorbidity profile was also different in a way that AAP visits had more comorbid conditions including FDA approved AAP indications, psychoses, neurotic disorder, disturbance and diabetes.

In the logistic regression analysis, having Medicaid as the primary payment source, more prescription medications, and comorbid mental disorders including FDA approved AAP indications, psychoses, neurotic disorder, disturbance or diabetes significantly increased the likelihood of having an AAP prescription in a pediatric ADHD visit. (Table 2. 2) However, having comorbid obesity decreased the likelihood of having an AAP prescription.

**D. Discussion**

The purpose of this study was to examine the national trend of pediatric AAP use in an outpatient health care setting in the US. The average AAP visit rates were estimated each year between 1993 and 2010, and events related with AAP use were explored during the period. Then, mental diagnoses related to AAP prescription and frequently used AAP agents were assessed for the period of 2007-2010. Lastly, we estimated the strength of independent association of patient/provider characteristics with AAP prescription among pediatric ADHD visits.

From 1993 and 2010, the overall visit rates of AAP prescription in pediatric outpatient visits showed an increasing pattern. There was approximately 5-fold significant increase from phase I (1993-1999) to phase II (2000-2002) and two-fold significant increase from phase II to phase III (2003-2010). When comparing with AAP related events occurred during each phase, as more AAP agents became available and more AAP indications were approved by FDA, the AAP visit rates also increased (Figure 2. 2). Also, it appeared that sudden increases of AAP visit rates were associated

with an FDA approval for an additional AAP indication. More specifically, in all AAP drug approval processes during 1993-2010, all AAP agents became initially available for schizophrenia. Years later, some AAPs changed labels by including additional indications including bipolar disorder, depression, and autism. Interestingly, bipolar disorder was first approved to be treated with olanzapine among AAP agents in 2000, and in the same year, there was an abrupt increase in AAP visit rates, which eventually initiated the next phase. Olanzapine was first approved for treatment of depression in 2003, and there was another abrupt increase in AAP visit rates leading to the next phase in the same year. Although it was less abrupt, when autism was first approved to be treated with risperidone in 2006, the AAP visits also showed the highest rate since the first depression approval in 2003. However, it is hard to argue that such increased visits are mostly to treat the additionally approved indication. For example, from phase I to phase II, AAP visits for FDA approved indications increased only 0.09 per 100 pediatric outpatient visits, while AAP visits for off-indication uses increased 0.57 per 100 pediatric outpatient visits. Similarly, from phase II to phase III, the increase in visits for off-indication usage was larger than for FDA approved indication. One of the plausible explanations for this phenomenon might be that having an approval for additional AAP indication impacted the AAP therapy decision-making process in a way that an AAP agent was thought to be also effective for conditions other than currently approved indications. However, my trend analysis does not control for any covariates and therefore, further investigation using carefully designed models is needed to clarify the association of a certain event with AAP visit rates.

My analysis for identifying mental diagnoses that are seemingly related with AAP prescription revealed that approximately 66 percent of total pediatric AAP visits did not include a diagnosis for FDA approved indications between 2007 and 2010. Of those, ADHD was the most common primary mental diagnosis. This finding is consistent with several previous studies that examined pediatric AAP use. Pathak et al. examined the dispensing pattern of AAPs using Arkansas Medicaid claims data and reported that ADHD was the most common condition for children and adolescents to be prescribed with AAPs between 2001 and 2005.[8] Cooper et al. reported the same finding from the NAMCS/NHAMCS data between 1995 and 2002.[22] Also, approximately 15 percent of total pediatric AAP visits did not include any mental diagnosis. A similar problem was previously concerned by Staller et al. who reported that 77 percent of outpatient antipsychotic visits by 18 year-old or younger patients did not have a mental diagnosis. They collected medical and prescription data from eight outpatient clinics in central New York in 2002. The fact that they had a much higher proportion of psychiatric visits without a mental diagnosis than my study could be explained a number of factors including different sampling method, different number of recorded diagnoses, or different inclusion criteria in defining antipsychotic visits. Nonetheless, both studies raise an important issue about current antipsychotic prescription pattern which suggests that antipsychotic medications could be frequently misused in pediatric population.

From my logistic regression model estimating the association between several factors and AAP prescription among pediatric ADHD visits, patient demographics and

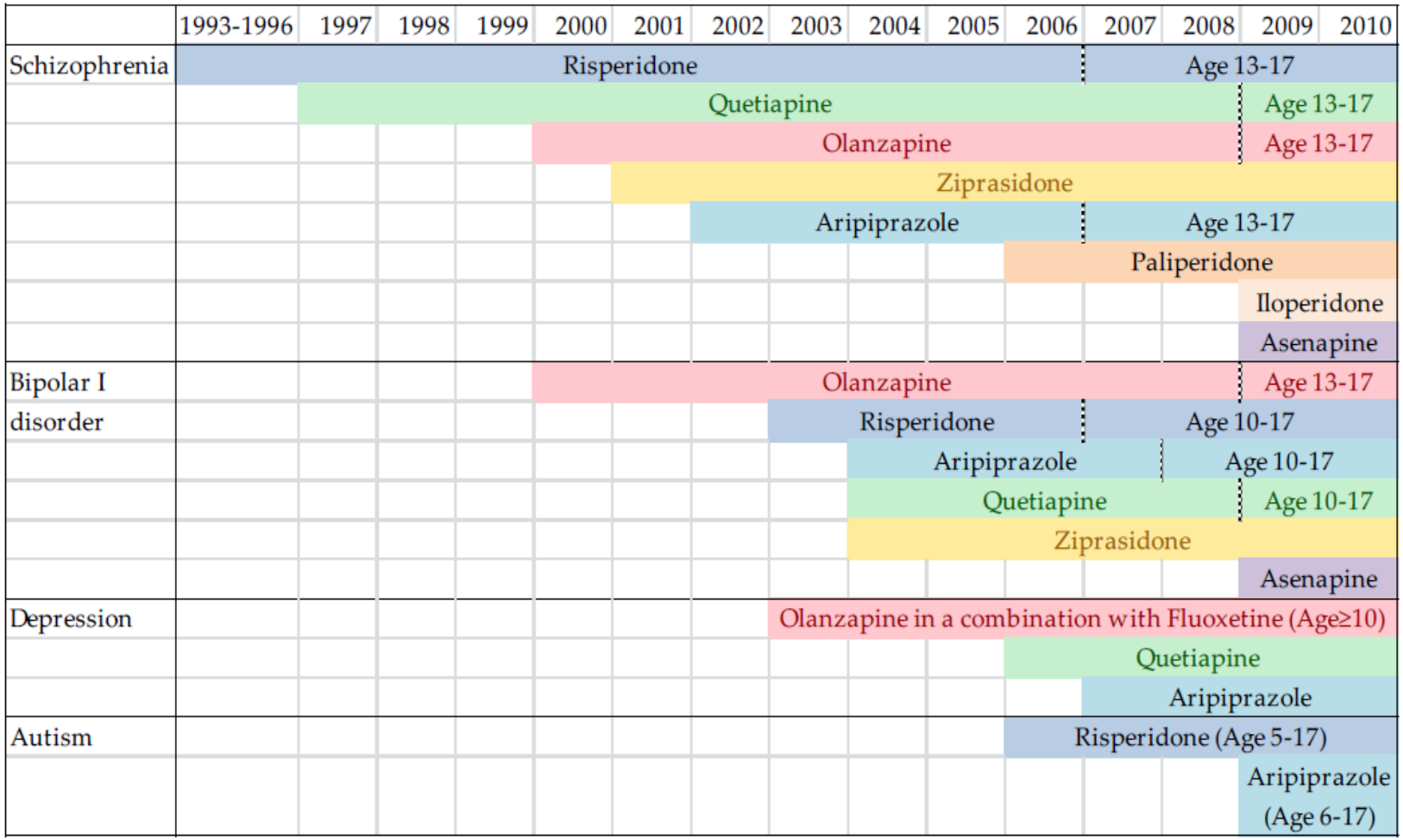
health care provider characteristics did not show a significant association with AAP prescription. Instead, patients' medical profiles showed much stronger associations with AAP prescription. More specifically, having more co-prescribed medications (i.e., other than AAPs) and comorbid mental disorders including FDA approved AAP indications, psychoses, neurotic disorder and disturbance increased the likelihood of having an AAP prescription. This result indicates that an AAP is more likely to be prescribed to ADHD patients when multiple health conditions are present, controlling for other patient/health care provider characteristics. The result of Medicaid being a significant factor could be also explained with this result, since chronic illness and other health risk factors are more prevalent among Medicaid enrollees compared to those who are covered by a private insurance. [54-56]

There are some limitations that should be noted. First, the survey may not capture sufficient information to estimate the AAP visit rates and characteristics of visits. I used six first-listed medications and three diagnosis codes for the study period. However, such limited availability of medical/pharmacy records may have misrepresented the true estimates in the study. For example, it is possible that some AAP treated patients had a severe physical illness in addition to mental disorders, and due to the limited space for the number of diagnosis codes on the survey form, their health care providers were only able to record diagnoses for physical illness. In this case, the visit data would have been categorized as an AAP visit with no mental disorder diagnosis code, although the visit actually had a mental disorder diagnosis. Second, NAMCS/MHAMCS for 1993-2010 were designed to obtain the national/regional estimate

of outpatient health care service measures. However, due to insufficient sample size, state-level estimates are usually unreliable. For this reason, we were unable to independently assess the association of states with the AAP prescription among pediatric ADHD visits. Third, due to the nature of micro visit level data, the temporal relationship of explanatory variables and AAP prescription was not identifiable. In other words, it is not possible to conclude that having comorbid conditions triggered the AAP use. Instead, we only know that comorbidities are associated with AAP use. Fourth, variables of obesity, diabetes and cardiovascular disease in our logistic regression model had only few observations, making the estimated values unreliable. Especially, the variable of cardiovascular disease was dropped from the estimation, because there was no variability between AAP prescription and cardiovascular disease. This is probably due to the small number of observations in the variable of cardiovascular disease.

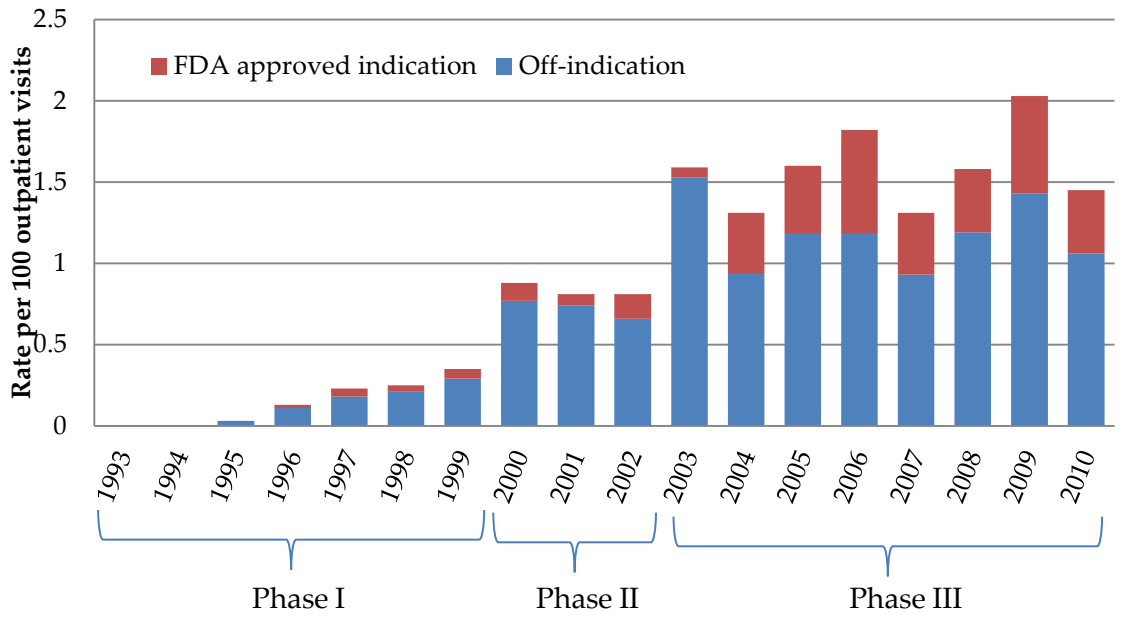
In conclusion, I showed that outpatient visits including an AAP among 4- to 18-year-old patients has significantly increased between 1993 and 2010 in the US, and over 65 percent of those visits did not have diagnoses for FDA approved AAP indications. During 2007-2010, the most common mental disorder was ADHD, accounting for 24 percent of total pediatric AAP visits. Among visits with ADHD diagnosis, those with comorbid mental disorders such as psychoses, neurotic disorder and disturbance were more likely to have an AAP prescription.

Figure 2. 1. FDA approved indications for atypical antipsychotics*




*These are FDA approved indications for adult AAP use. FDA approvals for pediatrics are indicated with the approved age group.

Figure 2. 2. Atypical antipsychotic use for children and adolescents (ages 4-18)




| | Phase I | Phase II | Phase III |
|---|---|---|---|
| **Newly available AAP agent** | risperidone, olanzapine, quetiapine | ziprasidone, aripiprozole | paliperidone, asenapine, iloperidone |
| **Newly approved indication (adult)** | schizophrenia, manifestations of psychoses* | bipolar I disorder | depression |
| **Newly approved indication (pediatric)** | | | schizophrenia, bipolar I disorder, depression, autism |
| **FDA warning** | | | metabolic syndrome, increased death in elderly dementia patients |

*Olanzapine was approved for the manifestations of psychoses in 1996-2000. Since 2000, olanzapine has been approved for schizophrenia and bipolar I disorder (adult).

Figure 2. 3. Mental diagnoses related with AAP visits

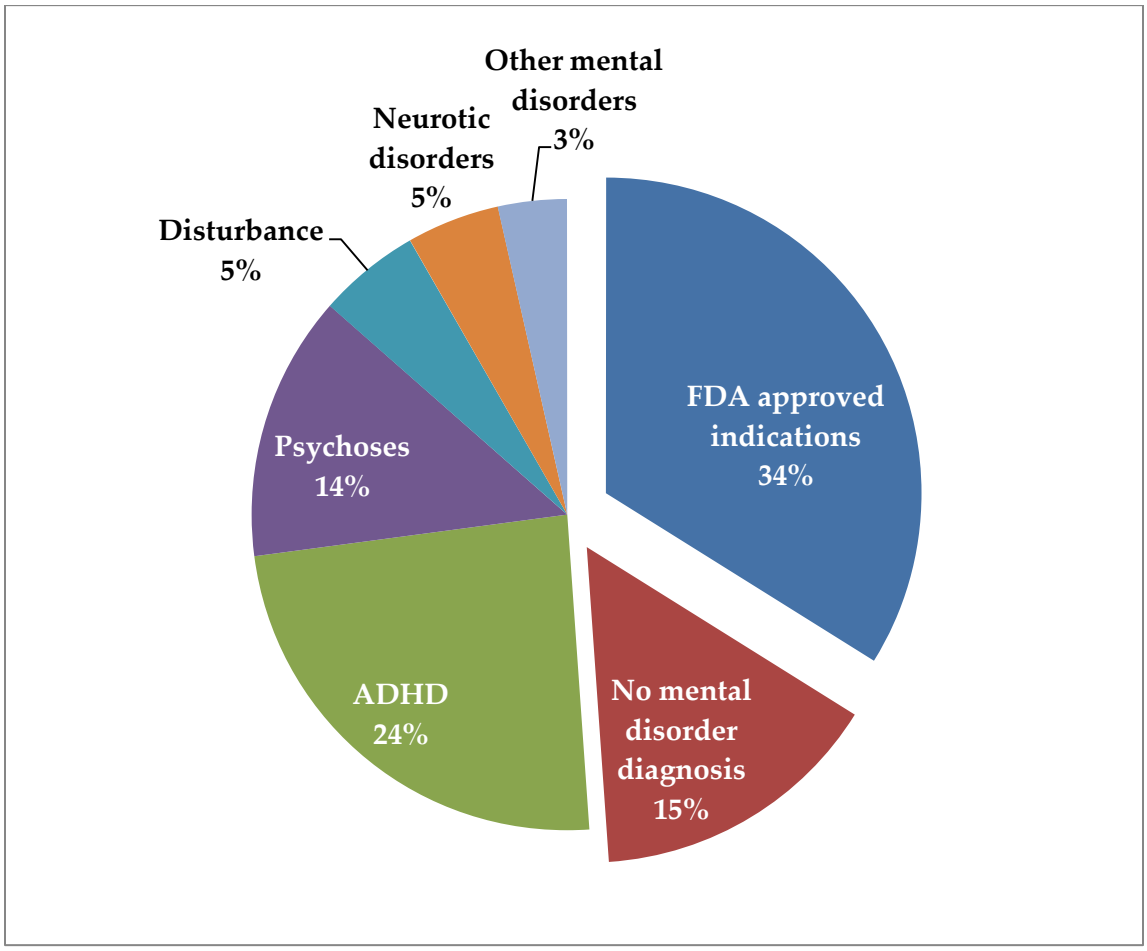


Figure 2. 4. Frequently used AAP agents

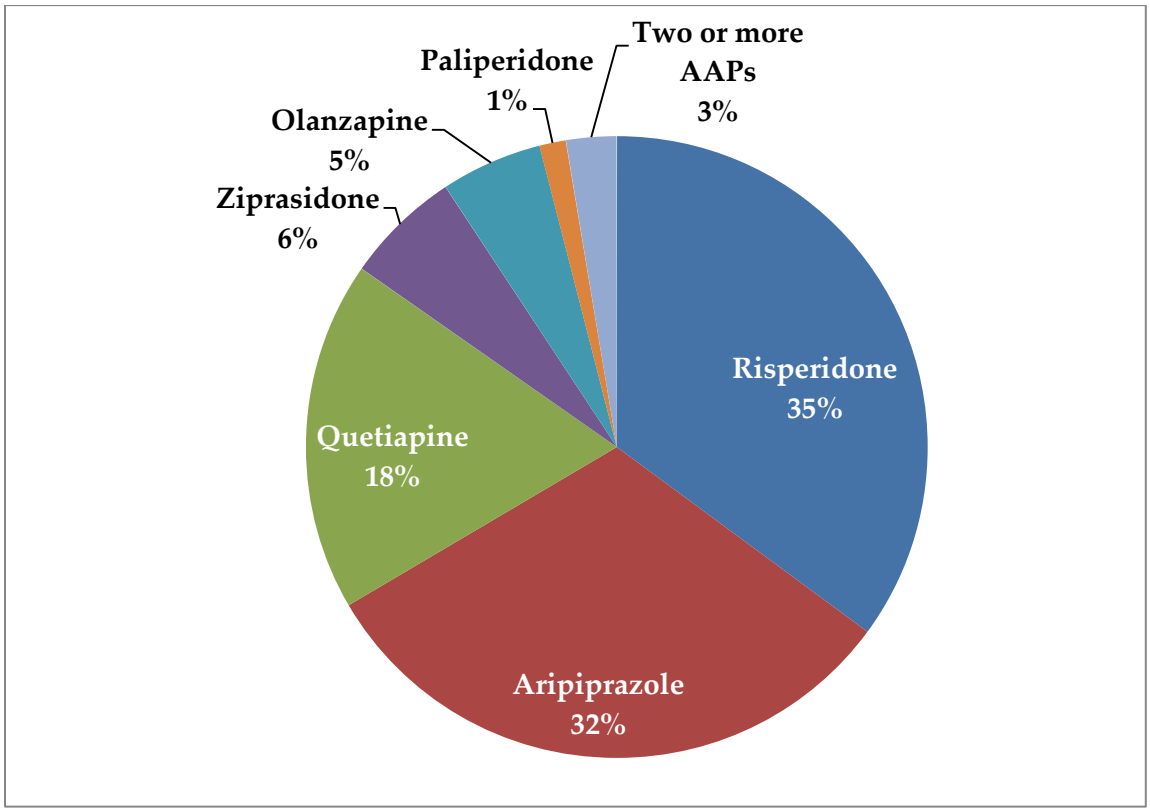


Table 2. 1. Baseline characteristics of pediatric ADHD visits*

| Baseline Characteristics | AAP visits (N=3,763) | | Non AAP visits (N=27,738) | | p Value |
|---|---|---|---|---|---|
| | N | % | N | % | |
| Age | | | | | |
| Pre-school child (age 4-5)** | 179 | 4.76 | 1,213 | 4.37 | 0.867 |
| Elementary child (age 6-11)** | 2,026 | 53.84 | 17,081 | 61.58 | 0.085 |
| Adolescent (age 12-18)** | 1,558 | 41.40 | 9,445 | 34.05 | 0.089 |
| Sex | | | | | |
| Male | 2,768 | 73.56 | 19,587 | 70.62 | 0.498 |
| Female | 995 | 26.44 | 8,151 | 29.38 | 0.498 |
| Race | | | | | |
| White | 2,948 | 78.34 | 22,427 | 80.85 | 0.449 |
| Black | 654 | 17.37 | 4,289 | 15.46 | 0.507 |
| Other | 162 | 4.30 | 1,021 | 3.68 | 0.744 |
| Region of residence | | | | | |
| Northeast | 726 | 19.28 | 4,876 | 17.58 | 0.681 |
| Midwest | 896 | 23.82 | 7,160 | 25.81 | 0.700 |
| South | 1,484 | 39.43 | 11,011 | 39.70 | 0.969 |
| West | 657 | 17.46 | 4,690 | 16.91 | 0.916 |
| Median household income in patient's zip code | | | | | |
| Quartile 1 | 1,086 | 28.85 | 5,886 | 21.22 | 0.160 |
| Quartile 2 | 859 | 22.84 | 8,292 | 29.89 | 0.067 |
| Quartile 3 | 792 | 21.05 | 6,106 | 22.01 | 0.837 |
| Quartile 4 | 1,026 | 27.26 | 7,454 | 26.87 | 0.942 |
| Percent population with Bachelor's degree or higher in patient's zip code | | | | | |
| Quartile 1 | 1,074 | 28.55 | 7,648 | 27.57 | 0.853 |
| Quartile 2 | 859 | 27.22 | 8,292 | 22.52 | 0.181 |
| Quartile 3 | 792 | 18.62 | 6,106 | 26.19 | 0.105 |
| Quartile 4 | 1,026 | 25.61 | 7,454 | 23.71 | 0.672 |
| Metropolitan statistical area | | | | | |
| No | 487 | 12.93 | 5,542 | 19.98 | 0.248 |
| Yes | 3,277 | 87.07 | 22,195 | 80.02 | 0.248 |
| Payer source | | | | | |
| Private | 1,533 | 40.75 | 14,726 | 53.09 | 0.035 |
| Medicaid | 1,976 | 52.50 | 10,593 | 38.19 | 0.013 |
| Self-pay | 296 | 7.87 | 1,706 | 6.15 | 0.610 |
| Other | 1,690 | 5.45 | 204 | 6.09 | 0.800 |
| Mental health provider | | | | | |
| No | 1,103 | 94.79 | 26,635 | 96.02 | 0.341 |
| Yes | 196 | 5.21 | 1,103 | 3.98 | 0.341 |
| Attention deficit disorder with hyperactivity | | | | | |
| No | 132 | 41.24 | 4,040 | 44.75 | 0.010 |
| Yes | 3,632 | 58.76 | 23,698 | 55.25 | 0.010 |
| Number of non-AAP prescribed (different generic names) | | | | | |
| 0 | 322 | 8.56 | 3,417 | 12.32 | 0.138 |
| 1 | 747 | 19.86 | 13,180 | 47.52 | <0.001 |
| 2 | 1,058 | 28.11 | 5,607 | 20.21 | 0.007 |
| 3 | 836 | 22.22 | 3,152 | 11.36 | 0.001 |
| 4+ | 800 | 21.25 | 2,382 | 8.59 | <0.001 |

Table 2. 1. Baseline characteristics of pediatric ADHD visits* - cont'd

| Baseline Characteristics | AAP visits (N=3,763) | | Non AAP visits (N=27,738) | | p Value |
|---|---|---|---|---|---|
| | N | % | N | % | |
| Comorbidities† | | | | | |
| FDA approved indications | 970 | 25.77 | 2,304 | 8.31 | <0.001 |
| Psychoses | 321 | 8.53 | 547 | 1.97 | <0.001 |
| Neurotic disorder | 466 | 12.39 | 1,316 | 4.75 | 0.001 |
| Adjustment disorder | 88 | 2.33 | 435 | 1.57 | 0.304 |
| Disturbance | 886 | 23.55 | 1,769 | 6.38 | <0.001 |
| Developmental disorder | 177 | 4.70 | 799 | 2.88 | 0.358 |
| Obesity | 2 | 0.04 | 371 | 1.34 | <0.001 |
| Diabetes | 7 | 0.18 | 4 | 0.01 | 0.008 |
| Cardiovascular disease | 0 | 0.00 | 10 | 0.04 | 0.611 |

*Data are given as weighted count of visits and percentage.

**These variables were tested as binary variables. That is, instead of testing as a single age variable with three categories, the three categories were tested individually as binary variables.

†These variables are not mutually exclusive.

Table 2. 2. Predictors of atypical antipsychotic prescription

| Covariates | Odds ratio | 95% Confidence interval |
|---|---|---|
| Age | | |
| Pre-school child (age 4-5) | Reference | |
| Elementary child (age 6-11) | 0.86 | 0.35-2.09 |
| Adolescent (age 12-18) | 1.11 | 0.49-2.53 |
| Sex | | |
| Male | Reference | |
| Female | 0.81 | 0.51-1.29 |
| Race | | |
| White | Reference | |
| Black | 0.86 | 0.48-1.55 |
| Others | 2.05 | 0.77-5.43 |
| Region of residence | | |
| Northeast | Reference | |
| Midwest | 0.84 | 0.40-1.75 |
| West | 0.84 | 0.38-1.84 |
| South | 0.90 | 0.43-1.89 |
| Median household income in patient's zip code | | |
| Quartile 1 | Reference | |
| Quartile 2 | 0.65 | 0.39-1.10 |
| Quartile 3 | 0.79 | 0.38-1.65 |
| Quartile 4 | 0.93 | 0.39-2.24 |
| Percent population with Bachelor's degree or higher in patient's zip code | | |
| Quartile 1 | Reference | |
| Quartile 2 | 1.31 | 0.73-2.33 |
| Quartile 3 | 0.77 | 0.31-1.88 |
| Quartile 4 | 1.02 | 0.41-2.50 |
| Metropolitan statistical area | | |
| Yes | Reference | |
| No | 0.52 | 0.21-1.30 |
| Payer source | | |
| Private | Reference | |
| Medicaid | 1.66* | 1.01-2.75 |
| Self-pay | 1.19 | 0.29-4.94 |
| Other | 1.08 | 0.38-3.09 |
| Mental health provider | | |
| No | Reference | |
| Yes | 0.77 | 0.31-1.92 |
| Attention deficit disorder with hyperactivity | | |
| No | Reference | |
| Yes | 3.00 | 0.75-11.93 |
| Number of non-AAP prescribed (different generic names) | | |
| 0 | Reference | |
| 1 | 0.94 | 0.58-1.52 |
| 2 | 2.60* | 1.38-4.90 |
| 3 | 3.06* | 1.48-6.32 |
| 4+ | 4.48* | 2.08-9.64 |

Table 2. 2. Predictors of atypical antipsychotic prescription – cont'd

| Covariates | Odds ratio | 95% Confidence interval |
|---|---|---|
| Mental Comorbidities | | |
| FDA approved indications | Reference | |
| Psychoses | 3.34* | 1.35-8.26 |
| Neurotic disorder | 2.67* | 1.27-5.61 |
| Adjustment disorder | 1.21 | 0.57-2.58 |
| Disturbance | 3.60* | 1.94-6.69 |
| Developmental disorder | 1.81 | 0.71-4.63 |
| Physical Comorbidities‡ | | |
| Obesity | 0.03 | 0.57-0.19 |
| Diabetes | 14.21* | 1.77-114.28 |
| Cardiovascular disease | dropped† | |

†The variable of cardiovascular disease was dropped because it predicted no AAP use (AAP=0) perfectly.

‡These variables are mutually exclusive.

*Significant at 5% significance level.

## Chapter 3: The Risk of Developing Type II Diabetes in Atypical Antipsychotic Users among Children and Adolescents

### A. Background

The increase in pediatric AAP use is concerning considering the potential risk of developing chronic conditions suggested by previous studies, such as obesity[31,34,35,38-40] or type II diabetes (T2DM) in children and adolescents taking these drugs.[45,46,57] While several post-marketing studies examined weight gain and obesity and provided solid support for the risk, the evidence regarding the risk of T2DM is still limited in younger populations. Although there are plausible mechanisms to support the hypothesized risk for T2DM, [58,59] several prior studies evaluating the relationship between AAP use and diabetes in children and adolescents failed to discriminate between type I and II DM[46], thus resulting in an underestimation of the true effect.[60] A recent study evaluated this specific AAPs-T2DM relationship, but the study population was restricted to a single state Medicaid population.[57] These findings from a single state Medicaid program may not be generalizable to a broader population.[55] Therefore, the purpose of this paper is to estimate the risk of developing T2DM for children and adolescents who are prescribed an AAP, using nationally representative health care claims data in the U.S.

### B. Materials and methods

*Data Source and Study Population*

Through a new user design approach,[61] we assembled a retrospective cohort of children and adolescents using enrollment files, medical and pharmacy claims data from the i3 Invision Data Mart (IVDM). These data contain information for a de-identified, nationally representative sample of 15 million commercially insured and Medicaid managed care patients. Dependents between the ages of 4 to 18 at index date (described below), who were continuously enrolled between January 1, 2007 and December 31, 2009, were considered for this study.

*Exposure*

Our study compared an AAP user to a similar group of subjects with no exposure to AAP (non-users). Subjects were considered to be exposed to an AAP if they had at least one prescription for any of the available AAPs, which include aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. AAP users were classified as incident or new users (AAP users, hereafter) and included in the analysis if they met all of the following eligibility criteria: (1) initial dispensing date of an AAP (defined as the index date) was preceded by a minimum of six months of continuous enrollment in the health plan (i.e., pre-index period); (2) did not have prescriptions for typical antipsychotics during the six months of the pre-index period; (3) had no history of type I or type II diabetes during the six months pre-index period; (4) had evidence of resource utilization in the database (i.e., at least one claim of any type during the pre-index period). This requirement was made to exclude individuals with multiple health insurance (i.e., a child whose parents hold multiple health insurance) and made claims

primarily to another plan other than the one used in this paper, thus to prevent misclassification due to out-of-insurance service utilization. For the comparison group of non-users, index dates were randomly assigned based on the distribution of time to AAP initiation after January 1, 2007 in the AAP treated group. With the randomly assigned index date, the same sample selection criteria described above for the AAP treated group (except for AAP prescription) were applied to the non-user group A flow diagram describing the identification process for the groups included in the analyses is depicted in Figure 3. 1.

The follow-up time for each subject started on the index date and was extended until the earliest of (1) T2DM onset, or (2) the end of the study period. This approach was intended in order to emulate an intention-to-treat analysis similar to randomized controlled trials.

*Outcome*

The outcome of interest in our study was new-onset T2DM and was identified using medical and pharmacy claims and following the algorithm developed by Bobo et al. (2012).[62] We used International Classification of Diseases, 9th Clinical Modification (ICD-9-CM) diagnosis codes (250; 250.0; 250.1; 250.2; 250.3; 250.9) and National Drug Codes (NDC) for anti-diabetic medications (insulin, insulin adjuncts, alpha-glucosidase inhibitor, amylin analogs, meglitinides, sulfonylureas, and thiazolidinediones) to identify diabetes-related medical/pharmacy care encounters. In order to classify a patient as having T2DM, we required (1) a hospital discharge with a primary diagnosis

code for T2DM as described above, or (2) a combination of at least 2 diabetes-related medical and/or pharmacy claims. When only prescription claims indicated diabetes, T2DM was further separated from type I diabetes by excluding those with an insulin prescription with no prescriptions for oral anti-diabetic medication. The date of onset for T2DM was determined as the date of the first medical/pharmacy care encounter related to T2DM. However, if a diabetes-related laboratory procedure (i.e., HbA1c, islet cell antibody test, insulin RIA, or metabolic panel) was performed within 30 days before the first diabetes-related medical/pharmacy care encounter, the date of the procedure was considered as the date of T2DM onset.

*Covariates*

To control for potential selection bias and confounding, non-users were matched to AAP users using the propensity score (PS) matching method. The PS for each resident was estimated through logistic regression as the probability of starting AAP treatment during our study period, based on their baseline characteristics. We used causal diagrams[63,64] to select important covariates for inclusion in the logistic regression model; specifically, the following covariates were included: age, sex, race, geographic region, household income, the year of index date, and the health care utilization intensity and medical history during the pre-index period. Health care utilization intensity was measured by four variables: the number of hospitalizations, the number of emergency room (ER) visits, the number of outpatient services, and the number of filled

prescriptions with different generic names. Medical history was measured through other medications used (i.e., benzodiazepines and antidepressants), as well as comorbidities (pregnancy, obesity, and cardiovascular diseases).

*Analysis*

Baseline characteristics of AAP users and non-users were compared and tested before and after PS matching using standardized differences.[65,66] Using PS, up to four non-users were matched to every AAP new user. The propensity to receive an AAP was estimated through unconditional logistic regression and the greedy matching algorithm[67] with calipers equal to 0.2 of the standard deviation of the logit of the propensity score was used for matching.[68]

The rates of developing T2DM in the AAP-treated group and control group were estimated and compared using the Kaplan-Meier (KM) estimator. Cox proportional hazard regression was performed to estimate the risk of T2DM associated with AAP initiation. We regarded that the proportional hazards assumption was not violated because no evidence of interaction between AAP use and time was observed. (HR 0.75; P=0.223).

**C. Results**

*Baseline characteristics of non-matched samples*

A total of 403,345 children and adolescents met our inclusion criteria. Among those, 6,510 individuals were new AAP users. A majority of AAP users received

risperidone (n=2608; 40.1%), aripiprazole (n=2044; 31.4%) or quetiapine (n=1439, 22.1%). Relatively small proportion of AAP users received olanzapine (n=239, 3.7%), ziprasidone (n=168, 2.6%) or paliperidone (n=50, 0.8%). There were 38 (0.6%) individuals who received two AAP agents on the index date. Other baseline characteristics before matching are summarized in Table 3. 1. In the non-matched sample, AAP users were more likely to be adolescents (ages 12-18) and male than non-users. On average, the annual household income was lower for AAP users. Also, the AAP users showed a higher level of health care utilization during the six month pre-index period, with respect to the number of outpatient service visits, hospitalizations, ER visits, and filled prescriptions. The baseline comorbidities and drug use profiles also showed large differences between the two groups in several respects: AAP users evinced higher prevalence rates of obesity and cardiovascular disease. Also, they showed a higher rate of use for benzodiazepines or antidepressants.

*Calculation of propensity scores*

The logistic regression model to evaluate AAP utilization is described in Table 3. 2. The results indicate that older patients were more likely to receive an AAP. Female patients were less likely to receive an AAP compared to male patients. Also, western regions of the US were more likely to use an AAP compared to northeastern regions. Annual household income was significantly associated with AAP use: the propensity to receive an AAP decreased as the level of household income increased (Table 3. 2). The higher level of health care utilization measured in the number of outpatient service visits,

hospitalizations, and prescriptions significantly increased the propensity to receive an AAP. The c-statistic was 0.876, indicating a good predictive accuracy of the logistic regression model.

*Baseline characteristics of propensity score-matched sample*

The final study sample after PS matching consisted of 6,236 incident AAP users and 22,080 non-users. The characteristics of matched samples are summarized in Table 2. 1 (right). In this matched sample, AAP new users and matched non-users were balanced on all of the characteristics included in the PS model (standardized differences were smaller than 5%). Figure 3. 2 shows the kernel density estimates of the PS distribution between the two groups. The upper panel is depicting the distribution for the non-matched sample, while the lower panel represents the matched sample showing the similarity between the two groups after PS matching.

*The Risk of Type II Diabetes*

The follow-up schedule was very similar between AAP user and non-user groups. In each group, the mean follow-up time was 1.3 (± 0.7) years with the minimum of 0 days and the maximum of 2.5 years. The total follow-up time was 8,161 person-years in the AAP user group, and 28,792 person-years in the non-user group. During the follow-up, a total of 64 subjects developed T2DM, 27 in the AAP user group (33.1 cases per 10,000 person-years), and 37 in the non-user group (12.9 cases per 10,000 person-years).

The rate of developing T2DM in the matched sample is represented using the Kaplan-Meier (KM) estimator (Figure 3. 3). The risk difference between two groups appeared at approximately 4 months after the index date, and it increased rapidly between 4 months and 6 months after the index date. After 6 months, the risk difference was almost constant until the end of the follow-up. The estimated risk of T2DM was twice higher in AAP users than non-users in the propensity score matched sample (HR 2.18; 95% CI 1.45-3.29).

**D. Discussion**

The purpose of this study was to examine the association between AAP initiation and T2DM in children and adolescents. We found that initiation of AAP medication increased the risk of developing T2DM about two-fold for those between the ages of 4 and 18. While T2DM is known to develop slowly over months and years, the fact that noticeable risk differences between AAP-treated and comparison groups emerged between 4 and 6 months is striking. This result is in good agreement with a recent study published by Bobo and collaborators.[57] They conducted a retrospective cohort study for children and youth, using Tennessee Medicaid health care claims data and reported a three-fold higher risk of T2DM imposed on antipsychotic medication users (both typical and atypical), compared to propensity score-matched users of other psychotropic drugs. Our observation on the probability of developing T2DM during the course of the follow-up assessment (Kaplan-Meier Curve) is very similar to the result reported in this paper (Figure 3. 2). For example, at the 20 months (600 days) follow-up the probability of

T2DM is approximately 0.004 for treatment group, and 0.002 for control group in both studies. The fact that the point estimate of the hazard ratio reported by Bobo et al. is different from what we found in our study is likely due to differences in study design, specifically (1) different follow-up periods (longer for Bobo et al.) and/or (2) study population (Tennessee Medicaid vs US commercially insured). Another study previously conducted by Andrade et al. concerned the risk of diabetes associated with antipsychotic medication use in children and adolescents (ages of 5 to 18).[46] They used a large diverse cohort from Health Maintenance Organization (HMO) databases and did not find a significant association between AAPs and diabetes in propensity score matched samples. One of the major differences between our study design and theirs was the inclusion of type I diabetes in study outcomes. However, a majority of diabetes patients in children are likely to be type I[60] and the concerns about AAP adverse side effects are often associated with type II.[58,59] Therefore, including type I diabetes in an outcome could have attenuated the risk of AAPs in their study.

In our propensity score matched cohort, a majority of individuals were adolescents with ages between 12 and 18 (61%), male (63%), and white (78%). Approximately 47% resided in the south region of the US and more than half of the sample belonged to households with an annual income greater than $60,000. During the 6 month pre-index period, 86% have not been hospitalized and 98% have not visited ER. Also, 5% used benzodiazepine and 31% used antidepressant during the period. These factors could have affected results and need be taken into account when implementing the findings of this paper.

It should be noted that the individuals who were identified as having new-onset T2DM are subject to a potential misclassification. The algorithm we adopted for this study was developed from a Tennessee Medicaid program, and it is possible that the algorithm did not effectively identify true T2DM cases in our database. If diabetes management or diabetes related claim filing process vary largely by the payer source or geographical regions, it may affect our conclusion about the impact of AAP on T2DM. Another limitation of our study is a relatively short follow-up. The longest possible follow-up period in this paper was 2.5 years and the follow-up term does not adequately capture the longer-term impact of AAPs on T2DM. Also, the small number of new-onset T2DM cases limited our ability to assess the differential impact of AAPs on different strata such as patient demographics and socioeconomic factors.

Having non-users as the comparison group might have overestimated the risk of T2DM for AAP users because AAP users are more likely to be monitored for T2DM than non-users. However, to minimize potential differences in monitoring between the two cohorts, we included non-users who had similar health conditions to AAP users during the pre-index period in the analysis. Moreover, that our study reports similar findings to previous studies supports the reliability of our study design.

Although it is not the primary interest for our paper, our logistic regression model revealed important factors associated with AAP use. (Table 3. 2) First, female patients were less likely to receive an AAP compared to male patients (OR 0.54; 95% CI 0.51-0.57). This is consistent with the national trend, in which female patients are outnumbered by male patients in children and adolescent psychiatric services.[69]

Secondly, the propensity of a patient to receive an AAP decreased gradually as the household income increased. In other words, if a patient was from a high-income family, the patient was less likely to use an AAP. This finding has an important implication about the role of one's socioeconomic status that affects the exposure to an AAP.

Our study adds strong evidence to the existing literature and overcomes some of the limitations of previous research. First, our report critically examined patients who possessed a commercial health care plan within the US, who were either commercially insured or enrolled in a Medicaid managed care plan. This consideration cannot be understated, because commercial insurance and Medicaid are the two largest payers of mental health services in the United States.[70] Therefore, the findings of this paper can be more generalizable to a larger population. Second, we sought to avoid the bias by matching subjects based on their propensity to receive an AAP. Before matching, there was a considerable difference observed in baseline characteristics between AAP users and non-users. Atypical antipsychotic users were more likely to be obese and receive intense health care services such as hospitalizations and ER visits. (Table 3. 1, left) This suggests the presence of potential selection bias in the non-matched cohort, in which AAP users had inherently higher risk of developing a chronic illness including T2DM than non-users before they were exposed to an AAP. In our propensity score matched cohort, baseline characteristics were much similar between AAP users and non-users.

In conclusion, we found that children and adolescents who use an AAP medication had a two times higher risk of developing T2DM within 6 months of initiating medication when compared to propensity score matched non-users from

nationally representative health care claims in the U.S. This raises questions about continued AAP use in children and adolescents. Considering that T2DM is a chronic condition that may persist the rest of a person's life, its risk that is imposed on children and adolescents could outweigh the benefit of AAP therapy in some patients.

Figure 3. 1. Sample selection flowchart

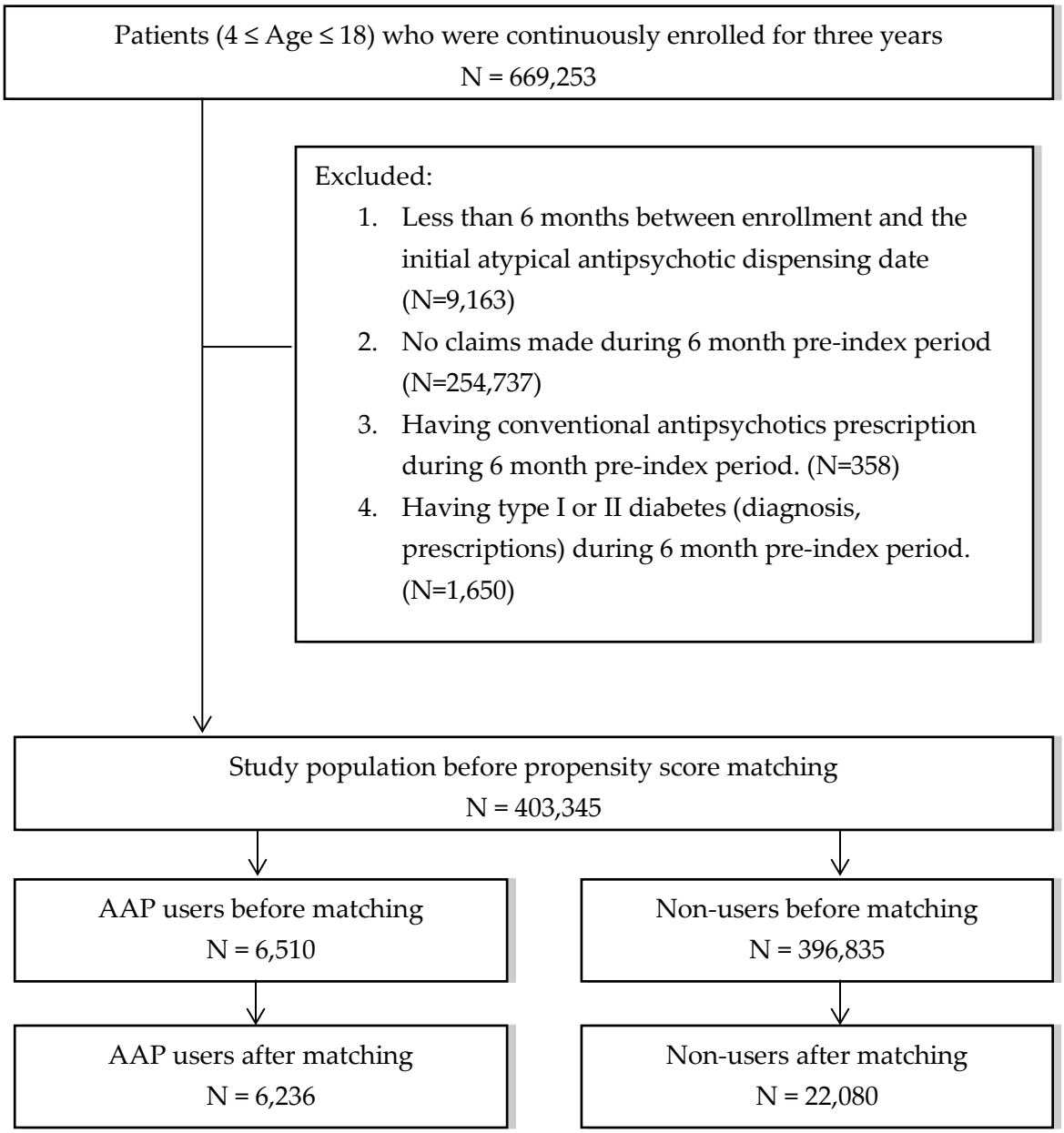


Table 3. 1. Baseline characteristics

| Baseline Characteristics | Before Matching | | | | | After Matching | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | AAP users (N=6,510) | | Non-users (N=396,835) | | d* | AAP users (N=6,236) | | Non-users (N=22,080) | | d* |
| | n | % | n | % | | n | % | n | % | |
| Age | | | | | | | | | | |
| 4-5 | 246 | 3.8 | 57,793 | 14.6 | 0.380 | 245 | 3.9 | 1,056 | 4.8 | 0.018 |
| 6-11 | 2,023 | 31.1 | 164,612 | 41.5 | 0.218 | 1,994 | 32.0 | 7,721 | 35.0 | 0.024 |
| 12-18 | 4,241 | 65.2 | 174,430 | 44.0 | 0.436 | 3,997 | 64.1 | 13,303 | 60.3 | 0.031 |
| Sex | | | | | | | | | | |
| Male | 3,978 | 61.1 | 203,505 | 51.3 | 0.199 | 3,802 | 61.0 | 13,901 | 63.0 | 0.030 |
| Female | 2,532 | 38.9 | 193,330 | 48.7 | 0.199 | 2,434 | 39.0 | 8,179 | 37.0 | 0.030 |
| Race | | | | | | | | | | |
| White | 5,126 | 78.7 | 297,885 | 75.1 | 0.087 | 4,910 | 78.7 | 17,274 | 78.2 | 0.008 |
| Black | 288 | 4.4 | 15,199 | 3.8 | 0.030 | 275 | 4.4 | 976 | 4.4 | 0.001 |
| Hispanic | 431 | 6.6 | 34,211 | 8.6 | 0.075 | 414 | 6.6 | 1,494 | 6.8 | 0.001 |
| Others | 617 | 9.5 | 46,812 | 11.8 | 0.075 | 592 | 9.5 | 2,087 | 9.5 | 0.003 |
| Region of residence | | | | | | | | | | |
| Northeast | 712 | 10.9 | 48,113 | 12.1 | 0.037 | 690 | 11.1 | 2,357 | 10.7 | 0.015 |
| Midwest | 1,731 | 26.6 | 102,996 | 26.0 | 0.014 | 1,647 | 26.4 | 5,826 | 26.4 | 0.007 |
| South | 3,074 | 47.2 | 190,671 | 48.1 | 0.017 | 2,944 | 47.2 | 10,430 | 47.2 | 0.006 |
| West | 993 | 15.3 | 54,942 | 13.9 | 0.040 | 955 | 15.3 | 3,464 | 15.7 | 0.013 |
| Annual household income | | | | | | | | | | |
| ≤ $29,999 | 207 | 3.2 | 10,152 | 2.6 | 0.037 | 193 | 3.1 | 764 | 3.5 | 0.020 |
| $30,000-39,999 | 364 | 5.6 | 17,593 | 4.4 | 0.053 | 348 | 5.6 | 1,350 | 6.1 | 0.017 |
| $40,000-49,999 | 585 | 9.0 | 32,271 | 8.1 | 0.031 | 558 | 9.0 | 1,974 | 8.9 | 0.004 |
| $50,000-59,999 | 596 | 9.2 | 35,877 | 9.0 | 0.004 | 570 | 9.1 | 2,102 | 9.5 | 0.010 |
| $60,000-74,999 | 790 | 12.1 | 51,644 | 13.0 | 0.027 | 757 | 12.1 | 2,702 | 12.2 | 0.001 |
| $75,000-99,999 | 1,170 | 18.0 | 81,702 | 20.6 | 0.066 | 1,133 | 18.2 | 3,880 | 17.6 | 0.013 |
| ≥ $100,000 | 1,563 | 24.0 | 115,304 | 29.1 | 0.114 | 1,520 | 24.4 | 5,171 | 23.4 | 0.024 |
| Number of outpatient service visits | | | | | | | | | | |
| 0-5 | 2,357 | 36.2 | 330,942 | 83.4 | 1.098 | 2,353 | 37.7 | 8,858 | 40.1 | 0.041 |
| 6+ | 4,153 | 63.8 | 65,893 | 16.6 | 1.098 | 3,883 | 62.3 | 13,222 | 59.9 | 0.041 |
| Number of drugs prescribed (difference generic name drugs) | | | | | | | | | | |
| 0-3 | 3,045 | 46.8 | 326,225 | 82.2 | 0.797 | 3,012 | 48.3 | 11,513 | 52.1 | 0.001 |
| 4+ | 3,465 | 53.2 | 70,610 | 17.8 | 0.797 | 3,224 | 51.7 | 10,567 | 47.9 | 0.001 |
| Number of hospitalizations | | | | | | | | | | |
| 0 | 5,214 | 80.1 | 392,254 | 98.9 | 0.642 | 5,202 | 83.4 | 19,315 | 87.5 | 0.007 |
| 1-3 | 1,273 | 19.6 | 4,500 | 1.1 | 0.635 | 1,012 | 16.2 | 2,721 | 12.3 | 0.006 |
| 4+ | 23 | 0.4 | 81 | 0.0 | 0.077 | 22 | 0.4 | 44 | 0.2 | 0.011 |
| Number of ER visits | | | | | | | | | | |
| 0 | 6,413 | 98.5 | 393,944 | 99.3 | 0.073 | 6,145 | 98.5 | 21,811 | 98.8 | 0.018 |
| 1+ | 97 | 1.5 | 2,891 | 0.7 | 0.073 | 91 | 1.5 | 269 | 1.2 | 0.018 |
| Baseline comorbidities and drug use | | | | | | | | | | |
| Obesity | 157 | 2.4 | 4,086 | 1.0 | 0.106 | 150 | 2.4 | 458 | 2.1 | 0.009 |
| Cardiovascular | 259 | 4.0 | 4,504 | 1.1 | 0.181 | 240 | 3.9 | 714 | 3.2 | 0.009 |
| Pregnancy | 9 | 0.1 | 336 | 0.1 | 0.016 | 9 | 0.1 | 30 | 0.1 | 0.001 |
| Benzodiazepine | 460 | 7.1 | 2,764 | 0.7 | 0.334 | 413 | 6.6 | 976 | 4.4 | 0.025 |
| Antidepressant | 2,648 | 40.7 | 9,439 | 2.4 | 1.053 | 2,374 | 38.1 | 6,409 | 29.0 | 0.033 |

*Standardized Difference.

Table 3. 2. Propensity score model of receiving an atypical antipsychotic medication

| Confounder | OR | 95% CI |
|---|---|---|
| Age | | |
| 4-5 | Reference | |
| 6-11 | 2.68* | 2.34-3.01 |
| 12-18 | 3.26* | 0.85-3.73 |
| Sex | | |
| Male | Reference | |
| Female | 0.54* | 0.51-0.57 |
| Race | | |
| White | Reference | |
| Black | 1.25* | 1.10-1.43 |
| Hispanic | 0.86* | 0.77-0.95 |
| Others | 0.88* | 0.80-0.97 |
| Region of residence | | |
| Northeast | Reference | |
| Midwest | 0.99 | 0.91-1.10 |
| West | 1.07* | 1.23-1.52 |
| South | 1.07 | 0.98-1.17 |
| Annual household income | | |
| ≤ $29,999 | Reference | |
| $30,000-39,999 | 1.01 | 0.89-1.15 |
| $40,000-49,999 | 0.80* | 0.72-0.89 |
| $50,000-59,999 | 0.74* | 0.66-0.82 |
| $60,000-74,999 | 0.63* | 0.57-0.69 |
| $75,000-99,999 | 0.58* | 0.53-0.63 |
| ≥ $100,000 | 0.48* | 0.44-0.52 |
| Number of outpatient visits | | |
| 0-5 | Reference | |
| 6+ | 3.84* | 3.61-4.08 |
| Number of drugs prescribed (different generic name drugs) | | |
| 0-3 | Reference | |
| 4+ | 2.04* | 1.93-2.17 |
| Number of hospitalizations | | |
| 0 | Reference | |
| 1-3 | 5.94* | 5.45-6.47 |
| 4+ | 3.10* | 1.78-5.40 |
| Number of ER visits | | |
| 0 | Reference | |
| 1+ | 0.77* | 0.60-0.98 |
| Baseline comorbidities and drug use | | |
| Obesity | 1.03 | 0.85-1.24 |
| Cardiovascular disease | 0.79* | 0.68-0.93 |
| Pregnancy | 0.31* | 0.15-0.65 |
| Benzodiazepine use | 1.95* | 1.71-2.22 |
| Antidepressant use | 12.01* | 11.28-12.80 |

*Significant at 5% significance level

Figure 3. 2. Propensity score distribution

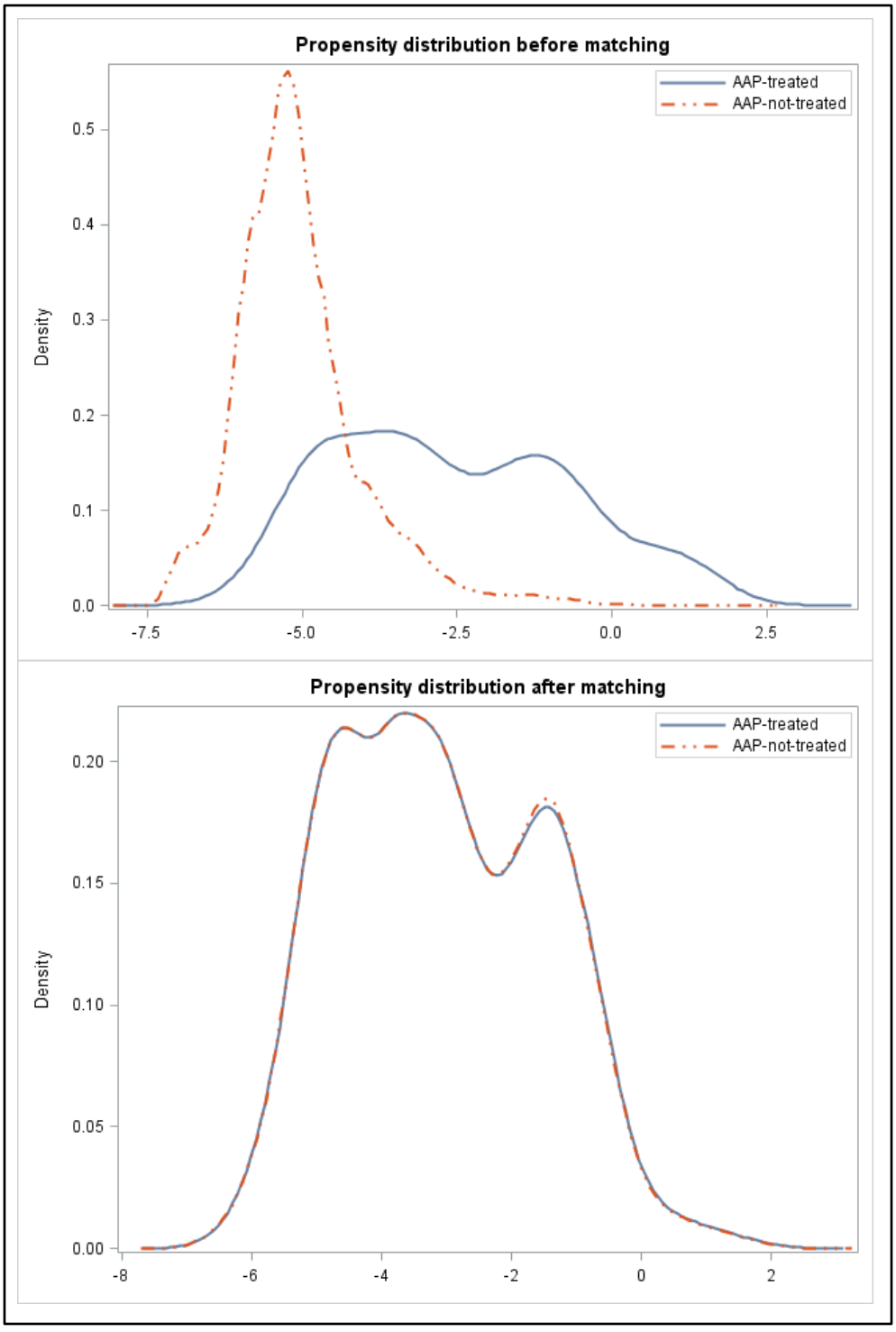
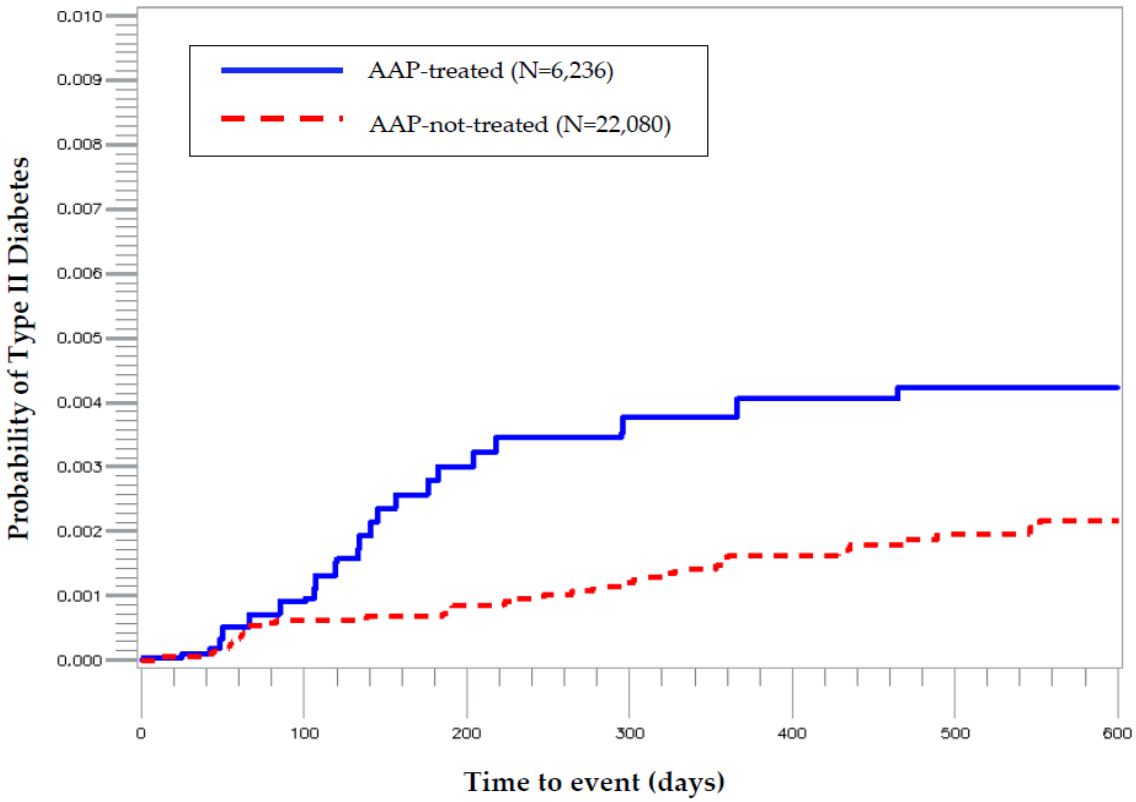


Figure 3. 3. Kaplan-Meier curve estimating the probability of type II diabetes



## Chapter 4: A decision analysis of atypical antipsychotics treatment in the stimulant failed ADHD children and adolescents.

### A. Background

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood, characterized by having trouble paying attention, not being able to control impulsive behaviors, and being overly active.[11] Those with ADHD may experience academic underachievement, troublesome interpersonal relationship development, and low self-esteem. While medication therapy and/or behavior therapy are recommended for the ADHD treatment, medication therapy has been reported as the most cost-effective choice.[71] Medication therapy usually initiates with stimulants such as amphetamine derivatives (e.g., Adderall), which are FDA-approved stimulant medications for ADHD. Although the symptoms are successfully managed with stimulants in most ADHD patients for the short term (6-10 weeks),[19-21] an alternative medication regimen is often considered due to the adverse side effects, tolerance development or lack of symptom improvement.[24] Some of selective norepinephrine reuptake inhibitor (atomoxetine) and selective $\alpha_2$-adrenergic agonists (clonidine, guanfacine) are non-stimulant ADHD medications approved by FDA and they are recommended as an alternative to stimulants.[11]

However, a growing number of ADHD children and adolescents are prescribed with atypical antipsychotics (AAPs),[8,22,23] although it is not yet justified with evidence. Findings about the clinical effectiveness of AAPs in ADHD are mixed with different

conclusions. Moreover, several adverse side effects were reported as being associated with AAPs, which include weight gain,[34,38,40] type II diabetes,[28,46,57] and QTc interval prolongation.[72,73] Therefore, the expected health outcomes based on clinical drug effectiveness and the risk of adverse effects need to be estimated for AAPs before considering them as a stimulant alternative. This is also true for other non-stimulant medications as they have risks of several adverse effects (e.g., high blood pressure[74] and/or suicidal ideation[75] in atomoxetine users, bradycardia[76,77] in clonidine or guanfacine users). Then, health care providers and patients will be able to compare the expected health outcomes between strategies and take that into account when they make decisions about their treatment strategy.

Furthermore, in addition to the expected health outcome, decision-making depends heavily on health care costs as well. Evaluating the combination of health outcomes and costs, which is referred to as "cost-effectiveness", is one of the most critical elements when choosing the appropriate therapy among multiple strategies.

Therefore, the aims of this paper are: (1) to estimate the expected health outcomes of AAPs and other non-stimulant ADHD medications based on trade-offs between clinical effectiveness and adverse effects and (2) to evaluate cost-effectiveness of AAPs compared to other non-stimulant ADHD medications. Both aims target the stimulant-failed ADHD children and adolescents.

**B. Material and methods**

We conducted a decision analysis estimating trade-offs between individual level health benefits and risks in treating ADHD children and adolescents who failed the initial stimulant treatment and require non-stimulant subsequent pharmacotherapy. The analysis is intended to address whether atypical antipsychotics (AAPs) should be recommended for ADHD children and adolescents, compared to other alternatives to stimulants.

*The Decision Tree*

Most of ADHD patients who choose to receive medication therapy start their treatment with a stimulant. However, due to a lack of effectiveness or tolerance development, a subset of the patients cannot be treated with stimulants anymore and this situation is where we intend our study to be implemented. In other words, the starting point of the decision tree is where the prescriber and patient seek an alternative treatment strategy as a replacement of stimulant, among three medication choices: (1) AAP (aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) (2) selective norepinephrine reuptake inhibitor (atomoxetine), and (3) alpha-2 adrenergic agonists (clonidine, guanfacine). (Figure 4. 1) The square box at the start of the decision tree is a decision node and represents the decision to be made by the prescriber and patient. The branches coming out of the decision node represent the range of possible pathways that could result from different choices. Each pathway consists of a series of branches that leads to particular events that might be experienced by a patient. In this

study, those events are ADHD symptoms, weight gain, type II diabetes, suicidal ideation, and cardiovascular events such as QTc interval prolongation, high blood pressure, or bradycardia. Since it is not certain which events a patient will experience, such uncertain events are defined by circular nodes (chance nodes). The endpoint of the decision analysis was 1 year of treatment with 28 different pathways. In this model, the expected health outcomes are estimated using quality-adjusted life years (QALYs) that are weighed on a basis of the probabilities of clinical drug effectiveness and side effects.

*Estimating Probabilities and Quality-Adjusted Life Years (QALYs)*

Probability estimates were derived from literature review. (Table 4. 1) Based on a systematic search of the literature, we chose a methodologically well-designed study to obtain a baseline estimate. If multiple studies exist for one estimate, the average was calculated.[78] The Supplementary Appendix provides the conversion process used to create probabilities that have the minimum value of 0 and the maximum value of 1.

For the baseline probability estimate of AAPs' effectiveness in ADHD, three randomized controlled trial (RCT) papers were used.[79-81] Although those studies are restricted to risperidone[79,80] and aripiprazole[81] only, we assumed that other AAP agents will have a similar effectiveness since they share the similar mechanism of action.

The adverse side effects associated with AAP including weight gain, type II diabetes, and QTc interval prolongation were examined. The baseline probability of weight gain was obtained from three cohort studies in which AAP users were compared with non-users.[34,38,40] For type II diabetes, we based our assumptions on two

observational studies.[46,57] For the AAP-associated cardiovascular events, we obtained the baseline probability of QTc interval prolongation by averaging the findings of a RCT conducted by Hough et al.,[72] and a case-control study conducted by Correll et al.[73]

We obtained our assumptions about the drug effectiveness of atomoxetine from RCTs.[82-86] The average estimate was 0.62 with a small variation. For the potential side effects of atomoxetine, there is a black-box warning on atomoxetine concerning suicidal ideation. The baseline probability of experiencing suicidal ideation in pediatric patients was estimated to be 0.0037 from a meta-analysis conducted by Bangs et al.[75] As another adverse side effect of atomoxetine, the baseline probability of having increased diastolic blood pressure was estimated from a RCT conducted by Wernicke et al.[74]

The baseline probability of the effectiveness of clonidine or guanfacine (hereafter referred to as clonidine/guanfacine) was obtained from three RCTs.[76,87,88] Similar to atomoxetine studies, the average estimates was 0.63 with a small variation in clonidine/guanfacine. One of the major adverse side effects in those medications, bradycardia, was examined in two RCTs and the average estimate was used as the baseline probability.[76,77]

In order to calculate QALYs for each pathway in the decision tree as the health outcome, we derived QALY weights from a literature review (Table 4. 2). Papers that were chosen to estimate QALY weights for ADHD, overweight/obese, diabetes, and cardiovascular events (QTc interval elongation, increased diastolic blood pressure, and bradycardia) were consistent in using PedsQL™ 4.0 (Pediatric Quality of Life inventory™ Version 4.0) as the measurement instrument.[89-92] The PedsQL is a scale

designed to measure quality of life in the pediatric population. However, to our knowledge, the QALY weights for suicidal ideation in the pediatric population have not been published, therefore, we chose a study conducted by Goldney et al., in which a QALY weight was estimated in those age 15 and over using the Assessment of Quality of Life (AQoL) instrument.[93]

The papers we used to estimate QALYs in our analyses also reported the average QALY weights from a healthy population as a control. Theoretically, a perfect health state has the QALY weight of 1 but the average QALY weights of the healthy population from papers were less than 1. In order to capture the QALY weight contributed to the conditions we are interested in, the QALY weights of health outcomes were rescaled to reflect the relative difference from the perfect health state which has the value of 1. This process involves taking the difference between the QALY weights of the study population and the healthy population, and use the difference as the disutility relative to the perfect health state.

Using QALY weights derived from literature, QALYs over one year of ADHD treatment were estimated. Health outcomes beyond this time were not estimated due to the short-term nature of better quality trials. Also, it was assumed that health benefits and adverse side effects seen within ~6 weeks after initial treatment will persist for a year as medication treatment continues. More specifically, this is applied to drug effectiveness, QTc interval prolongation, increased diastolic blood pressure, suicidal ideation and bradycardia. For the AAP-associated weight gain, since the significant weight gain was not observed in 6-week trial[79] but observed in 12-week trial[40], we

assumed that the notable weight gain would take effect approximately between 6 weeks and 3 months after initiating AAP treatment and persist throughout the treatment period. For the AAP-associated type II diabetes, it was assumed to occur within 6 months after initiation of therapy, as reported in several children/adolescent treatment trials.[94,95]

We were not able to find studies that measured health-related quality of life specifically associated with QTc interval prolongation, high blood pressure, and bradycardia in the pediatric population. Instead, we used a study conducted by Uzrak et al.(2008) in which quality of life scores were stratified by disease severity. They categorized disease severity as follows: 1, mild cardiovascular disease (CVD) requiring no therapy or effectively treated nonoperatively (cathether therapy); 2, moderate CVD requiring no therapy or surgically corrected (curative); 3, surgically treated CVD (≥1 procedure) with significant residua or need for additional surgery; 4, complex or severe CVD, uncorrectable or palliated (includes single ventricle). We took the average score of severity 1 and 2 as the baseline estimate of QTc interval prolongation, high blood pressure, and bradycardia, since those conditions may not require any medical procedure in some cases but they are risk factors of other heart diseases.

*Calculating the tree*

We used the 'rolling back' process to calculate the decision tree. This involves working from the right-hand side of the tree towards left, calculating expected QALYs at each chance node, until arriving at the index decision.

*Cost Estimation*

Expected costs were derived from a retrospective cohort study conducted by Sikirica et al.[24] In their study, ADHD children and adolescents who received non-stimulant therapy were followed for one or more years after the initiation of the treatment and total health care costs accrued to the patients were estimated in AAP users and non-AAP users (They grouped atmoxetine users and clonidine/guanfacine users together as non-AAP users). In order to control for potential selection bias, Sikirica et al. matched the two groups using patient demographics, geographic region, year of therapy initiation, stimulant use history, comorbidity, all-cause and mental health-related medical care utilization and pharmacy costs during the 6-month pre-index period. Also, they excluded patients who have any medical claims associated with conditions that are frequently treated with AAPs (schizophrenia, bipolar disorder, etc.) to increase the likelihood that patients received AAPs for ADHD and not other indications. The result indicated that the average annual total health care cost for AAP users were $6,934, while it was $4,748 for non-AAP users ($P<0.001$). For non-AAP users, we assumed that the expected costs of atomoxetine and guanfacine/clonidine would not be significantly different because they have the close estimates of the average monthly drug costs ($239 vs. $212, respectively)[96], drug effectiveness (0.63 vs. 0.63, respectively), and health outcomes (0.94 vs. 0.95, respectively).

*Sensitivity Analyses*

Multiple sensitivity analyses were conducted to evaluate the robustness of our conclusion. First, we conducted the one-way deterministic sensitivity analysis for estimating expected QALYs. In the analysis, the expected QALYs were examined as one variable varies across the plausible range (Tables 4. 1 and 4. 2), while holding other variables constant. Second, a Monte Carlo probabilistic sensitivity analysis was performed to examine the cost-effectiveness of three strategies in 50,000 simulations. The beta distribution was used for probabilities and QALYs, and the gamma distribution was used for costs.[viii]

**C. Results**

*Base Case Analysis*

Over one year of ADHD medication treatment, the highest QALY was estimated for clonidine/guanfacine (expected QALY 0.95), followed by atomoxetine (expected QALY 0.94). (Table 4. 3, left) Atypical antipsychotics yielded the lowest health outcome with the expected QALY of 0.84.

In the cost-effectiveness analysis, the strategy of AAPs was "dominated" as it was less effective and costed more than other two strategies. Compared to clonidine/guanfacine, AAPs provided a lower QALY (0.11 QALY lost) at an additional

[viii] The beta distribution restricts values from 0 to 1 and allows various shapes, and the gamma distribution restricts values zero or nonnegative and takes a right skewed form.

cost of $2,186 on average. Compared to atomoxetine, AAPs resulted in 0.10 QALY lost at an additional cost of $2,186.

*One-Way Sensitivity Analyses for Expected Health Outcomes*

One-way deterministic sensitivity analyses indicated that our finding from the base case analysis about AAPs as the less effective strategy was robust in all variables. Also, we identified variables with the most influence on incremental QALYs from the analyses. The result of comparing AAPs to clonidine/guanfacine is shown in a tornado diagram (Figure 4. 2). The QALYs of having untreated ADHD (i.e., medication is not effective) had the most impact on the change in health outcomes. The QALYs of having overweight/obesity were also shown to have a comparably large impact. Among probabilities, the probability of AAP effectiveness was the most influential variable, followed by the probability of having AAP associated type II diabetes. The comparison between AAPs and atomoxetine lead to the same conclusions; in which the QALYs of having untreated ADHD and having overweight/obesity, followed by the probability of AAP effectiveness, were the most influential variables.

*Probabilistic Sensitivity Analyses for Cost-Effectiveness*

The simulated cost-effectiveness derived from the Monte Carlo probabilistic sensitivity analysis is presented with a scatter plot in Figure 4. 3. The closer a point is to the right-bottom corner of the chart, the more cost-effective it is. It is observed that the cost-effectiveness points of clonidine/guanfacine and atomoxetine are relatively more

concentrated around the right-bottom corner of the chart than AAPs. The cost-effectiveness points of AAPs are spread over a larger area, indicating the higher frequency of being less cost-effective than other strategies.

The average costs and expected QALYs from the base case analysis were compared to the ones generated from the probabilistic sensitivity analysis (Table 4. 3, right). The average cost-effectiveness ratio is smaller in the probabilistic sensitivity analysis compared to the base case analysis for AAPs (Table 4. 3, left), while it is larger in the probabilistic sensitivity for other strategies. However, the conclusion about AAPs being the dominated strategy is consistent in both analyses.

**D. Discussion**

The aims of the study were to: (1) estimate expected QALYs for non-stimulant medications in ADHD children and adolescents who have failed stimulants and (2) examine whether atypical antipsychotics (AAPs) should be recommended for ADHD children and adolescents as a cost-effective strategy, compared to other alternatives of stimulants. We developed a decision tree with the probabilities and QALYs of events followed by a strategy. Our decision analysis showed that AAPs lead to the lower expected QALYs than other strategies. Also, AAPs were not a favored choice for the stimulant-failed ADHD pediatric population with respect to cost-effectiveness and should not be recommended over other strategies, since it is less effective and costs more. This is depicted on the cost-effectiveness plane, as drawn in Figure 4. 4, where point A represents the AAP pharmacotherapy. The incremental ratio, compared to other

strategies (O), is OA. The "northwest" quadrant of the cost-effectiveness plane for which cost is increasing and quality is decreasing ("dominated") is where the AAP pharmacotherapy is located. It is generally uncontroversial to reject such strategies, and therefore, we did not present an incremental cost-effectiveness ratio (ICER), although it is typically shown in many cost-effective analyses.

In our decision tree model, the option of "no treatment" was not included because we assumed that the decision about whether a patient will receive the pharmacotherapy or not occurs before they initiate a stimulant treatment. Once failed with stimulant, the patient would seek alternative medications to treat ADHD based on the prior decision. However, it is possible that the patient and his/her prescriber consider no treatment when they make a decision after the stimulant failure. If this is the case, the conclusions of this paper may not be applicable, depending on the costs and expected health outcomes of not treating ADHD.

The findings of this paper are best implemented in treating ADHD children and adolescents who do not have comorbid mental disorders for which AAPs are frequently prescribed, such as schizophrenia, bipolar disorder, or autism spectrum disorders. The estimated effectiveness of medications in our decision model is from clinical trials measuring the drug effectiveness on ADHD only. Therefore, the result could be different when another comorbid mental disorder is present.

Also, we used the QALY of overweight/obesity and the probability of weight gain when estimating the expected health outcomes in the analyses. However, one should note that the weight gain may not necessarily result in overweight or obesity.

Considering our tornado diagram identifying the QALYs of overweight/obesity as the second most influential variable on the change in health outcome (Figure 4. 3), the expected health outcomes in AAPs could have been underestimated.

When implementing the conclusions of this paper, our assumption that the health care costs of atomoxetine treatment were not significantly different from that of clonidine/guanfacine should be considered as a study limitation. For example, although our analyses suggested that the most cost-effective choice of stimulant alternative pharmacotherapy was clonidine/guanfacine over atomoxetine, the conclusion could be changed depending on the costs associated with each strategy, as the price differs by manufacturers (brand name drugs vs. generic drugs) and the formulation of the drug (extended release vs. immediate release). The rank of cost-effectiveness could be easily affected by the costs, because the expected health outcomes of clonidine/guanfacine and atomoxetine are similar (expected QALYs 0.95 vs. 0.94, respectively). The primary aim of the study was to evaluate the cost-effectiveness of AAP compared to other alternatives, and the decision making between the two non-AAP medications needs further specification.

Another study limitation was the inclusion of type I diabetes when estimating QALY weights for AAP associated side effects. We based our assumption about QALY weights for type II diabetes on the study conducted by Varni et al., in which the quality of life for the both of type I and type II diabetes pediatric patients were assessed. It is possible that the quality of life for type I diabetes patients is inherently different from

type II diabetes patients, and the estimated QALY in this paper may not reflect the true value of type II diabetes.

Clearly, the side effects associated with each strategy is not limited to the ones in the decision model. Some side effects associated with taking medications such as headache, nausea, vomiting, fatigue, dizziness, etc., were omitted because they are likely to be common in all strategies and the probabilities and impact on quality of life would be cancelled out during the analyses. However, side effects that are not included in the model but significantly affect expected health outcomes could draw different conclusions. For example, we used QTc interval prolongation as an AAP associated side effect, but the risk of other cardiovascular events including ischemic/pulmonary heart disease, arrhythmias and cardiomegaly was reported by McIntyre et al. They examined AAP-related cardiovascular events in children and adolescents at two levels of comparison: the primary comparison was performed between AAP users and non-users and secondary comparison was performed between single AAP users and multiple AAP users. We did not use their result for two reasons: (1) in the primary comparison, the confounders adjusted in the analysis were limited to age (≤ 12 years or ≥ 13 years), sex (male or female), and ethnicity (African American or other). The level of confounder adjustment is too weak to conclude a causal relationship between an AAP and cardiovascular events since AAP users are likely to be sicker than the untreated control group and cardiovascular events occurred in AAP users might not have been caused by an AAP. (2) While it is more appropriate to assume that our study population has not been treated with AAPs yet, they compared multiple AAP users to single AAP users in

the secondary comparison. However, it is possible that an AAP causes other cardiovascular events in addition to QTc interval prolongation and the expected health outcome could have been underestimated in this paper.

In the policy decision making process, benefit-cost analysis may lead to a substantially different ranking of alternatives than cost-effectiveness analysis. While cost-effectiveness analysis look for cost-saving alternatives given an equivalent outcome, benefit-cost analysis focuses more on options that have the highest magnitude of net benefits. For instance, it is possible that a therapeutic choice with a higher net health benefit may not be preferred by cost-effectiveness analysis due to its high costs. Such difference in decision making perspective ultimately leads our next step to using willingness to pay measures. Since the money value that people place on health improvement is usually not observable, health services researchers have been using contingent valuation in which subjects are asked how much they are willing to pay for a health change in a hypothetical market setting. By replacing our health outcomes measured in utility to willingness to pay, a decision can be made based on the magnitude of net benefit and it may affect our recommendations about AAP use.

Figure 4. 1. Structure of the decision tree

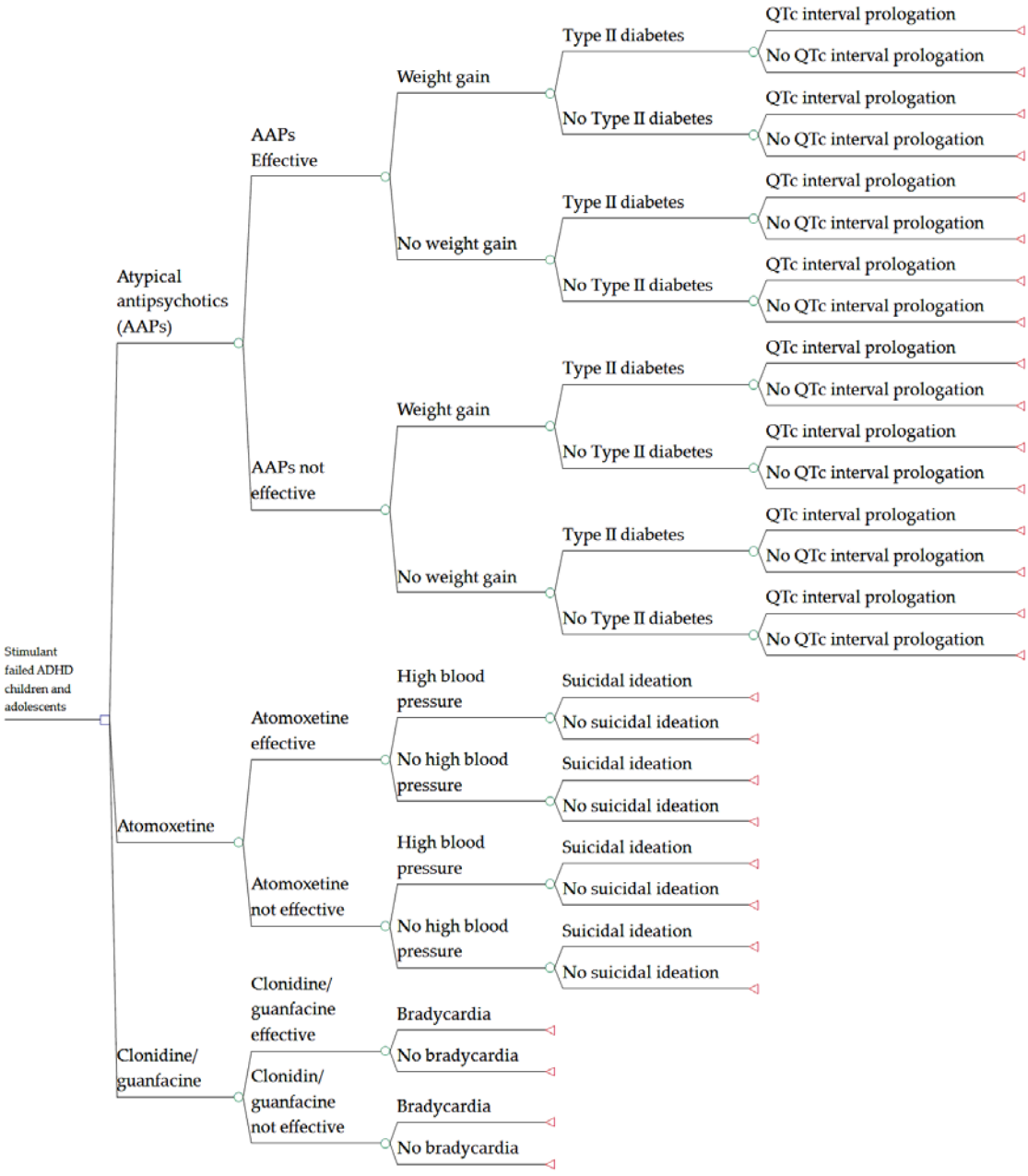


Table 4. 1. Probability estimates

| Variable | Baseline | Variation range | | References |
|---|---|---|---|---|
| | | Low | High | |
| Atypical antipsychotic | | | | |
| Effectiveness | 0.22 | 0 | 0.65 | 79-81 |
| Weight gain | 0.7 | 0.65 | 0.8 | 34, 38, 40 |
| Type II diabetes | 0.38 | 0 | 0.84 | 46, 58 |
| QTc interval prolongation | 0.53 | 0 | 0.97 | 48, 73 |
| Atomoxetine | | | | |
| Effectiveness | 0.63 | 0.6 | 0.64 | 82-86 |
| Increased blood pressure | 0.56 | 0 | 0.88 | 74 |
| Suicidal ideation | 0.0037 | 0.0007 | 0.0044 | 75 |
| Clonodine/guanfacine | | | | |
| Effectiveness | 0.63 | 0.6 | 0.65 | 76, 87, 88 |
| Bradycardia | 0.59 | 0.17 | 0.85 | 76, 77 |

Table 4. 2. Utility estimates

| Variable | Baseline | Variation range | | References |
|---|---|---|---|---|
| | | Low | High | |
| Untreated ADHD | 0.8673 | 0.5583 | 1 | 89 |
| Overweight/obese | 0.9249 | 0.74485 | 1 | 90 |
| Diabetes | 0.9847 | 0.92855 | 1 | 91 |
| QTc interval prolongation | 0.9913 | 0.727 | 1 | 92 |
| High blood pressure | 0.9913 | 0.727 | 1 | 92 |
| Bradycardia | 0.9913 | 0.727 | 1 | 92 |
| Suicidal ideation | 0.6156 | 0.4194 | 0.8118 | 93 |

Figure 4. 2. Tornado Diagram at AAPs vs. clonidine/guanfacine

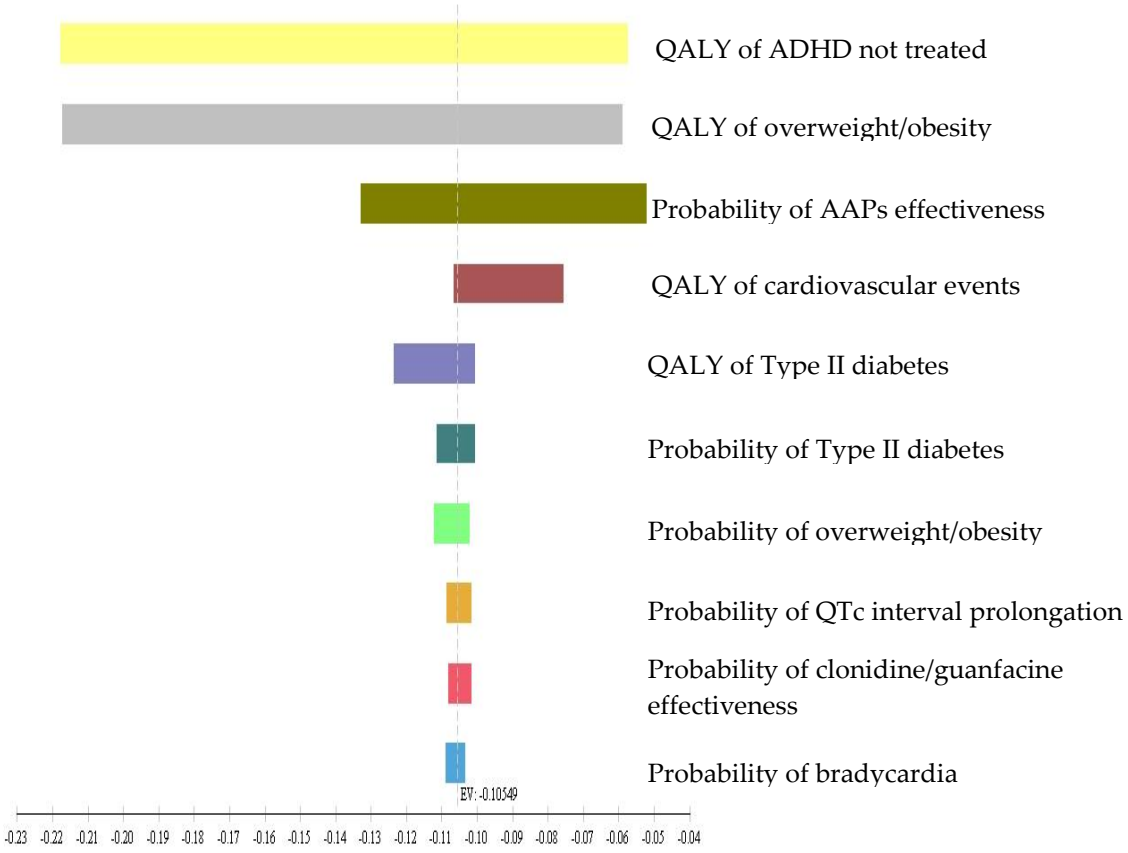


Table 4. 3. Estimated average costs and QALYs

| | Base Case | | | Probabilistic Sensitivity Analysis | | |
|---|---|---|---|---|---|---|
| | Total Cost | QALY | Cost/QALY | Total Cost (SD) | QALY (SD) | Cost/QALY |
| Atypical antipsychotics (AAPs) | $6,934 | 0.84 | 8254.76 (Dominated) | $6,906 ($8,625) | 0.84 (0.08) | 8221.43 (Dominated) |
| Atomoxetine | $4,748 | 0.94 | 5051.06 | $4,778 ($5,865) | 0.94 (0.04) | 5082.98 |
| Clonidine/guanfacine | $4,748 | 0.95 | 4997.89 | $4,778 ($5,865) | 0.95 (0.04) | 5029.47 |

Figure 4. 3. Cost-effectiveness scatter plot

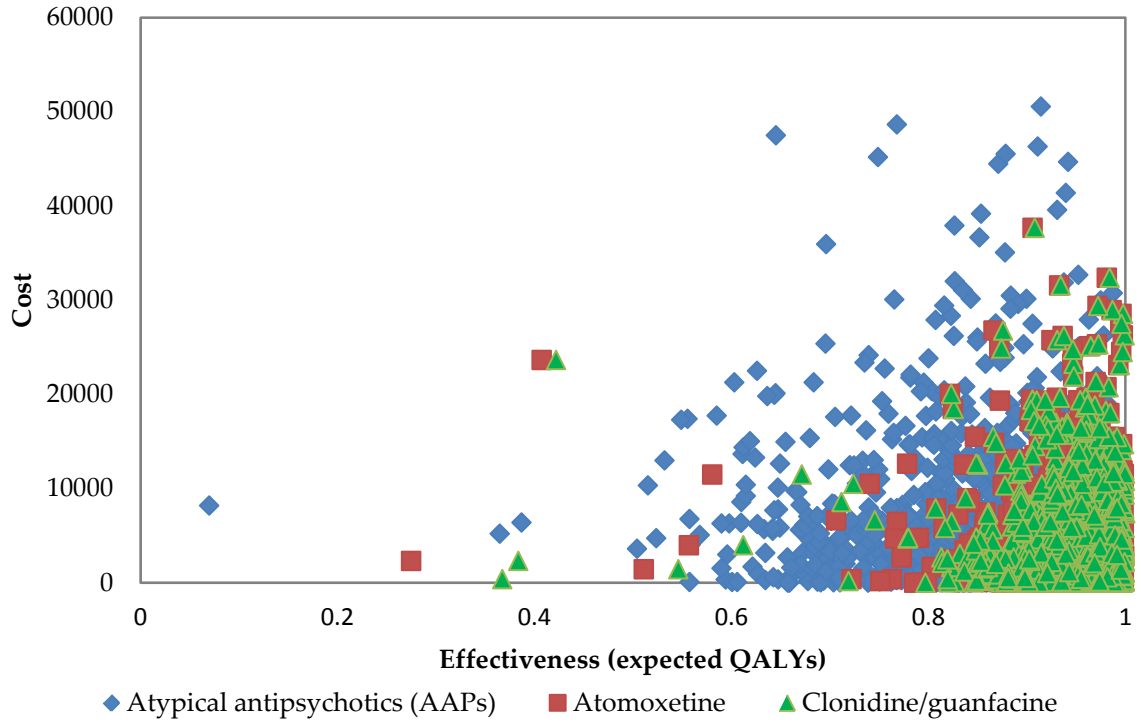
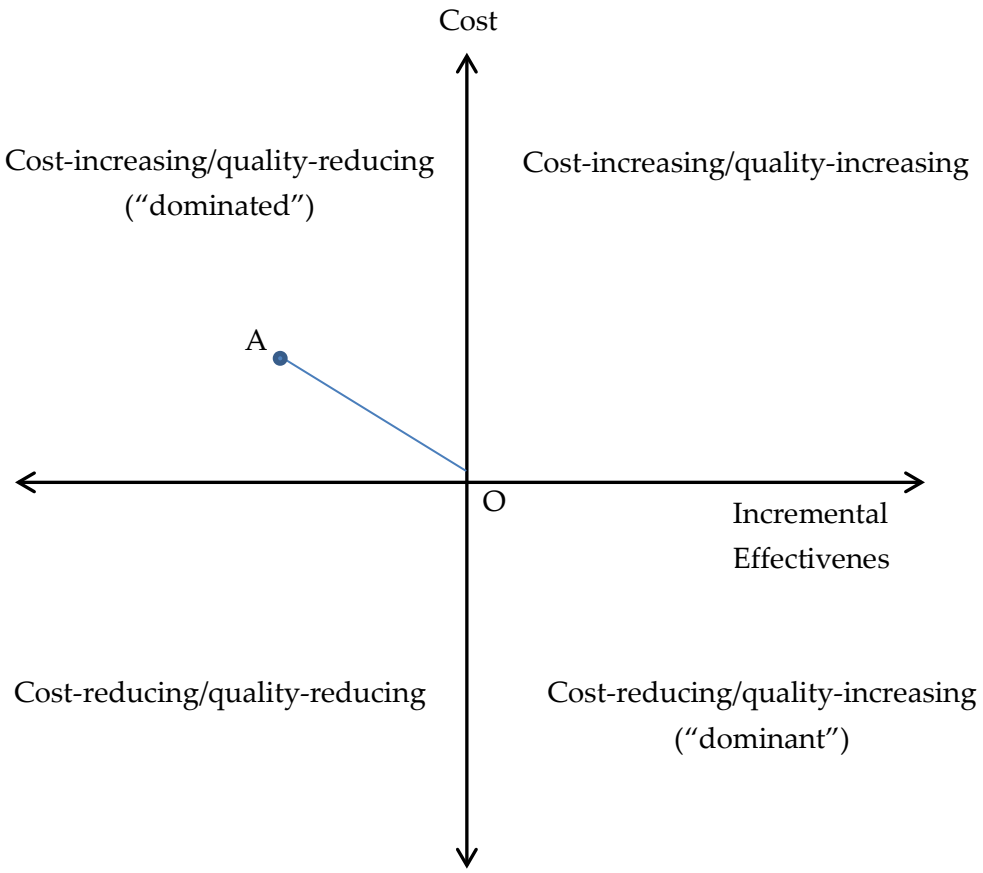


Figure 4. 4. Cost-effectiveness plane



**E. Supplementary Appendix**

This section provides supplementary material for the primary paper, including a more detailed presentation of several methodologic points. They should be read in conjunction with the primary paper.

Standardizing probabilities from different forms presented in literature

Probabilities of events in our decision tree were obtained in various forms from the literature. One of the typical ways of presenting the effectiveness/safety of a drug in a randomized control trial (RCT) is to use a two by two table. Also, many RCTs report effect size, which is calculated as the difference between the treatment group mean and the control group mean divided by pooled standard deviation (i.e., effect size = (treatment mean – control mean)/pooled SD). However, these are rarely used in observational studies. For example, studies that assessed antipsychotic agent associated weight gain reported the average change in body weights with standard deviation. In order to convert the different forms of probabilities into a standardized probability that takes 0 as the lowest possible value and 1 as the highest possible value, we used following methods.

a. Calculating the standardized probability from two by two table.[97]

   The effectiveness/safety of a drug can be expressed using two by two table in a RCT. For example, following table is based on the result of RCT conducted by Daviss et al. (2008).[77]

| | Bradycardia | No Bradycardia |
|---|---|---|
| Clonidine-treated (n=31) | 7 | 24 |
| Placebo (n=30) | 1 | 29 |

They reported that the probability of having bradycardia in clonidine treated children was 22.6% (7/31*100 = 22.6%) and the probability of having bradycardia in placebo group was 3.3% (1/30*100 = 3.3%). The probability of clonidine-associated bradycardia is calculated as the proportionate increase in the probability of bradycardia resulting from clonidine treatment, which is equal to 0.854 = (0.226-0.033)/0.226.

b. Calculating the standardized probability from effect size.[98]

The effect size is defined as the difference between the mean outcomes for treatment and control groups in standard deviation units. Tickle-degnen (2001) argues that because the effect size is a standard normal deviate, we can assume a normal distribution to describe the variation of individuals' responses around the average outcomes.[98] For example, if the effect size is 0.65 as shown in the guanfacine RCT study conducted by Sallee et al. (2012), the probability of effectiveness is simply the area under the standard normal curve at 0.65, which is equal to 0.627.

c. Calculating the standardized probability from the change in body weight.

The effect size of a drug with respect to weight gain is calculated based on the reported body weight changes of the treatment and control groups. Once the effect size is estimated, the standardized probability is obtained using the standard normal table.[98]

d. Calculating the standardized probability from hazard ratio. [99]

The hazard ratio is equivalent to the odds that a patient in the treatment group reaches the endpoint first.[99] For example, the probability of developing type II diabetes first can be derived from the odds of developing type II diabetes first; which is the probability of developing type II diabetes first divided by the probability of not developing first:

Hazard ratio (HR) = odds = P/(1 - P);

P = HR/(1 + HR)

## Chapter 5: Comparative health care cost and utilization in stimulant-treated ADHD patients

### A. Background

In chapter 4, the expected health outcome and cost-effectiveness of AAPs were assessed in hypothetical ADHD patients who were previously treated with a stimulant and needed a subsequent pharmacotherapy. One of the study limitations was that I relied on a single original study article when obtaining the health care cost estimates. Because the study setting is particularly restricted to post-stimulant therapy, to the best of our knowledge, a study estimating additional costs accrued to AAP users was not published until 2013.[24] Also, previous studies concerning pediatric AAP use have focused more on a clinical perspective, such as risks of developing chronic conditions including obesity[31,34,35,38-40] or type II diabetes (T2DM).[45,46,57] However, much more attention needs to be paid to the economic perspective, because a large proportion of pediatric AAP use is not evidence-based (i.e., ADHD) and potentially causes an overuse of healthcare resources. Therefore, the purpose of this chapter is to conduct an original study that compares resource utilization and costs between AAP users and non-AAP users in stimulant-treated ADHD children and adolescents.

**B. Materials and methods**

*Data Source and Study Population*

Through a new user design approach,[61] I assembled a retrospective cohort of 4- to 24-year-old members using enrollment files, medical and pharmacy claims data from the i3 Invision Data Mart (IVDM). These data contain information for a de-identified, nationally representative sample of 15 million commercially insured and Medicaid managed care patients. Members between the ages of 4 to 24 at index date (described below), who had one or more medical claims with a primary diagnosis of ADHD between January 1, 2007 and December 31, 2009, were considered for this study. The diagnosis of ADHD was identified using the ICD-9-CM codes of 314.00 (attention-deficit disorder without hyperactivity) and 314.01 (attention-deficit disorder with hyperactivity). Subjects were also required to have made one or more claims for a stimulant prescription. The stimulant prescription was identified using NDCs which corresponded to a generic drug name including dexmethylphenidate, mixed amphetamine salts, methylphenidate, lisdexamfetamine, or dextroamphetamine.

*Exposure*

My study compared an AAP user to a non-AAP user. Subjects were considered to be exposed to an AAP if they had at least one prescription for any of the available AAPs, which include aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. AAP users were classified as incident or new users (AAP users,

hereafter) and included in the analysis if they met all of the following eligibility criteria: (1) initial dispensing date of an AAP (defined as the index date) was preceded by a minimum of six months of continuous enrollment (i.e., pre-index period) and was followed by a minimum of six months (or a year) of continuous enrollment in the health plan (i.e., post-index period); (2) did not have medical claims for conditions that are commonly treated with AAPs.[ix]; (3) had a 30 day or less gap between stimulant use and the index date; (4) had greater than 30 days accumulated stimulant supply during the pre-index period. As a comparison group, subjects were considered non-AAP users if they had at least one prescription for any of the non-stimulant ADHD drugs, which include atomoxetine, clonidine or guanfacine. Using the initial dispending date of these drugs as the index date for non-AAP users, the same sample selection criteria described above for the AAP users were applied to the non-AAP users. Additionally, subjects with both AAPs and non-AAP drugs during the observation period were excluded from analyses. A flow diagram describing the identification process for the groups included in the analyses is depicted in Figure 5. 1.

The follow-up time for each subject started on the index date and was extended for six months (or a year) after the index date. This approach was intended in order to emulate an intention-to-treat analysis similar to randomized controlled trials.

[ix] Those conditions were reported by Sikirica et al. and include schizophrenia (ICD-9-CM, 295), bipolar disorder (ICD-9-CM, 296.0; 296.1; 296.4-296.8), psychotic disorder with delusions/hallucinations (ICD-9-CM, 293.81; 293.82), paranoia (ICD-9-CM, 297.1; 297.3), psychosis (ICD-9-CM, 298.8; 298.9), tics/Tourett's syndrome (ICD-9-CM, 307.2; 307.23), or dementia (ICD-9-CM; 290, 294.1)

*Outcome*

The outcome of interest in my study was health care service utilization and costs during six months (or one year) after the index date. Health care service utilization was assessed using the number of outpatient visits, inpatient visits, and emergency room visits. Total health care costs were calculated by adding total prescription costs to total medical costs. Total prescription costs were further categorized into index drug costs and non-index drug costs. Total medical costs were further categorized into mental health service related costs and non-mental health service related costs. For each category, costs associated with outpatient visits, inpatient visits, and emergency room visits were estimated. A mental health service refers to a medical visit with a primary diagnosis of a mental health disorder (ICD-9-CM 290.XX-319.XX). I used costs that occurred to third-party payers, which excludes deductibles, coinsurance, copayments and other out-of-pocket costs paid by patients. All costs were converted to 2012 US dollars based on the medical component of consumer price index.[x]

*Covariates*

To control for potential selection bias and confounding, I used the inverse probability of treatment weighting (IPTW) method in which each subject is weighted based on their inverse propensity to receive an AAP. The propensity for each subject was estimated through logistic regression as the probability of starting AAP treatment

[x] Source: U.S. Department of Labor, Bureau of Labor Statistics. Consumer Price Index. Available at: http://www.bls.gov.cpi/. Accessed April 7, 2014)

during my study period, based on their baseline characteristics. Specifically, the following covariates were included: age, sex, race, geographic region, household income, primary health care payer source, the duration of stimulant use, the number of different stimulants used, the presence of hyperactivity in attention deficit disorder, the health care utilization intensity and physical/mental comorbidity during the pre-index period. Health care utilization was measured by four variables: the number of hospitalizations, the number of emergency room (ER) visits, the number of outpatient services, and the number of filled prescriptions with different generic names (excluding sitmulants). For comorbidity, we looked for conditions that are not only associated with AAP use, but also likely to affect health care costs/utilization. Those conditions include physical conditions such as obesity, diabetes, cardiovascular disease , and epilepsy, and mental conditions such as neurotic disorder, mood disorder, disturbance, developmental disorder, and adjustment disorder.

*Analysis*

Baseline characteristics of AAP users and non-AAP users were compared and tested. All characteristics were included in the analysis as categorical variables and therefore, chi-square tests were used for all characteristics to assess statistical significances between the two cohorts. The additional health care costs accrued to AAP users compared to non-AAP users were estimated using the inverse probability of treatment weighting. The associated robust standard errors were derived from Taylor-

linearized variances. Event rate ratios and 95% confidence intervals for health care service utilization were estimated using the Poisson regression model.

## C. Results

*Baseline characteristics*

A total of 3,437 (2,189 for 12 month post-index observation cohort) patients met my inclusion criteria. Among those, 1,039 (639) individuals were new AAP users. Baseline characteristics of cohorts for the six month post-index observation period are summarized in Table 5. 1. At baseline, differences in patient demographics and socioeconomic characteristics between the two cohorts were not statistically different, except that AAP users were more likely to be older than non-AAP users (more adolescents and young adults). Instead, they were very different in terms of medical profiles and health care service utilization during the pre-index period. On average, AAP users used stimulants for a longer duration. Also, they were more likely to have hyperactivity in addition to the attention deficit disorder. While the presence of physical comorbidity was not statistically different between two cohorts, AAP users had a much higher rate of mental comorbidity. Also, the AAP users showed a higher level of health care utilization during the six month pre-index period, with respect to the number of outpatient service visits, hospitalizations, and filled prescriptions.

*Calculation of propensity scores*

The logistic regression model to evaluate AAP utilization is described in Table 5. 2. The results indicate that older patients were more likely to receive an AAP. Female patients were less likely to receive an AAP compared to male patients. Annual household income was significantly associated with AAP use: the propensity to receive an AAP decreased as the level of household income increased. Compared to private insurance policy holders, Medicaid enrollees were less likely to use an AAP. While the longer duration of stimulant use increased the likelihood of using an AAP, the number of different stimulants used and the presence of hyperactivity did not show a significant impact on the AAP use. The higher level of health care utilization measured in the number of outpatient service visits and prescription medications significantly increased the propensity to receive an AAP. Also, having comorbid mental disorders including neurotic disorder, mood disorder and disturbance significantly increased the likelihood of AAP use. The c-statistic was 0.716, indicating a good predictive accuracy of the logistic regression model.

*Health Care Service Utilization*

During the six month post-index observation period, over 96 percent of subjects utilized outpatient health care services one or more times. The average number of outpatient visits was ten per AAP user and seven per non-AAP user. From the Poisson regression analysis using IPTW, AAP users had a statistically significant increase in the likelihood of utilizing outpatient services than non-AAP users (event rate ratio, ERR 1.14; 95% CI 1.04-1.26) (Table 5. 3). For inpatient service utilization, approximately five

percent of AAP users (N=53) and two percent of non-AAP users (N=40) were hospitalized at least once. The average number of outpatient visits was 0.08 per AAP user and 0.02 per non-AAP user. In the IPTW estimation, AAP users showed a statistically significant increase in the likelihood of being hospitalized than non-AAP users. (ERR 1.77; 95% CI 1.05-2.98). Nearly everyone in each cohort (≈99%) did not visit an emergency room (ER) during the six month observation period. The average number of ER visits was 0.01 per AAP user and 0.02 per non-AAP user. In the Poisson regression model with IPTW, ER visit rates between two cohorts were not significantly different.

During the 12 month post-index observation period, the relative rate of outpatient visits between AAP users and non-AAP users were similar to the result for the six month observation period (ERR 1.18; 95% CI 1.04-1.33). However, the rates of inpatient and ER visits were not significantly different between two cohorts.

*Additional Health Care Costs Accrued to AAP users*

The average costs that are additionally accrued to AAP users compared to non-AAP users were estimated using the inverse probability of treatment weighting and results are shown in Table 5. 4. During the six month observation period after index date, AAP users had higher health care costs especially associated with prescription medications and mental health related services. The prescription costs for AAP users were $900 higher than non-AAP users, mostly owing to the cost of their index drug. The mental health related service costs for AAP users were $509 higher than non-AAP users. Non-mental health related costs were not significantly different between two cohorts in

all categories of services. During the 12 month post-index observation period, the prescription costs remained higher for AAP users with additional $1,672 vs. non-AAP users. However, except mental health related outpatient visit costs, both mental health and non-mental health related medical costs were not significantly different between the two cohorts.

**D. Discussion**

The purpose of the study was to compare health care resource utilization and costs between AAP users and non-AAP users in stimulant-treated ADHD patients. We found that AAP users were likely to visit a healthcare facility for outpatient and inpatient services more frequently than non-AAP users. Also, total health care costs were significantly higher for AAP users with additional costs of $1,393 during six months and $2,784 during a year after initiating the AAP treatment.

These findings are similar to the previous study conducted by Sikirica et al. Sikirica et al. used health administrative data collected from commercially insured members who were between ages sex and twelve. They reported that AAP users had a higher level of health care utilization and costs than non-AAP users during 12 months after index date. Interestingly, the additional total health care costs accrued to AAP users reported in their study are close to my result ($2,341, P<0.001 from Sikirica et al. vs. $2,784, P=0.007 from my study, both in 2012 dollars). However, it is different from my study in that their estimates were significantly higher for AAP users in all categories, while I observed the difference only in prescription costs and mental health related

outpatient service costs. There are a number of factors that could affect this difference, which include: (1) different sample size (larger for Sikirica et al.), (2) different age groups (more restricted for Sikirica et al.), and/or (3) different reimbursement policies implemented in different health insurance plans.

The additional total health care costs accrued to AAP users were mostly attributed to prescription medication costs, especially for the index drug. The additional expenses associated with the index drug for AAP users were $717 during the six month post-index period, and $1,249 during a year post-index period. This is probably due to the difference in drug price per unit. The average cost of risperidone, quetiapine and aripiprazole (the three most frequently used AAPs among pediatric patients) are estimated to be higher at $491 per month,[100] as compared to $239 per month for atomoxetine and $212 per month for clonidine/guanfacine.[96] In addition, during 2007-2009, none of the AAP agents were available as a generic drug while clonidine/guanfacine immediate release forms were available as generic drugs at the lower cost.

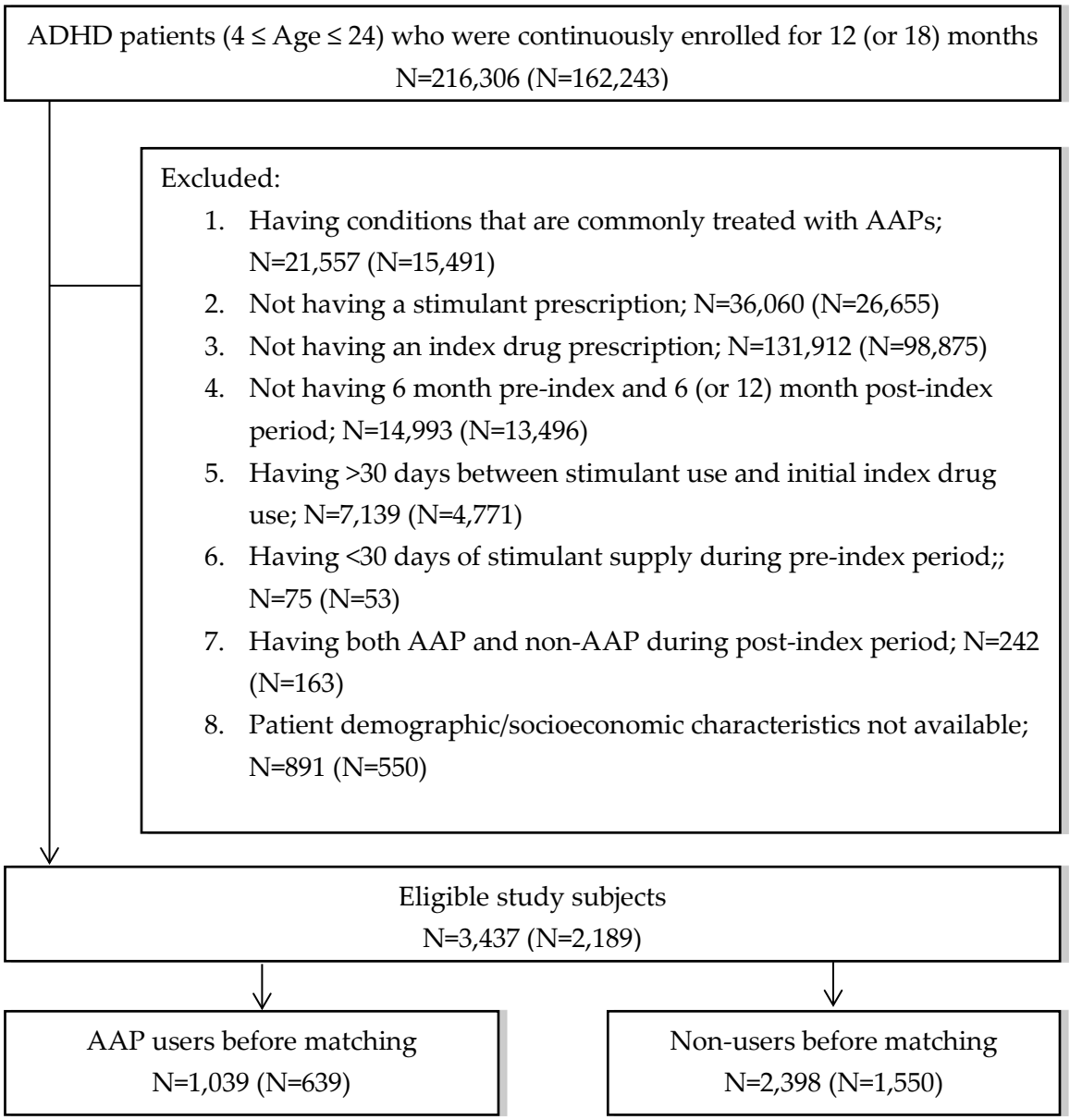
In the process of expanding the post-index observation period from six months to a year, we lost about a third of subjects (N=1,248). Many private health care enrollment decisions are made on a yearly basis, and requiring continuous enrollment during six month pre-index and one year post-index period would have excluded those who have changed their healthcare plan after a year of enrollment between January 1, 2007 and December 31, 2009. Compared to those who were qualified for the one year post-index observation period (continuously enrolled for at least 12 months but less than

18 months, N=2,189), those who were qualified only for the six month post-index observation period (continuously enrolled for at least 12 months but less than 18 months, N=1,248) were more likely to be older (young adults, OR 1.85; 95% CI 1.42-2.42) and covered by Medicaid (OR 1.35; 95% CI 1.05-1.73). Also, they had a longer duration of baseline stimulant use (four to six months, OR 1.24; 95% CI 1.05-1.47), more stimulants (three or more different generic names, OR 1.39; 95% CI 1.04-1.87) and other prescription medications (four or more different generic names, OR 1.31 95% CI 1.04-1.66), and more comorbid mood disorders (OR 1.27; 95% CI 1.06-1.52). Considering that these characteristics are associated with not only the AAP use, but also the increase in health care service utilization, our estimates from the 12-month post-index observation period might have underestimated the true difference in health care costs and utilization between AAP users and non-AAP users. Another limitation of the study is a relatively short follow-up. Although the purpose was to assess the health care utilization and costs during six months or a year after initiating the index drug, the long-term effects of AAPs are potentially greater when considering the risk of chronic illness associated with AAPs, which may take a longer time to develop after drug initiation.

Despite such limitations, our study provides strong evidence to the debate related to pediatric AAP use. There are a number of concerns regarding AAP unapproved effectiveness and risks of developing chronic conditions including obesity, cardiovascular disease, and type II diabetes. Whereas much more evidence is focused on clinical benefits and risks of AAP use, empirical findings about the economic costs are under-provided. With ADHD as one of the leading conditions for a pediatric patient to

receive an AAP, I believe that the findings of the study will have important implications for the decision-making related to pediatric AAP use.

Figure 5. 1. Sample selection flowchart*




*The number of subjects for 12 months post-index observation period is in parentheses.

Table 5. 1. Baseline characteristics – 6 month observation cohort

| Baseline Characteristics | AAP users (N=1,039) | | Non-AAP users (N=2,398) | | p Value |
|---|---|---|---|---|---|
| | N | % | N | % | |
| Age | | | | | |
| Children (age 4-11) | 503 | 48.41 | 1,463 | 61.01 | <0.001 |
| Adolescents (age 12-18) | 447 | 43.02 | 793 | 33.07 | <0.001 |
| Young adults (age 18-24) | 89 | 8.57 | 142 | 5.92 | 0.004 |
| Sex | | | | | |
| Male | 769 | 74.01 | 1,724 | 71.89 | 0.201 |
| Female | 270 | 25.99 | 674 | 28.11 | 0.201 |
| Race | | | | | |
| White | 858 | 82.58 | 2,015 | 84.03 | 0.292 |
| Black | 41 | 3.95 | 76 | 3.17 | 0.249 |
| Other | 140 | 13.47 | 307 | 12.80 | 0.591 |
| Region of residence | | | | | |
| Northeast | 103 | 9.91 | 190 | 7.92 | 0.055 |
| Midwest | 322 | 30.99 | 794 | 33.11 | 0.223 |
| South | 514 | 49.47 | 1,181 | 49.25 | 0.905 |
| West | 100 | 9.62 | 233 | 9.72 | 0.933 |
| Annual household income | | | | | |
| ≤ $49,999 | 260 | 25.02 | 551 | 22.98 | 0.194 |
| $50,000-74,999 | 281 | 27.05 | 643 | 26.81 | 0.888 |
| $75,000-99,999 | 217 | 20.89 | 556 | 23.19 | 0.138 |
| ≥ $100,000 | 281 | 27.05 | 648 | 27.02 | 0.989 |
| Payer source | | | | | |
| Private | 996 | 95.86 | 2,263 | 94.37 | 0.070 |
| Medicaid | 43 | 4.14 | 135 | 5.63 | 0.070 |
| Baseline stimulant use (duration) | | | | | |
| ≤ 2 months | 183 | 17.61 | 576 | 24.02 | <0.001 |
| 2-4 months | 378 | 36.38 | 876 | 36.53 | 0.933 |
| 4-6 months | 478 | 46.01 | 946 | 39.45 | <0.001 |
| Baseline stimulant use (number of different stimulant used) | | | | | |
| 1 | 720 | 69.30 | 1,705 | 71.10 | 0.287 |
| 2 | 266 | 25.60 | 577 | 24.06 | 0.335 |
| 3+ | 53 | 5.10 | 116 | 4.84 | 0.743 |
| Attention deficit disorder with hyperactivity (ICD-9-CM, 314.01) | | | | | |
| Yes | 878 | 84.50 | 1,942 | 80.98 | 0.014 |
| No | 161 | 15.50 | 456 | 19.02 | 0.014 |
| Number of non-stimulant drugs prescribed (different generic names) | | | | | |
| 0-1 | 206 | 19.83 | 837 | 34.90 | <0.001 |
| 2-3 | 415 | 39.94 | 986 | 41.12 | 0.520 |
| 4+ | 418 | 40.23 | 575 | 23.98 | <0.001 |
| Number of outpatient service visits | | | | | |
| 0-2 | 74 | 7.12 | 399 | 16.64 | <0.001 |
| 3-5 | 298 | 28.68 | 886 | 36.95 | <0.001 |
| 6-9 | 279 | 26.85 | 578 | 24.10 | 0.087 |
| 10+ | 388 | 37.34 | 535 | 22.31 | <0.001 |

Table 5. 1. Baseline characteristics –cont'd

| Baseline Characteristics | AAP users (N=1,039) | | Non-AAP users (N=2,398) | | p Value |
|---|---|---|---|---|---|
| | N | % | N | % | |
| Number of inpatient service visits | | | | | |
| 0 | 974 | 93.74 | 2,350 | 98.00 | <0.001 |
| 1 | 51 | 4.91 | 43 | 1.79 | <0.001 |
| 2+ | 5 | 0.21 | 14 | 1.35 | <0.001 |
| Number of emergency room visits | | | | | |
| 0 | 12 | 1.15 | 40 | 1.67 | 0.258 |
| 1+ | 1,027 | 98.85 | 2,358 | 98.33 | 0.258 |
| Baseline physical comorbidity* | | | | | |
| Obesity | 17 | 1.64 | 32 | 1.33 | 0.493 |
| Diabetes | 6 | 0.58 | 7 | 0.29 | 0.210 |
| Cardiovascular disease | 4 | 0.38 | 9 | 0.38 | 0.966 |
| Epilepsy | 11 | 1.06 | 19 | 0.79 | 0.441 |
| Baseline mental comorbidity* | | | | | |
| Neurotic disorder | 245 | 23.58 | 315 | 13.14 | <0.001 |
| Mood disorder | 286 | 27.53 | 217 | 9.05 | <0.001 |
| Disturbance | 249 | 23.97 | 324 | 13.51 | <0.001 |
| Developmental disorder | 58 | 5.58 | 147 | 6.13 | 0.533 |
| Adjustment disorder | 135 | 12.99 | 244 | 10.18 | 0.015 |

*These variables are not mutually exclusive.

Table 5. 2. Propensity score model of receiving an atypical antipsychotic medication

| Confounder | Odds ratio | 95% Confidence interval |
|---|---|---|
| Age | | |
| Children (age 4-11) | Reference | |
| Adolescents (age 12-18) | 1.47* | 1.24-1.75 |
| Young adults (age 19-24) | 1.59* | 1.16-2.19 |
| Sex | | |
| Male | Reference | |
| Female | 0.76* | 0.63-0.91 |
| Race | | |
| White | Reference | |
| Black | 1.65* | 1.10-2.51 |
| Others | 1.09 | 0.86-1.38 |
| Region of residence | | |
| Northeast | Reference | |
| Midwest | 0.70* | 0.52-0.94 |
| West | 0.82 | 0.57-1.18 |
| South | 0.76 | 0.57-1.01 |
| Annual household income | | |
| ≤ $49,999 | Reference | |
| $50,000-74,999 | 0.83 | 0.66-1.04 |
| $75,000-99,999 | 0.66* | 0.52-0.84 |
| ≥ $100,000 | 0.71* | 0.56-0.89 |
| Payer source | | |
| Private | Reference | |
| Medicaid | 0.59* | 0.39-0.89 |
| Baseline stimulant use (duration) | | |
| ≤ 2 months | Reference | |
| 2-4 months | 1.39* | 1.14-1.71 |
| 4-6 months | 1.98* | 1.59-2.48 |
| Baseline stimulant use (number of different stimulant used) | | |
| 1 | Reference | |
| 2 | 1.01 | 0.84-1.22 |
| 3+ | 0.95 | 0.66-1.37 |
| Attention deficit disorder with hyperactivity (ICD-9-CM, 314.01) | | |
| No | Reference | |
| Yes | 1.16 | 0.94-1.44 |
| Number of non-stimulant drugs prescribed (different generic names) | | |
| 0-1 | Reference | |
| 2-3 | 1.39* | 1.14-1.71 |
| 4+ | 1.98* | 1.59-2.48 |
| Number of outpatient service visits | | |
| 0-2 | Reference | |
| 3-5 | 1.49* | 1.12-2.00 |
| 6-9 | 1.80* | 1.32-2.45 |
| 10+ | 2.27* | 1.64-3.13 |

Table 5. 2. Propensity score model of receiving an atypical antipsychotic medication-cont'd

| Confounder | Odds ratio | 95% Confidence interval |
|---|---|---|
| Number of inpatient service visits | | |
| 0 | Reference | |
| 1 | 1.17 | 0.74-1.87 |
| 2+ | 2.55 | 0.74-8.80 |
| Number of emergency room visits | | |
| 0 | Reference | |
| 1+ | 0.45 | 0.20-1.00 |
| Baseline physical comorbidity | | |
| Obesity | 0.83 | 0.45-1.51 |
| Diabetes | 1.19 | 0.30-4.77 |
| Cardiovascular disease | 0.75 | 0.21-2.66 |
| Epilepsy | 1.03 | 0.44-2.42 |
| Baseline mental comorbidity | | |
| Neurotic disorder | 1.39* | 1.12-1.72 |
| Mood disorder | 2.54* | 2.03-3.17 |
| Disturbance | 1.79* | 1.45-2.21 |
| Developmental disorder | 0.81 | 0.57-1.14 |
| Adjustment disorder | 0.94 | 0.73-1.21 |

*Significant at 5% significance level.

Table 5. 3. Inverse probability of treatment weighted estimation of health care utilization of AAP users compared to non-AAP users

| Health care utilization | During 6 month observation period after index date (N=3,437) | | During 12 month observation period after index date (N=1,908) | |
|---|---|---|---|---|
| | Event rate ratio (95% confidence interval) | p Value | Event rate ratio (95% confidence interval) | p Value |
| Outpatient service visits | 1.14 (1.04-1.26) | 0.008 | 1.18 (1.04-1.33) | 0.009 |
| Inpatient service visits | 1.77 (1.05-2.98) | 0.033 | 1.48 (0.92-2.40) | 0.108 |
| Emergency room visits | 0.62 (0.23-1.65) | 0.342 | 0.99 (0.33-3.02) | 0.988 |

Table 5. 4. Inverse probability of treatment weighted estimation of incremental costs accrued to AAP users compared to non-AAP users

| Health care costs | During 6 month observation period after index date (N=2,895) | | During 12 month observation period after index date (N=1,908) | |
|---|---|---|---|---|
| | Incremental cost (± robust standard error) | p Value | Incremental cost (± robust standard error) | p Value |
| **Total prescription costs** | $ 900 (± 63) | <0.001 | $ 1,672 (± 155) | <0.001 |
| Index drug costs | $ 717 (± 35) | <0.001 | $ 1,249 (± 87) | <0.001 |
| Non-index drug costs | $ 184 (± 48) | <0.001 | $ 423 (± 115) | <0.001 |
| **Total medical costs** | $ 493 (± 350) | 0.159 | $ 1,113 (± 1,008) | 0.270 |
| Mental health related costs | $ 509 (± 170) | 0.003 | $ 573 (± 232) | 0.014 |
| - Outpatient visits | $ 196 (± 78) | 0.012 | $ 293 (± 157) | 0.062 |
| - Inpatient visits | $ 314 (± 139) | 0.024 | $ 281 (± 147) | 0.057 |
| - Emergency room visits | -$ 0.2 (± 0.3) | 0.485 | -$ 1 (± 1) | 0.092 |
| Non-mental health related costs | -$ 16 (± 282) | 0.954 | $ 539 (± 973) | 0.580 |
| - Outpatient visits | $ 124 (± 226) | 0.583 | $ 797 (± 868) | 0.359 |
| - Inpatient visits | -$ 135 (± 122) | 0.265 | -$ 258 (± 275) | 0.348 |
| - Emergency room visits | -$ 5 (± 4) | 0.222 | $ 0.3 (± 11) | 0.979 |
| **Total health care costs*** | $ 1,393 (± 362) | <0.001 | $ 2,784 (± 1,031) | 0.007 |

*Total prescription costs + total medical costs

## Chapter 6: Conclusion and Policy Recommendations

The extensive use of AAPs by pediatrics is an important policy problem that imposes serious concerns on public health and economy in the US. As discussed in chapter 2, a large proportion of total pediatric AAP use is off-label in which the safety and effectiveness are not yet established. Moreover, among the off-label conditions for which AAPs were used, ADHD was the most common primary mental diagnosis. Motivated by this phenomenon, this dissertation further addressed underlying problems about AAP utilization, and its implication to ADHD children and adolescents.

From public health perspective, the risk of type II diabetes in pediatric AAP users was estimated in chapter 3. A retrospective cohort study was conducted using nationally representative data, and the twice higher risk of developing type II diabetes was estimated for AAP users compared to non-users in pediatrics. Considering that T2DM is a chronic condition that may persist the rest of a person's life, its risk that is imposed on children and adolescents could outweigh the benefit of AAP therapy in some patients.

From economic efficiency perspective, chapter 4 estimated the cost-effectiveness of AAPs compared to other ADHD medications in pediatric ADHD patients who have failed a stimulant therapy. Among non-stimulant ADHD medication treatment strategies, AAPs resulted in the lower expected health outcome than other ADHD medications including atomoxetine, clonidine, or guanfacine. Also, AAPs were not a favored choice with respect to cost-effectiveness, and should not be recommended over

other strategies. While analyses in chapter 4 were based on estimates derived from literature review, the chapter 5 reports an original study that compares resource utilization and costs between atypical antipsychotic (AAP) users and non-AAP users in ADHD. I found that AAP users were likely to visit a healthcare facility for outpatient and inpatient services more frequently than non-AAP users. Also, total health care costs were significantly higher for AAP users with additional costs of $1,393 (2012 dollars) during six months and $2,784 (2012 dollars) during a year after initiating the AAP treatment.

With the defined problem and evidences reported in this dissertation, I propose solutions and policy recommendations that can be implemented at the national/state government level, the health care provider level and the patient/caregiver level.

First, at the national/state government level, it is important for healthcare service agencies to recognize that the pediatric AAP use is a potentially inappropriate utilization. Especially, as primary public organizations involved in regulating mental health service provision, Substance Abuse Mental Health Services Administration (SAMHSA), Centers for Medicare and Medicaid Services (CMS), and National Association of State Mental Health Program Directors (NASMHPD) should work together so that their funding and billing systems reflect the promotion of standardized mental health care. Also, current health care surveillance activities could be amended in a way that the pediatric AAP practice and its impacts are better captured and assessed by health services researchers. For example, Healthcare Effectiveness Data and Information Set (HEDIS) is a widely used set of healthcare quality measures in the US.

While it incorporates a number of measures that assess mentally ill patients' access to healthcare services and medication managements, it does not include a measure for assessing the potential overuse or misuse of antipsychotics. It is recommended that standard definitions for identifying inappropriate antipsychotic use are developed and included in the HEDIS and other healthcare quality surveillance tools.

Second, at the healthcare provider level, provider agencies and clinicians should ensure the provision of quality and evidence based care. One of the reasons why AAPs were largely used by pediatrics is because they were marketed as a safer choice compared to typical antipsychotics. However, when making decisions about the AAP therapy, it should be thoroughly considered that the risk of using an AAP may outweigh benefits in many children and adolescents.

Third, at the patient/caregiver level, they are encouraged to pursue patient centered care that is long-term wellness focused. Patient-centered care is defined as "care that is respectful and responsive to individual patient preferences needs, and values and ensuring that patient values guide all clinical decisions". It would be better implemented if patients/caregivers share information so that the mental health community becomes more aware of the clinical/economic impacts of pediatric AAP use.

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**VITA**

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2) Rhee YS, **Sohn M**, Woo BH, Thanoo BC, DeLuca PP, Mansour HM. Sustained-Release Delivery of Octreotide from Biodegradable Polymeric Microspheres. *AAPS PharmSchiTech.* 2011, 12(4), 1293-301.

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