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Resource Utilization and Costs Associated with Off-label use of Atypical Antipsychotics in an Adult Population

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RESOURCE UTILIZATION AND COSTS ASSOCIATED WITH OFF-LABEL USE OF ATYPICAL ANTIPSYCHOTICS IN AN ADULT POPULATION

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

by

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Dedication

To my Dad, who has been my pillar of strength and showed unwavering confidence in my abilities.

Love you daddy!

Acknowledgments

Even though there are innumerable people who have played important roles in shaping me to where I am today, there are a few people that I have to acknowledge and thank for their support, without which this research would not have been possible.

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Abstract

RESOURCE UTILIZATION AND COSTS ASSOCIATED WITH OFF-LABEL USE OF ATYPICAL ANTIPSYCHOTICS IN AN ADULT POPULATION

By Della Varghese, PharmD, MS, PhD

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

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Introduction: Atypical Antipsychotics (AAPs) are approved by the Food and Drug Administration (FDA) for the treatment of schizophrenia and bipolar disorder. AAPs are commonly used off-label to treat depression, post-traumatic stress disorder and neuropsychiatric symptoms in dementia due to lack of alternative treatment options and treatment resistance. Concerns for off-label use arise since AAPs increase the risk of cardiovascular events and death. The *objectives* were 1) describe patterns of RU and costs among off-label AAPs users in a nationally representative population 2) identify prevalence of off-label use in the Medicare population 3) compare RU and costs between off-label AAPs users and non-users with mental health conditions in Medicare.

Methods: For the first objective, the Medical Expenditure Panel Survey (MEPS) datasets were used. AAPs users greater than 18 years were identified in this cross-sectional study. Generalized Linear Models (GLM) were used to estimate costs among users and non-users after controlling for age sex, gender, insurance type, marriage status, income and comorbidity index. For the second and third objective, Medicare datasets were used to identify prevalence, RU, and costs of off-label use in

Medicare beneficiaries 18 years and older. RU and costs between propensity score matched AAPs user and non-user cohorts were compared in a retrospective cohort study.

Results: The adjusted odds of having an office-based outpatient (OR=2.47, 95%CI: 1.55-3.92) or inpatient (OR=1.63, 95%CI: 1.26-2.10) visit were significantly higher among off-label AAPs users. Adjusted office-based visit ($1,943 vs. $1,346), prescription ($4,153 vs. $1,252) and total ($10,694 vs. $4,823) costs were significantly higher among users ($p<0.0001$).

Among Medicare beneficiaries, approximately 37% of AAPs users had no FDA approved diagnosis. The typical off-label user was a white 70-year-old male. Common off-label uses were depression, anxiety and neurotic disorders and dementia. Off-label AAPs users had significantly higher mental health outpatient ($461 vs $297), prescription ($2,349 vs $282) and total ($3,665 vs $1,297) costs per beneficiary than non-users. About 30% of AAPs users had at least one mental health outpatient visit during the year versus 23% of non-users; no significant differences were found in inpatient visits. AAPs non-users had significantly higher all-cause inpatient costs ($6,945 vs. $4,841) per beneficiary ($p<0.0001$) but there were no differences in total costs.

Conclusion: In a nationally representative population comprising a younger age group AAPs users had higher all-cause RU and total costs than non-users. Off-label prescribing of AAPs continued to be a prevalent practice affecting 37% of Medicare AAPs users. Off-label AAPs users had higher mental health costs but no significant differences in all-cause total health care costs in a Medicare population. Off-label use of AAPs can be a cost-effective option if future research shows off-label use is associated with increased effectiveness, which offsets any additional costs.

Chapter 1: Introduction and Background

1.1 Introduction

Atypical antipsychotics (AAPs) have become the mainstay of treatment for a number of mental health disorders. Even though the Food and Drug Administration (FDA) has approved most AAPs only for the treatment of schizophrenia and bipolar disorder these drugs are used for other mental health conditions such as depression, dementia and post-traumatic stress disorder (PTSD) (Maglione et al., 2011). AAPs are now under increasing scrutiny for their increased "off-label" use which the FDA defines as, "Use for indication, dosage form, dose regimen, population or other use parameter not mentioned in the approved labeling." Studies have shown that off-label prescribing is a common phenomenon in outpatient care and off-label use of AAPs is prevalent in different settings and conditions (Leslie et al, 2009; Alexander et al., 2011; Kamble et al., 2010).

In 2011, the Agency for Healthcare Research and Quality (AHRQ) released a review that concluded that most off-label use of AAPs was not supported by moderate to strong evidence but at the same time highlighted that not all off-label prescribing may lead to adverse effects (Maglione et al., 2011). Concern for off-label use of AAPs arise from their propensity to cause metabolic and cardiac adverse effects (McIntyre et al., 2001; Chung & Murray, 2009). Steps, such as a FDA black box warning and Centers for Medicare and Medicaid Services (CMS) initiated partnerships, have been implemented to decrease off-label use of AAPs specifically in the elderly.

On the other hand, even though there is concern regarding the use of these agents, especially in vulnerable populations, the lack of alternative treatments and treatment resistance have paved the way for off-label use among patients with depression, dementia and anxiety

(Trivedi et al. 2006; Ravizza et al., 1995; Erzegovesi et al., 2001). Previous studies have shown that initiation of off-label use of AAPs in patients with mental health conditions has led to decreased hospitalization costs and decreased resource utilization (RU) from pre to post treatment since these patients were not seeking treatment for emergent care (Del-Paggio et al., 2002; Lage.& Rajagopalan,2006; Al-Zakwani, 2003). The main limitation of these studies was that they focused only on a young population primarily with private insurance. The estimates from these studies are also not nationally representative and do not focus solely on off-label use of AAPs.

This study aims to fill the gap in the literature by providing RU patterns and cost estimates among off-label AAPs users in a community dwelling population using nationally representative data. Secondly, this study also aims to compare RU and costs among AAPs users and non-users from a public payer perspective in a population that largely comprises older adults.

The specific aims and background are provided in the remainder of this chapter. Chapter 2 explores the literature that has assessed off-label use of AAPs and its effects on RU and costs. Chapter 3 presents the methods, results and discussion of a pilot study evaluating national patterns of inpatient, outpatient and emergency visits among off-label AAPs users and non-users in a community dwelling population of AAPs users and non-users. Chapters 4, 5 and 6 address the methods, results and discussion of a study comparing the RU and costs among AAPs users and non-users in the Medicare population.

1.2 Specific Aims

Specific Aim I:

A: Examine RU pattern and estimate costs among off-label AAPs users and non-users in a nationally representative sample

Specific Aim II:

A: Evaluate the prevalence of off-label and on-label use of AAPs and describe patient characteristics in a Medicare population.

Specific Aim III:

A: Compare all-cause RU and costs between Medicare beneficiaries using AAPs and those not using AAPs for off-label treatment of mental health conditions.

B: Compare mental health RU and costs between Medicare beneficiaries using AAPs and those not using AAPs for off-label treatment of mental health conditions.

Specific Aim IV:

A: Compare all-cause RU and costs between Medicare beneficiaries using AAPs and those not using AAPs for on-label treatment of mental health conditions.

B: Compare mental health RU and costs between Medicare beneficiaries using AAPs and those not using AAPs for on-label treatment of mental health conditions.

Specific Aim V:

A: Evaluate differences in RU and associated costs in Medicare beneficiaries using AAPs and those not using AAPs to treat specific mental health conditions.

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1.3 Background

Pharmacology

Antipsychotic medications have become the mainstay of treatment for a wide variety of psychiatric conditions. Second generation antipsychotics or AAPs have become increasingly popular as compared to first generation antipsychotics due to their better adverse effect profiles (Harrison et al., 2012) and because of their effectiveness in adults (Duggan et al., 2003; Srisurpanont et al., 2004; El-Sayeh et al., 2004; Bagnall et al., 2000; Hunter et al., 2003; Davis et al., 2003). They are one of the most widely used classes of drugs with sales exceeding $14 billion in 2008 and were the top selling drug class in United States in 2008 (Kuehn, 2010). The older generation of antipsychotics or the typical antipsychotics are well known for their propensity to cause undesirable side effects, primarily extrapyramidal symptoms (EPS), tardive dyskinesia and increased prolactin levels (Gardner et al., 2005). The undesirability of these effects and irreversibility of certain adverse effects have led to a rapid increase in the use of AAPs over the past years.

This class of drugs work by acting at the dopamine receptors. There are different kinds of dopamine receptors that are responsible for a variety of neurological processes. Broadly, the five-dopamine receptors are D1-D5. The D2 receptor is the site of action for antipsychotics (Mauri et al., 2014). Antipsychotics work by blocking the D2 receptor but unlike the first generation antipsychotics, the AAPs rapidly dissociate from the D2 receptors therefore leading to lower EPS. AAPs also act at certain serotonin receptors and this differential affinity for the different receptors makes the individual AAPs unique from each other. For example, AAPs ziprasidone and risperidone have high selectivity for both serotonin 5HT2A and D2 receptors, olanzapine and

quetiapine have affinity for 5HT2A and D2 receptors in addition to other receptors that are cholinergic, histaminergic, and 5HT1A, and aripiprazole is a partial dopamine receptor agonist.

Pattern of use

AAPs medications have become the mainstay of treatment for a wide variety of psychiatric conditions. There was a rapid increase in their utilization due to low propensity to cause EPS and other movement related adverse effects. Even though these agents were originally approved for the treatment of schizophrenia and bipolar disorder, they are widely used in the treatment of other mental health conditions such as depression, dementia in elderly and others (Maglione et al., 2011).

Bipolar disorder: AAPs are the main treatment modality for bipolar disorder, either as monotherapy or in combination with mood stabilizers. Almost 96.2% of patients who newly initiated AAPs were using it as a monotherapy (Chen et al., 2013). Quetiapine, olanzapine and risperidone were the most commonly used AAPs for the treatment of bipolar from 2002 to 2008 among patients newly initiating AAPs (Chen et al., 2013).

Depression: Data from the National Ambulatory Medical Care Survey (NAMCS) showed that the rate of AAPs use increased from 4.6% in 1999-2000 to 12.5% in 2009-2010. The odds of using AAPs to treat depression were 2.78 times higher in 2010 compared to 1999 (Gerhard et al., 2013). Gerhard et al. report that even though some AAPs are approved by the FDA as adjunctive treatment for depression in combination with antidepressants, there is a growing use of AAPs for non-psychotic depression in the absence of antidepressant therapy.

Dementia: The non-cognitive symptoms of dementia such as aggression and agitation were commonly treated using antipsychotics. In the early 1990s, there was a shift from using the typical antipsychotics to the AAPs for the treatment of these symptoms due to their better side effect

profile (Lopez et al., 2003). But in the 2000s concern developed over the propensity of AAPs to cause diabetes (ADA, 2004) and cerebrovascular effects (Brodarty et al., 2003; Wooltorton , 2002). As a result, the FDA released a black box warning in 2005: "Treatment of behavioral disorders in elderly patients with dementia with AAPs medications is associated with increased mortality". According to a study by Kales et al. which used national Veterans Affairs data, 10.72% of patients with dementia were being prescribed AAPs in 1999, and the use increased to 14.4% in 2003 but then declined to 14.15% in 2005 post the black box warning (Kales, 2011).

Anxiety: Due to the sedative property of AAPs these drugs have also been considered antineurotic and hypnotic medications (Linden & Thiels, 2001). AAPs use for anxiety increased from 3.8% in 1996 to 20.5% in 2007 according to a study conducted on NAMCS (Comer et al., 2011). During the same duration, use of typical antipsychotics decreased from 5.8% to 1.0% (Comer et al., 2011). Interestingly, even though AAPs use sharply increased (OR=3.34, $p<0.0001$) during the 12-year time frame, there was only a small increase in the use of FDA approved sedative/hypnotics (OR=1.52, $p<0.0001$).

Post-traumatic stress disorder (PTSD): Even though AAPs are still being used in the treatment of PTSD despite the availability of FDA approved first line treatments, the use showed a declining trend from 2002 to 2009 (Bernardy et al., 2012). The overall frequency of use had increased from 13.8% to 17.8% in 1999-2002 but declined to 10.4% in 2009 among veterans.

Safety concerns with AAPs use

Even though AAPs have a better side effect profile in terms of EPS and other movement related disorders, other safety concerns that have risen over the last few years. According to a national study that used Healthcare Cost and Utilization Project (HCUP) 2008 data, psychotropic

agents were in the top 5 classes of drugs that led to treat-and-release emergency department visits and in the top 10 classes that led to inpatient stays due to medication related adverse event (Lucado et al., 2011). Evidence from adult studies suggests that AAPs are linked with metabolic disturbances; most commonly weight gain, hyperglycemia, diabetes, and hyperlipidemia (McIntyre et al., 2001), stroke and cardiac deaths (Chung & Murray, 2009). In this section, the adverse effect profile and reasons for safety concerns with AAPs use are explored in detail.

Metabolic concerns: AAPs have received a lot of attention over the last decade for their propensity to cause a myriad of metabolic effects including weight gain, development of Type 2 diabetes and dyslipidemia.

- Weight gain: The weight gain associated with AAPs use typically occurs within the first 12 weeks of initiation of treatment and is believed to be linked with the affinity of the molecule to the 5HT2 receptor (Tschoner, 2007). Since olanzapine has the highest affinity for the receptor, it is also the agent with the highest weight gain profile (Reynolds & Kirk, 2010). Patients using olanzapine gained up to 4.15 kg in 10 weeks (Allison et al., 1999). Even though olanzapine users had the highest weight gain, quetiapine and risperidone users have also been shown to gain weight but ziprasidone users experienced weight loss in a trial (Lieberman et al., 2005).
- Type 2 diabetes: Due to the propensity to cause maximum weight gain, olanzapine also is also associated with an increased risk for treatment-induced type 2 diabetes (Deberdt et al., 2005; Newcomer, 2005; Lieberman et al., 2005). Patients developed signs of hyperglycemia as early as within 6 weeks of initiation with AAPs (Tschoner, 2007) and 7% of AAPs patients were diagnosed with diabetes at the end of one year in a veteran population (Leslie & Rosenheck2004).

- Dyslipidemia: Olanzapine was also associated with increased risk of dyslipidemia (Deberdt, et al., 2005; Newcomer, 2005; Chaggar, 2010). In a double blind clinical trial patients had an increase of 12.3 mg/dL total cholesterol levels after 8 weeks of olanzapine (Lindenmayer et al., 2003).

In addition to the metabolic effects in all AAPs users, AAPs are known to be associated with other adverse effects that affect the elderly in particular.

Risk of Death: In 2005, the FDA released a public health advisory based on a meta-analysis of 17 studies of four drugs (aripiprazole, olanzapine, quetiapine, and risperidone). The meta-analysis showed that these studies, which cumulatively enrolled 5,106 elderly patients with dementia, showed a 1.6-1.7 fold increase in mortality among AAP users versus non-users (Schneider et al., 2005). Other studies have reported similar results wherein AAPs users were associated with higher rates of mortality as compared to patients using other psychotropic medications and the risk was seen to last over 6-12 months (Kales et al. 2007; Gill et al. 2007; Ray et al., 2009).

Cerebrovascular Risk: A meta-analysis by Hermann et al. combined the results from 11 trials including 11,400 people over the age of 65 who were using risperidone, olanzapine or typical antipsychotics. The study showed that that there was an increased risk of cerebrovascular adverse events when compared to placebo (Herrmann & Lanctot, 2005). Similar results were reported by Douglas et al. There is an increased risk of stroke in patients receiving AAP versus typical agents (Douglas & Smeeth, 2008). Other studies reported similar risk of stroke among typical and atypical users especially in patients with dementia (Gill et al. 2005; Liperoti et al. 2005; Shin, 2013).

Cardiac Risk: A recent study by Pariente et al. showed that concurrent antipsychotic (both typical and atypical) and cholinesterase inhibitor use led to increased risk of myocardial infarction

within 30 days of use, but the risk significantly decreased after 30 days (Pariente et al. 2012). Ziprasidone is also known to induce QTc prolongation that can increase the risk of torsade de pointes (Glassman & Bigger, 2001).

Nephrological Risk: According to a new study AAPs can also cause acute kidney injury (AKI) in adults aged 65 years and older which could lead to hospitalizations (Hwang et al., 2014).

Other Risks: Use of certain AAPs in patients with Parkinson's disease is associated with an increased risk of falls and fractures among the elderly. It was found that quetiapine (AOR=2.4), risperidone (AOR=1.2) and olanzapine (AOR=1.7) were associated with higher rates of fracture (Dore et al., 2009). Bauer et al. also reported that clinical characteristics such as diabetes, hyperlipidemia, obesity, and overall cardiovascular risk were associated with use of AAP agents in patients with PTSD ($P<0.0001$) (Bauer et al. 2014). Studies have also found that elderly AAPs users have significant risk to develop pneumonia (Trifiro et al., 2010; Star et al., 2010) and deep venous thromboembolism (Liperoti et al., 2005).

Due to these safety concerns, in 2005, FDA required all manufacturers of AAPs to include a black box warning on their product label to warn patients about "an increased mortality in elderly patients with dementia-related psychoses". In 2012, the CMS initiated partnerships with multiple stakeholders to decrease the off-label usage of AAPs among nursing home residents (Mort et al., 2014).

Off-label Use

The Food and Drug Administration (FDA) defines off-label use as, "Use for indication, dosage form, dose regimen, population or other use parameter not mentioned in the approved labeling." Radley et al. showed that off-label prescribing is a common phenomenon in outpatient

care and antipsychotics were among the top five classes of drugs for off-label use (Radley et al., 2006).

Even though off-label prescribing is not illegal, off-label promotion of drugs by manufacturers is. This is in order to prevent drug companies from trying to promote the use of drugs for non-FDA approved indications. A number of lawsuits were filed against drug manufacturers including Pfizer, Eli Lilly, Bristol-Myers Squibb, Novartis and AstraZeneca within the past several years for same (Field, 2010). Majority of the litigation was based on claims that the manufacturers promoted the use of AAPs in the elderly population even though the drugs were only FDA approved for use in adult patients 18 to 65 years with schizophrenia or bipolar disorder. Negative publicity over these large settlements has bought the off-label use of AAPs to the forefront.

In 2011, the Agency for Healthcare Research and Quality (AHRQ) published a systematic review of approximately 170 studies and concluded that the most common off-label uses of these drugs were for anxiety, dementia in elderly patients, depression, and post-traumatic stress disorder (PTSD) (Maglione et al. 2011). Other studies have shown that 60.2% of veterans in 2007, 66% of outpatient AAPs users in 2008, and 20.3% of nursing home residents in 2004 used AAPs for off-label conditions (Leslie et al, 2009; Alexander et al., 2011; Kamble et al., 2010).

Reasons for Off-label Use

Despite safety concerns, AAPs continue to be used in the treatment of a spectrum of mental health conditions and the driving reasons behind this practice are a lack of alternative treatments and treatment resistance for many mental health conditions (Tabarrok, 2000).

Depression: Current practice guidelines state that patients with depressive disorders should be treated using antidepressants (selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), monoamine oxidase inhibitor (MAOI)) in addition to psychotherapy (APA, 2010). AAPs should be reserved for patients with severe depression with psychotic features. Despite the availability of FDA approved first-line therapy AAPs continue to be used as adjunct and monotherapy since 30-40% of depressed patients do not receive any significant relief of signs and symptoms after two attempts of antidepressant therapy (Thase et al., 1998). The STAR*D study reported that only one third of depressed patients had remission after a vigorous initial trial of a SSRI (Trivedi et al. 2006). Treatment resistant patients had significantly higher health care costs and utilization (Lepine et al., 2012). AAPs have shown to be effective as adjunctive treatment for depression (Mahmoud et al. 2007).

Dementia: Current treatment guidelines state that cholinesterase inhibitors should be initiated in patients with mild to moderate dementia (APA, 2014). There are no FDA approved treatments for psychotic symptoms. AAPs have been shown to have some effect in decreasing the psychotic symptoms associated with personality disorders and neuropsychiatric symptoms of dementia (NPSD), neither of which have FDA approved first line treatments (Maher et al. 2011; Rosenbluth & Sinyor, 2012). There is an increasing need for pharmacologic interventions to treat NPSD in the presence of the rapidly aging baby boomer generation (Maher et al. 2011).

Anxiety and other neurotic disorders: In addition to psychotherapy, the FDA approved certain antidepressants and benzodiazepines for the first line treatment of generalized anxiety, panic disorders, phobias and obsessive-compulsive disorder (OCD). Even though 50-60% of patients with anxiety respond to their treatment, only one-third to one-half attain full recovery during the acute phase (Rickels et al., 2006) similar to 40-60% patients with OCD who failed to

respond adequately to treatment with SSRI (Ravizza et al., 1995; Erzegovesi et al., 2001). A systematic review suggested that there was some efficacy in using AAPs as augmentation therapy in patients with treatment refractory anxiety though the report highlighted the need for more rigorous studies (Lorenz et al., 2010).

PTSD: Current guidelines recommend the use of antidepressants such as sertraline and paroxetine for the first-line treatment of PTSD. AAPs are effective as adjunctive treatment for PTSD (Hamner et al., 2003; Petty et al. 2001; Sokolski et al., 2003; Stein et al., 2002), particularly in presence of psychotic symptoms (Ahearn et al., 2003). Current treatment guidelines therefore recommend the off-label use of AAPs only as adjunctive therapy in patients who have partially responded to SSRIs and have psychotic symptoms (APA, 2009).

1.4 Rationale

With increasing need and limited resources, it has become imperative to assess appropriate use of health care resources and to identify areas of overuse. In psychiatry, AAPs are the cornerstone of mental health pharmacotherapy. Even though AAPs are primarily approved for schizophrenia and bipolar disorder, there is evidence for efficacy as well as evidence for adverse effects in treating indications that are not approved by the FDA such as dementia and depression. Due to the varying level of evidence, practitioners have little guidance as to when to prescribe AAPs for off-label treatment and payers, such as CMS, have little information about the impact of using these medications in the off-label treatment of mental health conditions on health care resources.

The aim of this descriptive study was to estimate the costs and RU associated with using AAPs in the off-label treatment of mental health conditions. The results can help inform public policy and assist health care professionals in designing health care guidelines targeting specific high-risk mental health conditions.

Our study aims to describe treatment patterns and examine costs during 2008-2010. The CMS initiatives to decrease AAPs use have been implemented since 2012 (Mort et al., 2014). Going forward, the results of this study will provide baseline RU and costs associated with off-label use of AAPs before the regulatory changes were implemented. This will enable us to evaluate the changes in treatment patterns, RU and costs after the regulatory changes.

Chapter 2: Literature Review

2.1 Summary of Literature on RU and costs of off-label AAPs Use

A review of the existing body of literature conducted using PubMed/MEDLINE and CINAHL used the following search terms: ("Antipsychotic Agents" [Mesh] OR "Atypical Antipsychotics") AND ("Adult" [Mesh]) AND ("Mental Health Services" [Mesh] OR "Resource Utilization" OR "Health Care Service"). The following inclusion and exclusion criteria were applied after screening through the titles and abstracts:

Inclusion criteria:

1. Evaluates health care RU by patients using AAPs for off-label treatment.

Exclusion criteria:

1. Only evaluates RU in patients using AAPs to treat schizophrenia or bipolar disorder.
2. Studies that are not conducted in the United States.
3. Studies that assess RU in a pediatric population.

The search in PubMed and CINAHL initially yielded 431 articles. After screening titles and abstracts, removing duplicate articles and applying the inclusion and exclusion criteria, two studies were extracted for final review. The references of these two studies were reviewed to evaluate if any other studies met the inclusion criteria but were missed during the literature search but no additional articles were found from the references. Upon reviewing articles on Google Scholar, one more article was found which was not available on the databases.

Table 1: Articles included in the summary of literature

Author	Comparators	Mental health conditions	Data source	Outcome	Findings
Lage et al. (2005)	-Olanzapine -Quetiapine -Risperidone	-Schizophrenia -Bipolar disorder -Dementia -Depression	-MarketScan commercial claims	-Hospitalizations -Emergency visits	-Olanzapine and risperidone users had higher rates of hospitalizations and ED visits from baseline to EOS -Quetiapine users had lower number of hospitalizations and ED visits from baseline to EOS
Al-Zakwani et al. (2003)	-Olanzapine -Quetiapine -Risperidone -Clozapine	-All mental health conditions (ICD-9-CM: 290-319)	-Private claims data from a health plan	-Outpatient visits -Hospital admissions -Hospital outpatient visits -Emergency visits	-AAPs users were compared to typical antipsychotic users and AAPs users experienced fewer office visits, hospital admissions, and ED visits compared to typical antipsychotic users
Del Paggio et al. (2002)	-Olanzapine	-Thought disorders -Other disorders (bipolar disorder, depressive disorder, OCD, PTSD)	-Large county operated mental health care system	-Hospital costs -ED costs -Medication costs -Outpatient costs	-Patients had significantly decreased hospital costs, and ED costs in the 12 month follow up period from baseline -Medications costs and outpatient costs increased in the olanzapine users from baseline to EOS

*AAPs: Atypical antipsychotics, OCD: Obsessive-compulsive disorder, PTSD: Post-traumatic stress disorder, ED: Emergency department, EOS: End Of Study

Summary

Lage et al. (2006)

Lage et al. conducted a retrospective study using a large claims database to evaluate differences in hospitalizations and emergency department visits among patients with mental illness who were initialized on different AAPs. The study utilized the MedStat MarketScan Commercial Claims and Encounters (CCE) database (Thomson MedStat). The database includes health related data from approximately 100 payers. The dataset contains information on health care utilization (inpatient, outpatient, prescription drug and carve-out services) and the associated expenditures.

Only patients newly initiated on olanzapine, quetiapine or risperidone between July 1, 1998 and July 2, 2002 were included in the study. The index date was the date of first antipsychotic prescription fill. All included subjects had continuous enrollment for the six months before and after the index date. The outcomes of interest were the differences in rates of inpatient hospitalizations and emergency department (ED) visits between the pre and post index date periods.

Of the 23,778 patients that met the inclusion criteria, 8,730 received olanzapine, 5,709 received quetiapine and 9,339 received risperidone mostly for schizophrenia, bipolar disorder, dementia or depression. The results indicate that for all three antipsychotic drugs, there were significant differences in the outcomes between the pre and post period. Patients initiated on olanzapine and risperidone had significantly higher RU in the post period as compared to the pre period. Olanzapine users had higher rates of hospitalization (2.47% higher), higher ED visit rates (3.87%) and an increase in the mean number of hospitalizations by 0.13. Similarly, risperidone users had 1.71% and 4.69% more hospitalizations and ED visits respectively and an increase in

the mean number of hospitalizations by 0.12. On the other hand, quetiapine users showed significantly reduced RU with a 4.37% decrease in hospitalizations and 2.98% reduction in ED visits. Upon comparing across the three cohorts of patients who were treated with olanzapine, quetiapine or risperidone after controlling for age, gender, region and mental illness diagnosis, quetiapine users had significantly lower RU after initiation of therapy. Patients initiated on risperidone were also younger and more likely to be male as compared to olanzapine and quetiapine users. There were also significant differences among the cohorts with respect to mental health diagnoses, olanzapine users were more likely to have bipolar disorder and quetiapine users were less likely to be depressed.

The results of this study indicated that there were differences in the measured RU (hospitalizations and ED visits) when comparing the periods before and after initiation of AAPs. The results from this study did not provide conclusive evidence of whether initiation of AAPs increased or decreased RU among patients since the results varied by the drug used. Patients who initiated quetiapine experienced significantly lower RU after initiation but patients using olanzapine and risperidone had higher RU in the post initiation period. Since ED visits and hospitalizations can drive up the health care costs, the authors point out the importance of identifying therapies that can assist in decreasing the costs and improving patient outcomes. In previous studies Leal et al. and Dickson et al. reported lower RU after treatment with risperidone in patients with schizophrenia (Leal et al., 2004; Dickson et al., 1999) but the study by Lage et al. had also included patients with depression and dementia, neither of which is approved to be treated with AAPs.

One of the main limitations of the study was the lack of generalizability of the results. The study sample comprised privately insured patients while a large proportion of the population who

are diagnosed with mental health conditions have public insurance either via Medicaid or via Medicare. The sample also comprised young cohorts of patients with mean age from 37 to 40 years, therefore the results cannot be extrapolated to an older population who are most vulnerable to the adverse effects of AAPs. Other limitations include the inability of the study to capture outcomes such as quality of life and functional status of patients due to the nature of the data and only evaluating hospitalizations and ED visits as RU.

Al-Zakwani et al. (2003)

Al-Zakwani et al. conducted a study to examine the effects of both atypical and typical antipsychotics on healthcare RU. For the study, reimbursement data from a private health plan was used which contained information on approximately 500,000 beneficiaries. Only patients between six and 65 years of age who had newly initiated an antipsychotic agent between July 1, 1999 and September 30, 2000 were included in the study. The date of the first antipsychotic prescription fill was the index prescription date (IPD). Only patients who were continuously enrolled in the health plan for six months before and 12 months after the IPD were included in the study. Patients were categorized as the atypical drug cohort or the typical drug cohort. One of the outcomes of interest was RU, which was measured as the number of office-based outpatient, hospital inpatient and outpatient, emergency room, and mental health visits. All mental health diagnoses were included in the study.

A total of 469 patients were included in the study of which 82% were AAPs users and only 18% were using typical antipsychotics. Majority of the patients were using the medications to treat some form of psychosis (79%) and neurosis (42%). Some of the other main mental health

conditions included drug and alcohol dependence, depressive disorders, and mental disorders of childhood origin.

As compared to the typical drug class users, AAPs users experienced 45% fewer office visits, 76% fewer hospital admissions, 41% fewer hospital outpatient visits and 67% fewer emergency room visits after controlling for age, gender, medication possession ratio (MPR), length of therapy, treatment augmentation and switches. The mean age of the AAPs users was only 34 years and almost 75% were prescribed concomitant antidepressants.

The result of this study indicate AAPs users have lower hospital admission rates and office-based outpatient and emergency visits over the one-year period after initiation of AAPs compared to typical antipsychotic users. The major strength of this study is that it assessed RU among all mental health disorders and did not exclude patients who were using AAPs for off-label treatment. The authors also note that AAPs users had higher rates of concomitant psychotropic drug use such as antidepressants and mood stabilizers and this association could drive down the rates of RU.

As with the study by Lage et al. this study used data from a private health insurance plan therefore the results are only generalizable to a population comprising private health plan beneficiaries and not to patients who have public insurance. Another major limitation is that the study explicitly stated that patients over 65 years were not included in the study. Therefore, even though this study assessed RU among off-label AAPs users, the results cannot be extrapolated to an elderly population who are more prone to the adverse effects of AAPs. The authors note other limitations due to the retrospective nature of the study and secondary database. Confounding due to unobserved factors such as physician's justification for selection of different therapies and selection bias are also limitations to the study.

Del Paggio et al. (2002)

Del Paggio et al. conducted a study within the Alameda County Behavioral HealthCare Services (BHCS) which is a non-profit organization located in California. The BHCS serves approximately 1.4 million residents, provides community-based treatment for the severely mentally ill patients, and covers all services such as inpatient hospitalization, emergency services, residential treatment, outpatient services and medications. All outpatients who received coverage by BHCS and began olanzapine treatment between November 1, 1996 and April 30, 1998 were included in the study. Economic and RU data were collected from the Insyst database (countywide system maintained by BHCS) and the Pharmaceutical Care Network's MedIntelligence Access Database (a pharmaceutical benefits management company that was contracted to automate the pharmacy providers within the county network). The date of the first olanzapine fill was the index date and only patients continuously enrolled 12 months before and after the index date were included in the study.

One hundred and eighty nine patients were identified in the BHCS system who had been initiated on olanzapine during the study period. The mean age of the patients was approximately 36 years reflective of a younger population. Majority of the patients (66%) had diagnosis for thought disorders whereas the other 34% comprised patients with bipolar disorder, depressive disorder, obsessive-compulsive disorder, adjustment reactions and post-traumatic stress disorder. Of the 189 patients, 78 continued olanzapine therapy for 12 months or switched to another agent. These patients had significantly decreased hospital, and emergency costs in the 12 month follow up period. There was a mean decrease of $4,423 per patient in hospital costs and $203 per patient in emergency costs from before the index date to after the index date. On the other hand, medications costs significantly increased by $1,585 per patient. Even though the individual

components showed significant changes, the overall RU difference was non-significant with a mean decrease of $1,991 per patient. Among the 58 patients who continued olanzapine therapy for the 12 months there were significant decreases in the hospital and emergency costs but significant increases in the medication and outpatient costs.

The results of this study indicated a significant decrease in hospital and emergency costs even though it failed to achieve significance in total RU. Olanzapine users incurred increased medication and outpatient costs but this was offset by the decrease in hospital and emergency visits. The study results indicated that olanzapine users were able to achieve positive clinical outcomes through decreased Positive and Negative Syndrome Scale (PANSS) and the declining RU suggesting that off-label treatment of mental health conditions with olanzapine could be cost-effective.

Several limitations existed with this study. First, the authors note that there could have been undetected or unaccounted changes in the health care policy that they were unaware of which could have resulted in decreased RU. Second, the population included in the study was eligible to receive treatment through the BHCS because of the severity of illness, therefore it may be relatively easier to show clinical improvement and decreased RU. Another limitation stated by the authors is the lack of control group due to which one cannot establish causality between olanzapine use and the decreased RU.

Apart from the limitations stated by the authors, the study also lacks generalizable results since the study consists of severely ill patients who are eligible to receive state provided financial coverage in one small health system in California. These patients are a small subset of the population and therefore the results cannot be extrapolated to a larger population. As with the previous studies, the sample also consisted primarily of a young group of patients. Despite the

limitations, the study does provide evidence that olanzapine use shifts costs away from hospitalization and emergency costs towards medication and outpatient costs.

The three studies that have evaluated RU among off-label AAPs users have found mixed results. One study showed that RU varied by the specific AAPs used with quetiapine being the preferred drug of choice to decrease hospitalizations and emergency department visits (Lage et al., 2006). The other two studies concluded that AAPs use does decrease inpatient and emergency visits but reached different conclusions regarding outpatient visits. Al-Zakwani et al. reported lower outpatient visits while Del Paggio et al. reported an increase in the number of outpatient services and costs.

2.2 Gaps in Literature

To the best of our knowledge, there are only three studies that have assessed RU among those who are using AAPs for off-label treatment of mental health conditions. All used data from private claims data or from a specific county operated mental health care system. By using data from private sources, the results are only applicable to a similar segment of the population. None of the studies evaluated RU from a public payer perspective.

Another gap in the literature is that all the studies either exclusively included patients less than 65 years of age or had minimal patients over 65 years of age since the source of data was private payers and not Medicare. As discussed in the earlier section, elderly patients over 65 years are most vulnerable among adults to the adverse effects of AAPs and this cohort of patients are usually excluded from studies. There is a need to conduct studies that focus on elderly AAPs users and assess RU pattern and risks in this cohort.

Another feature common to all three studies is that none of them evaluated RU solely among off-label AAPs users. The studies included patients with a myriad of mental health conditions including schizophrenia and bipolar disorder for which treatment with AAPs is FDA approved. No study has assessed RU among patients who are solely using the AAPs for off-label treatment.

Finally, as mentioned earlier, all three studies used data from private sources and therefore the results are not generalizable to a large population.

Chapter 3: Resource Utilization Patterns and Costs Associated with Off-label Use of AAPs in a Community-Dwelling Adult Population

Specific Aim I: Examine RU patterns and estimate costs among off-label AAPs users and non-users in a nationally representative sample

3.1 Methods

Study Design: A retrospective cross-sectional study was conducted using a publicly available national database to compare RU and costs among respondents using AAPs off-label to treat mental health conditions to those not using AAPs.

Data Source: This retrospective study was done using Medical Expenditure Panel Survey (MEPS) data that is sponsored by the Agency for Healthcare Research and Quality (AHRQ). MEPS is a nationally representative survey of civilian non-institutionalized US individuals and households, that collects information on patient demographics, employment, income, access to health care, health care use, medical expenditures, insurance coverage and sources of payment. MEPS can be used to produce national estimates of health care RU and expenditures. Household survey data are collected by computer-assisted personal interviews. Each year MEPS enrolls a new sample of households which is followed for 2.5 years over five interviews. This study utilized the household component of the MEPS data from 2009-2013. Five years of data were pooled to increase the sample size and reduce the standard error of the estimates. Since each year represents a nationally representative sample for that given year, respondents were included twice if they completed all five panel interviews during the span of two consecutive years. Even though this led to correlation in the data from year to year, specifying the stratum and the primary sampling unit (PSU) in the variance estimation accounted for any correlation. All information on patient

characteristics, RU and costs were obtained from the Full-Year Consolidated files, information on chronic conditions was obtained from the Medical Conditions files and information on medication use was obtained from the Prescribed Medicines event files.

Study sample: The study included all MEPS respondents 18 years and older who reported a diagnosis for a mental health condition for which treatment with AAPs would be off-label. That is, all patients with schizophrenia or bipolar disorder were excluded. In this study, mental health conditions were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Since only schizophrenia (ICD-9-CM: 295) and bipolar disorder (ICD-9-CM: 296) have received approval to be treated with AAPs, all other mental health conditions (ICD-9-CM: 290-319) were defined as conditions for which treatment with AAPs would be off-label and were included in the study sample.

Exposure: The study sample was categorized into users and non-users based on their AAPs use. Respondents were categorized as users if they had at least two claims for an AAP within the same year. AAPs medications were identified using the therapeutic sub-classification variable (TC1S1_1) in the Prescribed Medicines file.

Independent variables: The primary independent variable was AAPs use. Covariates included age, gender, race, education, marital status, insurance, income level and the Charlson Comorbidity Index (CCI) score. The demographic variables were categorized as following: age in two categories of 18-64, 65 and older; race in three categories of White, Black and other; education in three categories of high school or less, some college or more and never went to school; marital status in four categories of married, widowed, divorced/separated, and never married; insurance in three categories of private, public and uninsured; and income level in four categories of poor, low,

medium and high. Comorbidities were measured using the CCI, a continuous variable, which was calculated using ICD-9-CM codes.

Outcomes: The primary outcome of interest in the study was select RU (office-based medical provider visits, outpatient visits, inpatient visits and emergency room visits) for the given year. The secondary outcome of interest was the person-level mean health care expenditure per year. Drug expenditures were included in the expenditure variable. In MEPS, expenses are defined as payments for care from all sources. These include patient out-of-pocket and all third party payers (e.g., Medicare, Medicaid, private insurance, others).

Statistical analyses: Demographic characteristics of AAPs users and non-users were compared using chi-square tests. The unadjusted mean RU and expenditures for users and non-users were compared using t-tests. Multivariable logistic regression models were used to assess the association between AAPs use and RU. Several regression models were developed to model overall RU, inpatient use, office-based medical provider use, outpatient use and emergency room use. The variables controlled for in the regression models included age, gender, race, education, marital status, insurance, income and CCI.

Generalized linear model (GLM) was used to estimate the adjusted medical costs associated with off-label use of AAPs. Due to the presence of excessive zero costs and highly skewed data, traditional ordinary least square (OLS) estimates are ineffective in modeling costs data. Even though log-transformed OLS can account for skewed data, the retransformation to the original scale makes interpretation of the estimates difficult. Additionally, heteroscedasticity in the data might also lead to biased estimates. Therefore a GLM model with the appropriate link function is more appropriate to model cost data as it relaxes the assumptions of normality and homoscedasticity. A GLM with gamma distribution and a log link was used to estimate costs.

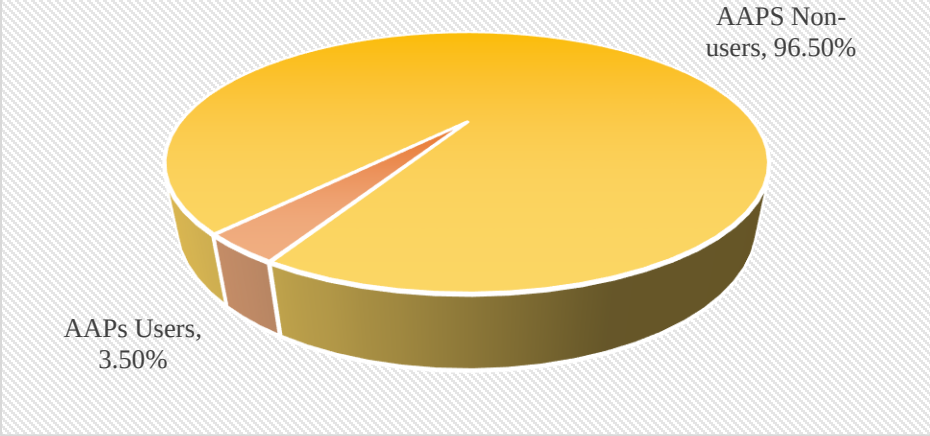
Since the number of observations with zero costs was less than 6% in our study a 2-part model was not used.

To generate national estimates, the complex sampling design of the MEPS dataset was taken into account by using person-level weights, primary sampling unit and variance estimation strata. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC) and STATA software version 12. A p-value < 0.05 was considered statistically significant.

3.2 Results

Of the survey respondents in 2009-2013, 18,246 (weighted N= 40,939,089) respondents were adults 18 years and older who reported being diagnosed with an off-label mental health condition. This sample of MEPS respondents had positive weights and was included in the final analysis. Of these, 3.5% (weighted n=1,422,307) were AAPs users and the remaining 96.5% were non-users (Figure 1).

Figure 1: Prevalence of AAPs use in respondents without FDA approved indications



Study population characteristics: Table 2 reports the demographic characteristics of survey respondents included in the study. Statistical differences among users and non-users were found for race, education, marital status, insurance, income level and the CCI score. AAPs users were more likely to be black (15.80%), high school educated or less (55.64%), never married (34.31%), with public insurance (46.41%) and poor income (37.09%) as compared to the non-users. The CCI score was significantly higher (1.24±0.05) among users.

Table 2: Demographic characteristics of study population

Characteristic	AAPs users (%) (Unweighted N =770) (Weighted N=1,422,307)	AAPs non-users (%) (Unweighted N=17,476) (Weighted N=39,516,782)	p-value
Age			0.2904
18-64	82.36	79.88	
65+	17.64	20.12	
Gender			0.1561
Male	40.77	36.36	
Female	59.23	63.64	
Race			**<0.0001**
White	79.34	88.07	
Black	15.80	7.18	
Other	4.86	4.75	
Education			**<0.0001**
High school or less	55.64	43.22	
Some college or more	43.36	56.62	
Never been to school	1.00	0.16	
Marital Status			**<0.0001**
Married	30.86	48.00	
Widowed	11.11	8.42	
Divorced/separated	23.72	19.81	
Never married	34.31	23.77	
Insurance			**<0.0001**
Private	47.04	66.80	
Public	46.41	22.90	
Uninsured	6.55	10.30	
Income			**0.0001**
Poor	37.09	19.55	
Low	16.58	13.63	
Medium	22.25	30.18	
High	24.08	36.64	
CCI (SE)	1.24 (0.05)	1.05 (0.01)	**0.0007**

Abbreviation used: CCI, Charlson Comorbidity Index

Unadjusted RU and costs in off-label AAPs users: Respondents using AAPs had more office-based provider visits, emergency room visits and inpatient visits, and higher mean office-based provider, inpatient, prescription and total costs compared to non-users (Table 3). Users were estimated to have unadjusted mean total costs of $15,157 per respondent relative to non-users of

$7,304 (p<0.0001). Therefore, the total cost for people 18 years and older with an off-label mental health condition using AAPs (weighted N=1,422,307), was estimated to be $21.5 billion.

Table 3: Mean utilization and expenditures among respondents by AAPs use

Utilization Measure (#)	**AAPs users Mean (SE)**	**AAPs non-users Mean (SE)**	**p-value**
Office based provider visits	15.1 (1.02)	9.93 (0.19)	**<0.0001**
Outpatient visits	1.20 (0.26)	0.84 (0.05)	0.1875
Emergency room visits	0.49 (0.05)	0.33 (0.01)	**0.0022**
Inpatient visits	0.37 (0.05)	0.17 (0.01)	**<0.0001**
Expenditure Measure ($)	**AAPs users Mean (SE)**	**AAPs non-users Mean (SE)**	**p-value**
Office based provider visits	2,474 (186)	1,953 (47)	**0.0063**
Outpatient visits	844 (144)	673 (37)	0.2562
Emergency room visits	437 (72)	311 (11)	0.0800
Inpatient visits	4,887 (900)	2,223 (98)	**0.0033**
Prescription	6,516 (423)	2,144 (5)	**<0.0001**
Total	15,157 (1226)	7,304 (151)	**<0.0001**

Abbreviation used: SE, standard error

Adjusted RU in off-label AAPs users: After adjusting for covariates, off-label AAPs user was associated with greater resource utilization (Table 4). The odds of having an office based outpatient or inpatient visit were significantly higher among respondents who used AAPs off-label to treat their mental health conditions as compared to respondents not using AAPs. The odds of using any health care resource among users were also twice the odds of non-users (p=0.0006).

Table 4: Adjusted regression model estimates for resource utilization by AAPs use

Resource Utilization	**OR**	**Lower 95%CI**	**Upper 95% CI**	**p-value**
Office based outpatient visits	2.47	1.55	3.92	**0.0001**
Outpatient visits	1.28	0.96	1.71	0.0873
Emergency room visits	1.09	0.87	1.38	0.4476
Inpatient visits	1.63	1.26	2.1	**0.0002**
Any utilization	2.42	1.46	4.03	**0.0006**

Abbreviation used: OR, odds ratio; CI, confidence interval

Adjusted costs in off-label AAPs users: Office based visits and prescription costs were found to be significantly higher among those using AAPs as compared to non-users ($p<0.0001$). Inpatient and prescription costs were the major contributors to costs.

Table 5: Adjusted cost estimates for respondents with off-label mental health conditions

Resource Utilization	**AAPs Users**		**AAPs non-users**		**p-value**
	Mean ($)	SE	Mean ($)	SE	
Office based outpatient visits	1,943	189	1,436	107	**<0.0001**
Outpatient visits	1,632	324	1,457	235	0.4255
Emergency room visits	1,722	280	1,438	122	0.1935
Inpatient visits	24,543	4580	18,839	2372	0.0643
Prescription	4,153	354	1,252	88	**<0.0001**

3.3 Discussion

The sample used in these analyses was MEPS respondents greater than 18 years with mental health conditions not approved by the FDA to be treated with AAPs. Based on this study, 3.5% of the non-institutionalized US population with conditions other than schizophrenia or bipolar disorder was AAPs users. The typical AAPs user was a 18-64 year old white female with a high school education, never married with a very low income. Compared to those not using AAPs, users also had higher proportion of respondents who were on public insurance and had higher comorbidity index. These results were similar to what was reported by Domilano & Swartz in a study which examined changes in prevalence of AAPs use from 1996/1997 to 2004/2005 in a MEPS sample. The study reported AAPs users to be primarily 18-64 year old, white females with low family income and public insurance (Domilano & Swartz, 2008).

This study found that AAPs users had higher odds of having an office-based outpatient and inpatient visit after adjusting for covariates age, gender, race, education, income, insurance, marriage status and comorbidity index. Users also had higher odds of having any RU as compared to non-users. Office based visit costs and prescription costs were found to be significantly higher among AAPs users as compared to non-users ($p<0.0001$).

These results were not similar to what was reported in the study by Al-Zakwani et al. in a private health plan sample comprised 6 to 65 year olds with any mental health conditions (Al-Zakwani et al., 2003). They reported AAPs users to have fewer office visits, hospital admissions, and hospital-based outpatient visits compared to those using typical AAPs. These differences could be due to the different sample (private health plan beneficiaries' vs. survey respondents) and different comparator groups (typical antipsychotic users vs. respondents with mental health conditions without AAPs claims). In the study by Lage et al., the authors found that among individuals with dementia, depression, schizophrenia and bipolar disorder, patients using olanzapine and risperidone experienced significantly higher rates of hospitalizations and emergency room visits from baseline to post treatment and patients using quetiapine experienced significantly lower hospital admission rates and emergency visits from baseline to post treatment (Lage et al., 2006). Our study reflects the pattern that was observed in the olanzapine/risperidone cohort but no conclusions can be determined until the RU pattern by AAPs agent is determined.

Even though AAPs use has evidence for efficacy in patients with schizophrenia and bipolar disorders (Maglione et al., 2011) and may improve quality of life due to lower risk of EPS and related disorders, these benefits may be overshadowed by their propensity to cause metabolic risks (Gareri et al., 2014). Therefore the use of these agents in treating conditions not FDA approved or backed by evidence such as OCD and PTSD, may only further increase health care RU and costs.

With increasing affordability as more of these drugs come off patent, there could be a further increase in the rate of use of AAPs to treat off-label mental health conditions.

On the other hand, restrictive policies introduced by regulatory bodies, such as the CMS partnerships to decrease AAPs use in elderly population, aim to decrease the use of AAPs especially in a vulnerable population. These steps are backed by the premise that most off-label use is not backed by clinical evidence. Even though these steps are undertaken to ensure the safety of the patients, it raises the question of whether these policies are also restricting access to much needed medications for certain patients.

Limitations

This study provided an initial insight into the pattern of RU and costs among off-label AAPs users in a non-institutionalized US population. GLM was used to describe costs controlling for differences between users and non-users. There are also some limitations in the study. First, the cross-sectional study design does not help establish causality; it can only identify an association between off-label AAPs use and higher RU and costs. It is therefore important to conduct a longitudinal cohort study design to establish a causal relationship. Second, the users and non-users were different in their baseline characteristics since this was not a randomized controlled trial. We tried to address this limitation within the scope of the project by controlling for such variables in the regression models even though we could not control for variables such as severity of disease. Third, since MEPS is collected from self-reported surveys, there is the possibility of selection and recall bias. Since mental health conditions are often associated with stigma, patients may underreport the presence of these conditions. This could potentially underestimate the prevalence of mental health conditions despite the presence of medication claims. On the other hand, patients who are active participants in their health may be more likely to be a MEPS respondent leading to

selection bias. Fourth, MEPS data only allows for identification of ICD-9 codes up to three digits; therefore patients with bipolar disorder and depression (identified using ICD-9-CM: 296) were grouped in one category thereby overestimating the FDA approved use. A longitudinal study using claims data (described in the next section) was done to address some of these limitations.

Chapter 4: Methods

This chapter describes the methods used to address specific aims II, III, IV and V. It includes details on data source, study design, study population, variables and statistical analyses.

Data source

The data used in this project was obtained from the Centers for Medicare and Medicaid Services (CMS). The study employed data from 2008 to 2010 Chronic Condition Data Warehouse (CCW) Medicare files which are managed by the Research Data and Assistance Center (ResDAC). A random sample of one million beneficiaries and their beneficiary summary, inpatient, outpatient and prescription claims were used in the study. Beneficiary information was de-identified and a unique patient identification number was used to link the beneficiaries across files.

This particular data source was used for this study since Medicare is a good source of information for people over 65 years. Using Medicare data enables capturing real data on an elderly population who are normally excluded from adult studies and adults over 18 years who are eligible for Medicare due to their disability. Additionally, the use of a claims database removes the potential for recall and self-reported bias that are associated with survey data.

A number of files were used to meet the study objectives. The Master Beneficiary Summary File (MBSF) was used to identify demographic and enrollment eligibility information. The inpatient, outpatient and prescription drug event (PDE) files were used to identify claims for RU and to compute costs. The CCW Chronic Conditions File and Other Chronic Conditions file were used to identify comorbidities including mental health conditions. The files and the variables that have been used are described below.

Table 6: Master Beneficiary Summary File (MBSF)

SAS Variable Name	**Description**
BENE_ID	An unique encrypted beneficiary identification number that was used to link the beneficiaries across files
AGE	Beneficiary's age at the end of the year
SEX	Beneficiary's gender
RACE	Beneficiary's race was categorized as White, Black and Others
ESRD_IND	Indicator of End-stage Renal Disease (ESRD)
CREC	Current reason for Medicare entitlement, used to identify beneficiaries with disabilities
A_MO_CNT	Count of months with Part A coverage, used to identify continuous Part A enrollment
B_MO_CNT	Count of months with Part B coverage, used to identify continuous Part B enrollment
PLNCOVMO	Count of months with Part D coverage, used to identify continuous Part D enrollment
CNTRCT	Type of Part D contract, used to identify those with stand-alone drug plan to serve as proxy for fee-for-service beneficiaries
HMO_MO	Number of months of HMO coverage, used to identify beneficiaries with fee-for-service versus HMO coverage

Table 7: Inpatient and Outpatient files

SAS Variable Name	Description
BENE_ID	An unique encrypted beneficiary identification number that was used to link the beneficiaries across files
CLM_ID	Unique encrypted claim identification number used to identify duplication of claims
PMT_AMT	Amount paid by Medicare for the services covered by claim
UTIL_DAY	Number of days utilized by claims, used in calculating amount paid by Medicare not included in the claim payment amount
PER_DIEM	Pass through amount not included in the claim payment amount
PRPAYAMT	Amount paid by primary payer if not Medicare
DED_AMT	Beneficiary deductible amount
COIN_AMT	Beneficiary coinsurance amount
BLDDEDAM	Beneficiary blood deductible liability amount
ADMTG_DGNS_CD	Admitting diagnosis ICD-9-CM code
PRNCPAL_DGNS_CD	Primary diagnosis ICD-9-CM code
ICD_DGNS_CD1-25	Claim diagnosis code

Table 8: Part D Event (PDE) file

SAS Variable Name	**Description**
BENE_ID	An unique encrypted beneficiary identification number that was used to link the beneficiaries across files
PDE_ID	Unique encrypted prescription claim identification number used to identify duplication of claims
SRVC_DT	Date of service of prescription claim
PTPAYAMT	Amount paid by patient for claim
CPP_AMT	Amount paid by Medicare for claim
GNN	Generic name of drugs

Table 9: MBSF Chronic Conditions and Other Chronic Conditions files

SAS Variable Name	Description
BENE_ID	An unique encrypted beneficiary identification number that was used to link the beneficiaries across files
AMI	Acute myocardial infarction
ALZ	Alzheimer's disease
CHRNKIDN	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CHF	Congestive heart failure
DIABETES	Diabetes Mellitus
RA_OA	Rheumatoid and Osteoarthritis
CNCRBRST	Breast cancer
CNCRCLRC	Colorectal cancer
CNCRPRST	Prostate cancer
CNCRLUNG	Lung cancer
DEPRESSN	Depression
ANXI_MEDICARE	Anxiety disorders
AUTISM_MEDICARE	Autism spectrum disorders
BIPL_MEDICARE	Bipolar disorder
ACP_MEDICARE	ADHD, conduct disorders and hyperkinetic syndrome
INTDIS_MEDICARE	Intellectual disabilities and related conditions
LEADIS_MEDICARE	Learning disabilities
OTHDEL_MEDICARE	Other developmental delays
PSDS_MEDICARE	Personality disorders
PTRA_MEDICARE	Post-traumatic stress disorder
SCHI_MEDICARE	Schizophrenia
SCHIOT_MEDICARE	Schizophrenia and other psychotic disorders

Approvals

The proposal for this project was approved by the Virginia Commonwealth University institutional review board (IRB) under expedited review. In addition, the proposal was also approved by ResDAC and CMS.

4.1 Specific Aim II

Specific Aim II: Evaluate the prevalence of off-label and on-label use of AAPs and describe patient characteristics in a Medicare population.

Study design

A retrospective, cross-sectional study was employed using Medicare secondary databases to compute the prevalence of off-label and on-label use of AAPs. AAPs users were identified and the prevalence of off-label and on-label use in 2008, 2009 and 2010 was computed.

Population of interest

For the first Specific Aim, the population of interest was AAPs users 18 years and older within each year. Beneficiaries were considered to be AAPs users if they had at least two claims (>1 day and < 60 days apart) for AAPs during the year. A minimum of two claims for the same agent was chosen to eliminate beneficiaries who had been given a one-time dose as part of their emergent care. Only AAPs with registered National Drug Codes (NDC) numbers before January 1, 2008 were included in the study. The drugs and their FDA approved indications have been denoted in Table 10 as obtained from the FDA website

https://www.accessdata.fda.gov/scripts/cder/drugsatfda/

Table 10: List of atypical antipsychotics agents of interest

Drug Name	**FDA approved indications before January 1, 2008**
Olanzapine (Zyprexa)	-Oral: Schizophrenia, Bipolar disorder (monotherapy and in combination with lithium or valproate) -IM: agitation associated with schizophrenia or bipolar mania
Quetiapine (Seroquel)	Schizophrenia, Bipolar disorder (Depression, mania, maintenance)
Risperidone (Risperdal)	Schizophrenia, Bipolar (manic or mixed) disorder (monotherapy and in combination with lithium or valproate)
Aripiprazole (Abilify)	Schizophrenia, Bipolar (Manic or mixed), adjunctive therapy to Major Depressive disorder (adjunct to AD)
Ziprasidone (Geodon)	Oral: Schizophrenia, Bipolar Mania IM: Acute agitation in schizophrenic patients

IM: Intra-muscular AD: Anti-depressants

Off-label use: For this study, an indication-based definition of off-label use was applied i.e., indications that were not approved by the FDA to be treated with AAPs were categorized as off-label use. All the AAPs of interest have been approved by the FDA for the treatment of schizophrenia and bipolar disorder. Therefore use of AAPs in absence of these two indications was deemed off-label use. Claims for mental health conditions were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. These diagnosis claims were identified from the principal diagnosis, admitting diagnosis or any of the 25

ICD-9-CM variables in the inpatient and outpatient file or from the Other Chronic Conditions file. All AAPs users who had at least one inpatient or two outpatient claims for schizophrenia (ICD-9-CM: 295.xx) and/or bipolar disorder (ICD-9-CM: 296.0, 296.1, 296.4 – 296.9) were classified as FDA approved or on-label users. All other AAPs users were considered off-label users.

Statistical Analysis

Descriptive analysis of the study population was conducted. Continuous variables were described using means and standard deviation and categorical variables were described using counts and percentages. Prevalence of off-label and on-label use of AAPs for each year was calculated as follows:

$$Offlabel\ Use = 100\ X\ \frac{Number\ of\ beneficiaries\ without\ Schiophrenia\ or\ Bipolar\ disorder}{Number\ of\ beneficiaries\ using\ AAPs}$$

$$Onlabel\ Use = 100\ X\ \frac{Number\ of\ beneficiaries\ with\ Schiophrenia\ or\ Bipolar\ disorder}{Number\ of\ beneficiaries\ using\ AAPs}$$

The pattern of use of AAPs and indications for use were reported as percentages along with the characteristics of beneficiaries using AAPs off-label and on-label. All statistical analyses were conducted using SAS 9.4.

4.2 Specific Aim III and IV

Specific Aim IIIA: Compare all-cause RU and costs between Medicare beneficiaries using AAPs and those not using AAPs for off-label treatment of mental health conditions.

Specific Aim IIIB: Compare mental health RU and costs between Medicare beneficiaries using AAPs and those not using AAPs for off-label treatment of mental health conditions.

Specific Aim IVA: Compare all-cause RU and costs between Medicare beneficiaries using AAPs and those not using AAPs for on-label treatment of mental health conditions.

Specific Aim IVB: Compare mental health RU and costs between Medicare beneficiaries using AAPs and those not using AAPs for on-label treatment of mental health conditions.

Study design and index period

For Specific Aims III and IV a retrospective cohort study design was employed using Medicare 2008-2010 data. For this section of the study January 1, 2009 – December 31, 2009 was defined as the index period enabling the use of 12 months of baseline and 12 months of follow up period.

Eligibility criteria

From the random sample of one million beneficiaries only those with fee-for-service benefit and continuous Medicare enrollment from 2008-2010 across Part A, Part B and Part D were included. Fee-for-service beneficiaries were identified using the CNTRCT and HMO_IND

variables from the MBSF files. Beneficiaries with a "Stand Alone Prescription Drug Plan" with zero months of HMO coverage were considered to be fee-for-service beneficiaries. To have continuous enrollment beneficiaries had to have 12 months of Part A, B and D access as denoted in the A_MO_CNT, B_MO_CNT and PLNCOVMO variables for each year from January 1, 2008 to December 31, 2010.

Population of interest

The population of interest was Medicare beneficiaries 18 years and older with a mental health condition. Even though Medicare is primarily for patients over 65 years of age, beneficiaries who are 18 to 64 years of age were also included since severe mental illness is prevalent among Medicare beneficiaries under 65 years who are entitled to Medicare due to a disability. According to the Social Security Administration around 37% of all the Medicare disabled beneficiaries have severe mental disorders (SSA, 2011). The presence of mental health conditions was identified using one of two methods:

(3) Beneficiaries had to have at least one inpatient or two outpatient mental health claims between January 1, 2008 and December 31, 2010. Mental health claims were identified using ICD-9-CM codes. These claims were identified from the principal diagnosis, admitting diagnosis or any one of the 25 ICD-9-CM variables in the inpatient and outpatient files. Mental health claims were identified using ICD-9-CM codes 290.xx – 319.xx as presented in Table 11.

Table 11: List of ICD-9-CM codes for mental health conditions from inpatient/outpatient files

ICD-9-CM	Condition	ICD-9-CM	Condition
290.xx	Dementia	298.xx	Non-organic psychoses
291.xx	Alcoholic psychoses	299.xx	Psychoses with childhood origin
292.xx	Drug psychoses	300.xx	Anxiety and neurotic disorders
293.xx	Transient organic psychoses	301.xx	Personality disorders
294.xx	Other organic psychoses	302.xx	Psychosexual disorders
295.xx	Schizophrenia	303.xx – 305.xx	Psychoactive substance abuse disorders
296.0, 296.1, 296.4-296.9	Bipolar disorder	306.xx – 310.xx	Other mental disorders
296.2, 296.3, 311.xx	Depression	312.xx – 316.xx	Other child and adolescent origin mental disorders
297.xx	Paranoid states	317.xx – 319.xx	Mental Retardation

(ii) Beneficiaries who were flagged as having specific mental health conditions in the MBSF Other Chronic Conditions file were also included in the study sample. Medicare uses this file to flag beneficiaries who have had at least one inpatient or two outpatient claims for a particular condition since the beneficiary enrolled in Medicare. The conditions identified from this file are

presented in Table 12. The variables in the Other Chronic Conditions file were reassigned to different categories of mental health conditions to match the categories described in Table 11.

Table 12: List of mental health conditions identified from Other Chronic Conditions File

Variable (As denoted in Medicare)	**Condition (Reassigned variable names)**
Depression; Depressive disorders	Depression
Alzheimer's disease	Dementia
Anxiety disorders	Neurotic disorders
Autism spectrum disorders	Psychoses with childhood origin
Bipolar disorder	Bipolar disorder
ADHD, conduct disorders; Learning disabilities; Other developmental delays	Other child and adolescent origin mental disorders
Intellectual disabilities	Mental retardation
Personality disorders	Personality disorders
Post-traumatic stress disorder	Other mental disorders
Schizophrenia; Schizophrenia and other psychotic disorders	Schizophrenia

Study groups

The population of interest was then divided into two groups for each Specific Aim. Beneficiaries who had a diagnosis of schizophrenia and/or bipolar disorder were categorized as the *on-label cohort*. Beneficiaries who did not have claims for schizophrenia and/or bipolar disorder were categorized as the *off-label cohort*. The off-label cohort was used in the analysis of Specific Aim II and the on-label cohort for Specific Aim III.

Exposure variable

The exposure of interest for Specific Aims III and IV was AAPs use during the index period. Beneficiaries were considered to be AAPs users if they had at least two claims (>1 day and < 60 days apart) for the same antipsychotic agent between January 1, 2009 and December 31, 2009. The AAPs of interest were aripiprazole (Abilify), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal) and ziprasidone (Geodon) and were identified using their generic names. The off-label cohort and the on-label cohort were further divided based on their AAPs use. The groups identified were:

Specific Aim 2: Off-label AAPs user and Off-label AAPs non-user

Specific Aim 3: On-label AAPs user and On-label AAPs non-user

Exclusion criteria

Beneficiaries who met the following criteria were excluded from the study.

1) Beneficiaries who had claims for both an off-label and on-label mental health condition were excluded from the study analysis in order to create two mutually exclusive groups. These beneficiaries were excluded since there was no conclusive evidence to identify whether or not the AAPs were being used to treat on-label conditions.

2) Beneficiaries with prescription claims for asenapine (Saphris), lurasidone (Latuda) and iloperidone (Fanapt) were excluded from the study since these agents received FDA approval during and not at the beginning of the index period. Similarly beneficiaries with claims for olanzapine/fluoxetine (Symbyax) and 47aliperidone (Invega) were excluded from the study since

these agents received approvals for only one of the two FDA approved conditions (schizophrenia or bipolar disorder).

3) Among beneficiaries identified as AAPs non-users, those with prescription claims for AAPs of interest in 2008 were excluded to ensure that the non-users were truly not using AAPs during the study period.

After the exclusions were applied to the patient population, the final groups were identified for propensity score matching (Figure 2).

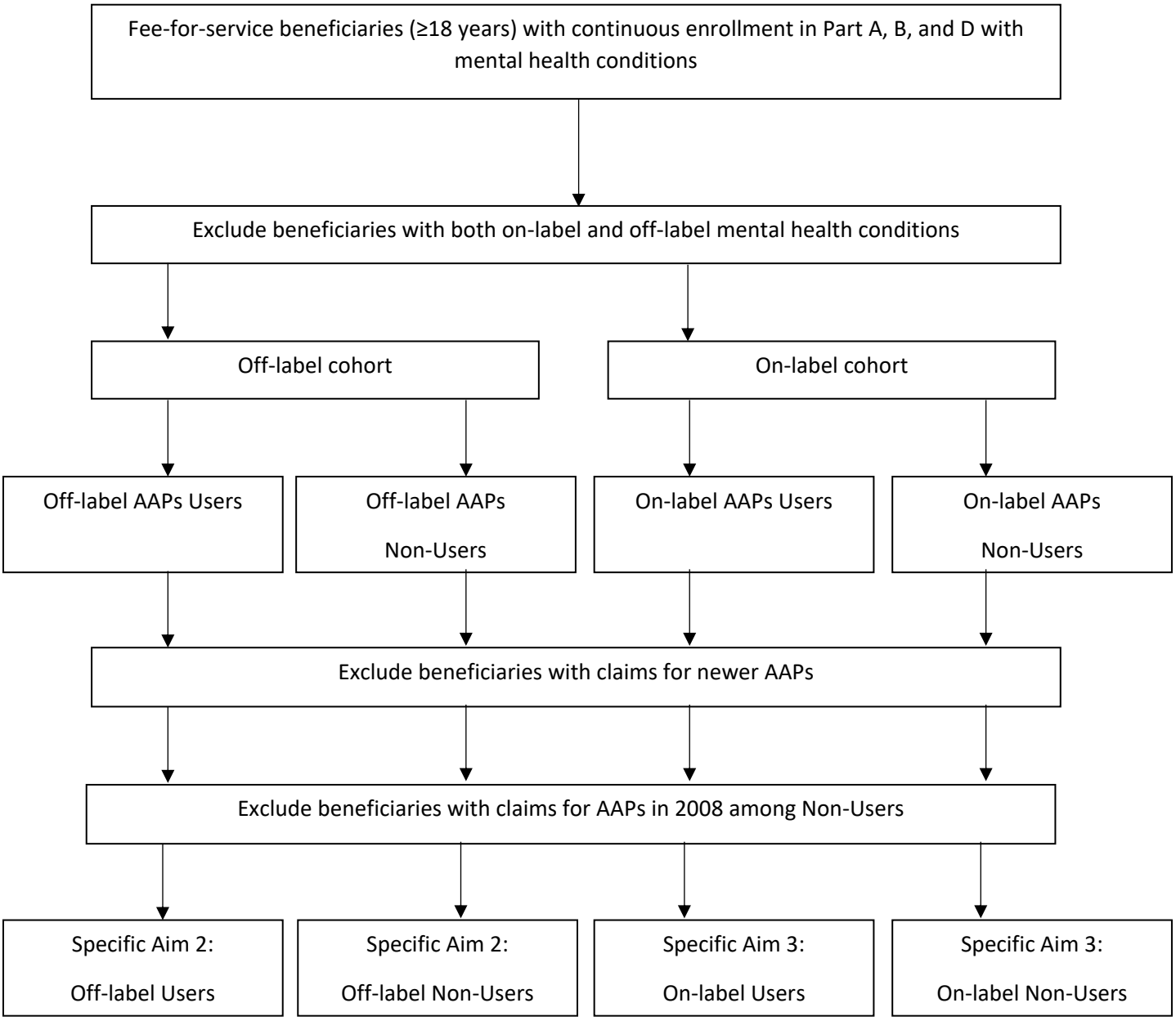


Figure 2: Flowchart of inclusions and exclusions from original sample

4.3 Specific Aim V

Specific Aim V: Evaluate differences in RU and associated costs in Medicare beneficiaries using AAPs and those not using AAPs to treat specific mental health conditions.

After the eligible population of interest was identified as described for Specific Aims 3 and 4 the study groups for Specific Aim 5 were identified.

Study groups:

The population of interest that met the eligibility criteria was further divided into mutually exclusive groups based on the presence of certain mental health diagnoses. These disease states were identified using ICD-9-CM codes: schizophrenia (ICD-9-CM: 295.xx), bipolar disorder (ICD-9-CM: 296.0, 296.1, 296.4 - 296.9), depression (ICD-9-CM: 296.2, 296.3, 311.xx), dementia (ICD-9-CM: 290.xx, 294.00, 294.10, 294.11, 294.20, 294.21, 294.8), post-traumatic stress disorder (ICD-9-CM: 309.81) and obsessive compulsive disorder (ICD-9-CM: 300.3). The *exposure of interest* was AAPs use as described earlier and the groups were categorized into AAPs users and non-users.

Matching: To control for observable differences, the groups were matched using propensity score matching. For Specific Aim III, the off-label users and non-users were matched, for Specific Aim IV the on-label users and non-users were matched, and for Specific Aim V, the AAPs users and non-users within each study group were matched. Matching was used to address potential selection bias and confounding between the study groups. The propensity score or the

probability of having prescription claims for AAPs of interest was estimated using logistic regression wherein AAPs use was coded as a dummy outcome variable.

Covariates: The covariates in the logistic regression model included age, gender, race, end-stage-renal-disease indicator, disability indicator, number of unique medications, Charlson-Comorbidity Index (CCI), mental health conditions, and non-mental health inpatient and outpatient visits during the pre-index period.

Age:

This variable was identified from the MBSF file and was coded as a continuous variable based on the age of the beneficiary at the end of 2008. Age, found to affect RU in patients with mental health disorders (Ginsberg et al., 1997, Twomey et al., 2015), was also coded as categories "65 years and under" and "Greater than 65 years" for descriptive purposes.

Gender:

This variable was identified from the MBSF file and was coded as a dummy variable. Men and women had different comorbid mental health condition profiles (Sajatovis et al., 1997, Dagher et al., 2015, Twomey et al., 2015) therefore the variable was retained in the model. For example, the study by Twomey et al. reported that adult female patients with mental disorders were associated with increased health service utilization.

Race:

This variable was identified from the MBSF file and was collapsed to variables "White", "African American" and "Others". Disparities in mental health care utilization among the different races, especially among non-white ethnicities, were reported in previous studies (Wu et al., 2012,

Twomey et al., 2015). In order to control for any disparities, this variable was introduced in the propensity model.

End-Stage-Renal-Disease (ESRD):

This variable identified from MBSF was coded as a dummy variable. This variable denotes if the beneficiary has been diagnosed with ESRD, which could also be the reason they are eligible for Medicare even if they are younger than 65 years. ESRD is associated with increased health care costs and RU (Khan et al., 2002; Blanchette et al., 2015) and accounted for 7.1% of overall Medicare paid claims (USRDS, 2014).

Disability:

This variable was identified from the MBSF file and was coded as a dummy variable to indicate presence or absence of disability. This was an important variable to include since beneficiaries who are eligible for Medicare due to their disability versus their age might have different RU compared to Medicare beneficiaries over 65 years of age (Ettner, 1998).

Unique number of medications:

This quantitative variable was calculated from the PDE file using prescription claims data. Unique medications were identified using the GNN variable which lists the drug in its generic name. This is an important variable to control for since increased medication use such as antidepressant and typical antipsychotic use has led to increased RU (Sheehan et al., 2012).

Charlson Comorbidity Index:

Comorbidity was found to be significantly associated with RU among patients with mental disorders (Twomey et al., 2015) and therefore was added to the propensity model. The CCI

variable was a continuous variable that assigned scores to each beneficiary based on the presence of 17 comorbid conditions. The conditions were identified using inpatient claims, outpatient claims, the Chronic Conditions file, and the Other Chronic Conditions CCW files using ICD-9-CM codes (Table 13). This variable was used in retrospective claims database studies to account for beneficiary comorbid condition, disease severity and mortality risk (Charlson et al., 1987). Even though several adaptions of this variable had been made, Deyo et al. adapted one based on ICD-9-CM codes for administrative data (Deyo et al., 1992) and was used in this study. For each beneficiary, corresponding scores were identified for each comorbid condition and the sum of the scores was the assigned CCI score. For example, a diabetic (CCI score of 1) patient with AIDS (CCI score of 6) would have a total CCI score of seven.

Mental health conditions:

The different mental health conditions were included as dummy variables in the regression model. The conditions were identified from the inpatient and outpatient claims (Table 11) and from the CCW files (Table 12). Mental health comorbidities were reported to be important predictors of RU (Twomey et al., 2015; Wu et al., 2012; Kawatkar et al., 2014) and were included as dummy variables in the matching regression model.

Baseline RU:

The number of outpatient visits and inpatient visits were included as two separate quantitative variables based on claims data from 2008. Baseline RU was used as a proxy variable for severity of illness (Crivera et al., 2011; He at al., 2015).

Table 13: Conditions included in Charlson Comorbidity Index (CCI)

Medical Condition	**ICD-9-CM codes**	**Score**
Myocardial infarction	410,412	1
Congestive heart failure	428	1
Peripheral vascular disease	441, 443.9, 785.4	1
Cerebrovascular disease	430-438	1
Chronic obstructive pulmonary disorder	490-496, 500-505, 506.4	1
Dementia	290	1
Paralysis	342, 344.1	1
Diabetes	250.0-250.3, 250.7	1
Chronic liver disease and cirrhosis	571.2, 571.4-571.6	1
Ulcers	531.0-531.7, 532.0-532.7, 533.0-533.7, 534.0-534.7	1
Rheumatoid arthritis	714.81, 725, 710, 710.1, 710.4, 714.0-714.2	1
Diabetes with sequelae	250.4-250.6	2
Chronic renal failure	582,585, 586, 588, 583.0-583.7	2
Any malignancy	140-172.9, 174-195.8, 200-208.9	2
Moderate-severe liver disease	572.2-572.8, 456.0-456.1, 456.20, 456.21	3
AIDS	042-044	6
Metastatic solid tumor	196-199.1	6

After computing propensity scores, users (cases) and non-users (controls) were matched using the Greedy 5→1 technique (Parsons, Retrieved June 2016). In this method, cases and controls were initially matched based on five digits of the propensity score, then matched on four digits if appropriate matches were not found. This continued until one digit matching. This technique was chosen since it maximizes the number of matched pairs.

Propensity score matching is framed on two theoretical assumptions; the conditional independence assumption (CIA) and the common support condition (CSC) (Rosenbaum & Rubin, 1983). The CIA assumes that after the groups are matched and covariates are controlled, the groups have similar probability of receiving AAPs treatment. This assumption heavily relies on the researcher's ability to include all variables that are relevant to the decision of receiving treatment. This assumption cannot be directly tested and hence it is assumed that all relevant variables are included in the model. The CSC assumes that there is sufficient overlap among the characteristics of the cases and controls to ensure adequate matching. This assumption was tested in two ways:

1) Using a visual overlap plot of the propensity scores of the cases and controls. The scores were plotted as box-plot and histogram plots and were visually compared to determine if appropriate overlap existed.

2) By comparing the means of the propensity scores between cases and controls using the Kolmogorov-Smirnov non-parametric test to statistically determine if overlap existed.

Absolute standardized difference was used to assess balance among the covariates between cases and controls before and after matching since p-values depend on the type of statistical test used and sample size (Sullivan & Feinn, 2012). The categorical variable Race was represented

using binary indicator variables. Absolute standardized differences less than 10% indicated negligible differences between the groups.

For continuous variables the absolute standardized difference is

$$d = \frac{|\bar{x}_t - \bar{x}_c|}{\sqrt{\frac{s_t^2 + s_c^2}{2}}},$$

For categorical variables,

$$d = \frac{|p_t - p_c|}{\sqrt{\frac{p_t(1-p_t) + p_c(1-p_c)}{2}}},$$

where $\bar{x}_t$ and $\bar{x}_c$ are the means of the variables in the exposed and unexposed cohorts, s_t^2 and s_c^2 denote the variances of the variables and p_t and p_c denote the proportion in the groups.

Index dates: For the AAPs users the date of the first AAPs prescription claim received during the index period (January 1, 2009 and December 31, 2009) was assigned as the index date. AAPs non-users, since they do not have a claim for AAPs during the index period, were assigned the corresponding date as their matched case.

Outcome measure

The primary outcome of interest was all-cause RU and associated costs during the 12 month follow up period after the index date. RU included inpatient visits, hospital outpatient visits and prescription claims. The costs associated with these resources and total costs were also assessed and reported. The amounts paid by Medicare and other third party payers were obtained from the base inpatient and outpatient claims files but the beneficiary share was obtained from the Revenue Center files which were cross-linked using unique Claim IDs. A third party payer was

any entity, such as private health plans that paid for a share of the costs along with Medicare and the beneficiary. The individual cost components were computed as follows:

$$Medicare\ share = Amount\ paid\ by\ Medicare + (Diem\ amount\ paid * Number\ of\ days\ in\ claim)$$

$$Benficiary\ share = Deductible + Coinsurance + Blood\ deductible$$

$$Total = Medicare\ share + Third\ party\ payment + Benficiary\ share$$

All costs associated with emergency department visits were captured in either the inpatient or outpatient billing depending on whether the patient was admitted (inpatient) or discharged (outpatient) after their emergency visit. All positive costs were inflated to 2015 U.S. dollars using the Medical component of Consumer Price Index (CPI) obtained from the Bureau of Labor Statistics (BLS, Retrieved August 2016) (Table 14).

Table 14: Consumer Price Index (CPI) 2009-2015

	2009	**2010**	**2015**
Prescription	391	407.8	483
Medical Care Services	397	411	483.6

The secondary outcome was mental health RU and costs. Mental health inpatient and outpatient visits were identified using ICD-9-CM codes 290.xx – 319.xx in the principal diagnosis, admitting diagnosis or the first three diagnosis variables in the inpatient and outpatient files. Mental health medication costs included prescriptions for antipsychotics, antidepressants, anxiolytics, and mood stabilizers.

Statistical analyses

Descriptive analysis of the study population was done before matching. Continuous variables were described using means and standard deviations and categorical variables were described using counts and percentages. The sample after matching was described similarly and balance between covariates was assessed using absolute standardized differences.

RU and costs were assessed for 12 months after the index date and compared between users and non-users. RU was estimated as mean number of visits and compared using the paired t-test. Whenever the normality assumption was violated the Wilcoxon sign-rank test was used. Normality was assessed using Q-Q plots and Kolmogorov-Smirnov test. RU was also reported as the percentage of beneficiaries who utilized the services. Conditional logistic regression analysis was used to assess the risk of utilizing inpatient or outpatient services among users and non-users. For this analyses, separate regression models were created for inpatient and outpatient visits and the visit was dichotomized as a dummy variable.

Costs were estimated as mean inpatient, outpatient, prescription, and total costs. The breakdown of these costs based on payers was also reported to include Medicare, beneficiary and other primary payers. The difference in the paired costs was assessed using both the mean (paired t-test) and the median (Wilcoxon sign-rank test and Sign test) since cost data is not normally distributed but is typically right skewed with a long tail. The results of all 3 tests were reported as paired t-tests are sensitive to outliers unlike the other two tests but the Wilcoxon does take into account the extreme observations unlike the Sign test. SAS v 9.4 (SAS Institute, Cary, NC) was used for all analyses and a significance level of $\alpha = 0.05$ was set a-priori.

4.4 Sensitivity Analyses

A sensitivity analyses is recommended anytime there is uncertainty within the data (Briggs, 1999). It is therefore good practice to examine the changes in the RU and costs patterns when some of the assumptions in the study are varied.

1) AAPs users were defined as those beneficiaries who had claims for AAPs in 2009 which included both existing and new users. In the sensitivity analyses all beneficiaries who had AAPs claims in 2008 were excluded to estimate the differences in follow up RU and costs for new AAPs users and those not using AAPs.

2) Another assumption in the study was to only include schizophrenia and bipolar disorder as FDA approved conditions for aripiprazole even though it has been approved for adjunctive treatment of depression. Therefore, there may be aripiprazole users with depression in the off-label cohort, thus overestimating costs in that group. The results were tested after excluding aripiprazole from the AAPs of interest.

Chapter 5: Results

5.1 Specific Aim II

Specific Aim II: Evaluate the prevalence of off-label and on-label use of AAPs and describe patient characteristics in a Medicare population.

Population of interest: In the random sample obtained from CMS for 2008 (N=891,082), 2009 (N=905,814) and 2010 (N=922,202), a cohort of 813,656 beneficiaries was followed across all three years. Within each year the population of interest i.e. AAPs users was identified. The beneficiaries using AAPs are described in Table 15 and the distribution of use among the AAPs is shown in Figure 3. The prevalence of AAPs use has remained constant across the years with majority of beneficiaries using quetiapine and risperidone.

Table 15: Overall annual trend of atypical antipsychotic users from 2008-2010

	2008	**2009**	**2010**
Total Beneficiaries	891,082	905,814	922,202
AAPs Users	28,537 (3.20%)	29,280 (3.23%)	29,831 (3.23%)
Age			
-Mean (years)	64.04±19.40 (18-106)	63.50±19.17 (20-106)	63.24±19.04 (20-107)
-Less than 65 years	14,065 (49.29%)	14,913 (50.93%)	15,442 (51.76%)
-65 years and older	14,472 (50.71%)	14,367 (49.07%)	14,389 (48.24%)
Sex			
-Male	10,858 (38.05%)	11,296 (38.58%)	11,646 (39.04%)
Race			
-White	22,560 (79.06%)	23,122 (78.97%)	23,458 (78.64%)
-African American	4,001 (14.02%)	4,068 (13.89%)	4,158 (13.94%)
-Others	1,976 (6.92%)	2,090 (7.14%)	2,215 (7.43%)
ESRD	199 (0.70%)	222 (0.76%)	204 (0.68%)
Disability	14,255 (49.95%)	15,155 (51.76%)	15,756 (52.82%)

Abbreviation used: ESRD, End-Stage Renal Disease

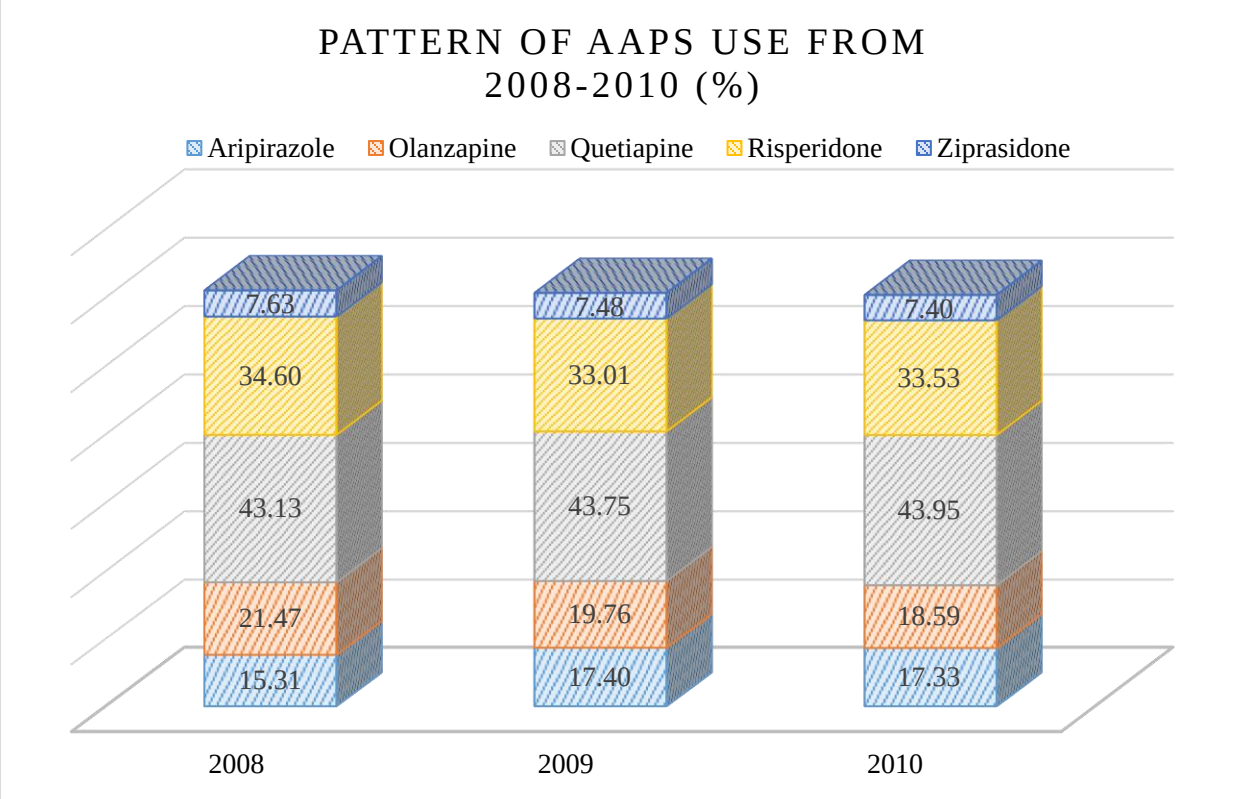


Figure 3: Pattern of atypical antipsychotic use from 2008-2010

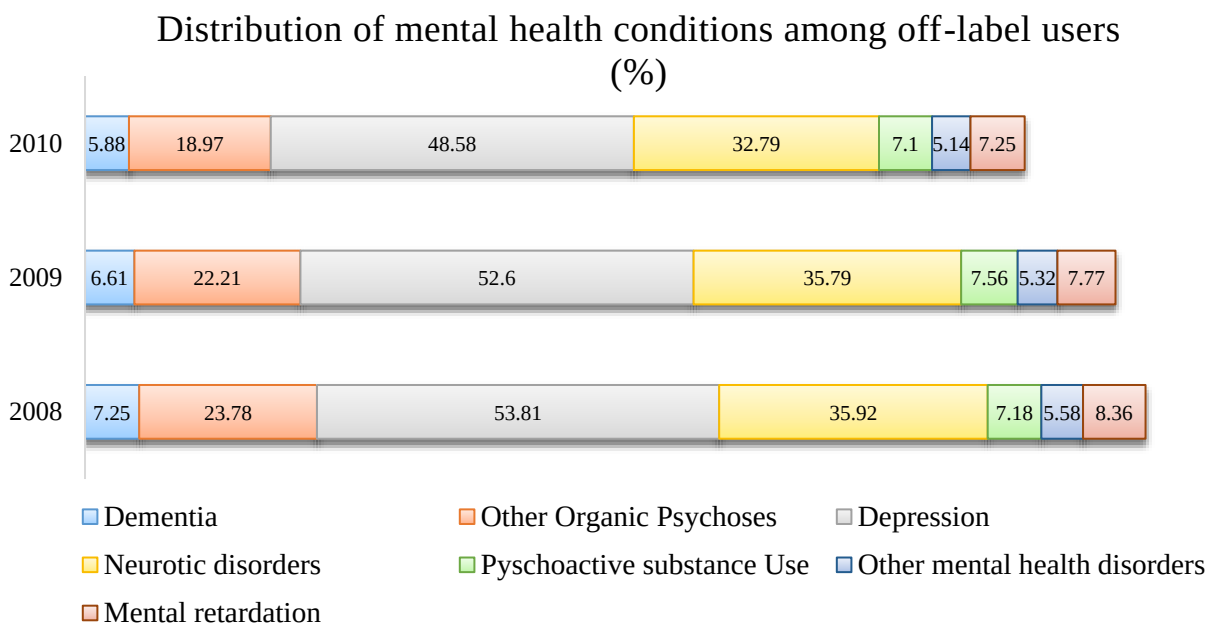
Off-label use: The prevalence of off-label and on-label use of AAPs and the characteristics of the beneficiaries are described in Table 16. Approximately 37% of total AAPs use was in the absence of an FDA approved indication and this was consistent across the three years. More than 60% of the beneficiaries receiving AAPs for off-label treatment of mental health conditions were older than 65 years and majority were white females without ESRD or a disability. . Among AAPs users older than 65 years, 49% were off-label users. Majority of these beneficiaries had indications for depression, neurotic disorders or other organic psychoses (Figure 4). In 2008, 53.8% of the off-label AAPs users had depression and approximately 31% had dementia and other related organic psychosis. By 2010, these numbers had decreased to 48.6% depression and 24.8% dementia and related psychosis.

On-label use: The prevalence of beneficiaries using AAPs in the presence of an FDA approved indications remained 63% across the three years (Table 16). Of these on-label AAPs users; 82.46%, 80.47% and 78.33% had diagnosis for schizophrenia and 55.47%, 56.48% and 56.91% had diagnosis for bipolar disorder in 2008, 2009 and 2010 respectively

Table 16: Patterns of off-label and on-label use of AAPs from 2008-2010

	2008 (N=28,537)	**2009 (N=29,280)**	**2010 (N=29,831)**
Off-label Users	**10,476 (36.71%)**	**10,679 (36.47%)**	**10,876 (36.46%)**
Age			
-Mean (years)	70.69±18.71 (18-104)	69.90±18.66 (20-106)	69.54±18.58 (20-107)
-Less than 65 years	3,409 (32.54%)	3,684 (34.50%)	3,867 (35.56%)
-65 years and older	7,067 (67.46%)	6,995 (65.50%)	7,009 (64.44%)
Sex			
-Male	3,397 (32.43%)	3,546 (33.21%)	3,678 (33.82%)
Race			
-White	8,575 (81.85%)	8,714 (81.60%)	8.846 (81.34%)
-African American	1,131 (10.80%)	1,125 (10.53%)	1,116 (10.26%)
-Others	770 (7.35%)	840 (7.87%)	914 (8.40%)
ESRD	79 (0.75%)	90 (0.84%)	73 (0.67%)
Disability	3,448 (32.91%)	3,735 (34.98%)	3,954 (36.36%)
On-label Users	**18,061 (63.29%)**	**18,601 (63.53%)**	**18,955 (63.54%)**
Age			
-Mean (years)	60.18±18.74 (20-106)	59.83±18.48 (20-105)	59.63±18.34 (20-106)
-Less than 65 years	10,656 (59.00%)	11,229 (60.37%)	11,575 (61.07%)
-65 years and older	7,405 (41.00%)	7,372 (39.63%)	7,380 (38.93%)
Sex			
-Male	7,461 (41.31%)	7,750 (41.66%)	7,968 (42.04%)
Race			
-White	13,985 (77.43%)	14,408 (77.46%)	14,612 (77.09%)
-African American	2,870 (15.89%)	2,943 (15.82%)	3,042 (16.05%)
-Others	1,206 (6.68%)	1,250 (6.72%)	1,301 (6.86%)
ESRD	120 (0.66%)	132 (0.71%)	131 (0.69%)
Disability	10,807 (59.84%)	11,420 (61.39%)	11,802 (62.26%)

Abbreviation used: ESRD, End-Stage Renal Disease



**Percent's do not add to 100 since some patients had more than one condition*

Figure 4: Distribution of mental health conditions among off-label AAPs users

In the following section the population of interest and study groups identified for Specific Aims III, IV and V are described. This is followed by the description of the outcomes for the individual aims.

Population of interest: From the random sample of one million beneficiaries, 238,127 beneficiaries met the eligibility criteria i.e., fee-for-service beneficiaries with three years of continuous enrollment in Medicare Part A, B and D. Of the beneficiaries who met the eligibility criteria N=108,937 were identified to be the population of interest (Figure 5). These beneficiaries were greater than 18 years and had a diagnosis for a mental health condition as identified from the inpatient, outpatient and other chronic conditions files. The population of interest was divided into two mutually exclusive groups; the off-label cohort (N=78,708) comprised beneficiaries with any mental health conditions except bipolar disorder or schizophrenia and on-label cohort (N=3,846)

comprised beneficiaries with only schizophrenia and/or bipolar disorder. A subset of 26,383 beneficiaries was excluded since they had a diagnosis for both an off-label and on-label condition.

AAPs users: The off-label and on-label cohort were categorized into AAPs users and non-users based on AAPs claims. The Part D claims file was used to identify 16,056 AAPs users with a mental health condition in 2009. Quetiapine was the most frequently dispensed AAPs while ziprasidone was the least frequent (Figure 6). Of these beneficiaries, 21.6% were using AAPs in the absence of a FDA approved indication (Figure 7). The off-label and on-label cohorts were further categorized based on their AAPs use. In the off-label cohort there were 3,468 (4.41%) beneficiaries who were AAPs users and 1,242 (32.29%) beneficiaries were AAPs users in the on-label cohort (Figure 5). After beneficiaries who had prescription claims for newer AAPs (N=107) and who had prescription claims for AAPs the previous year (N=772) were excluded, the final study groups for each Specific Aim were shown in Figure 5.

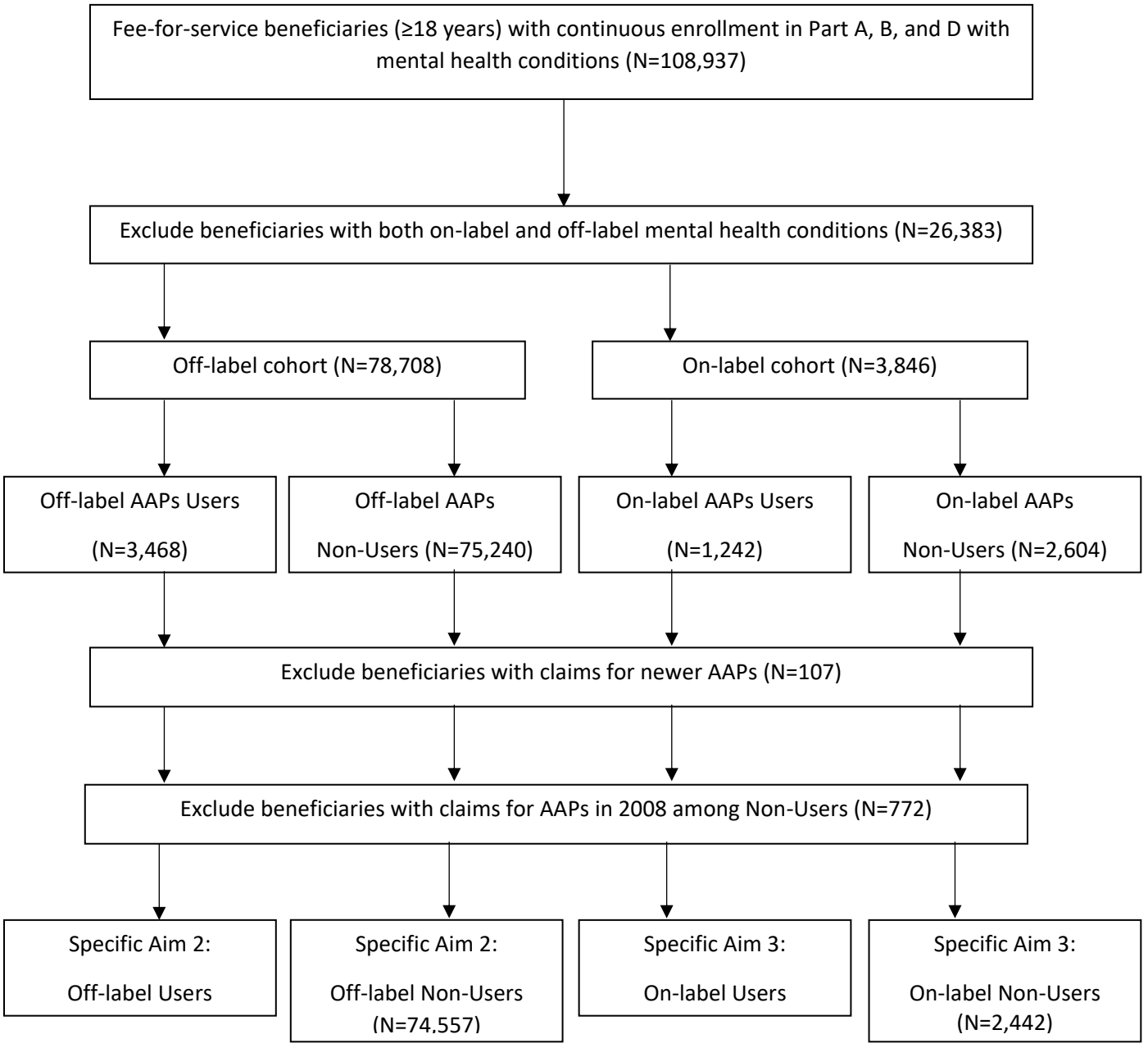


Figure 5: Flow of beneficiaries to identify study groups for Specific Aims III and IV

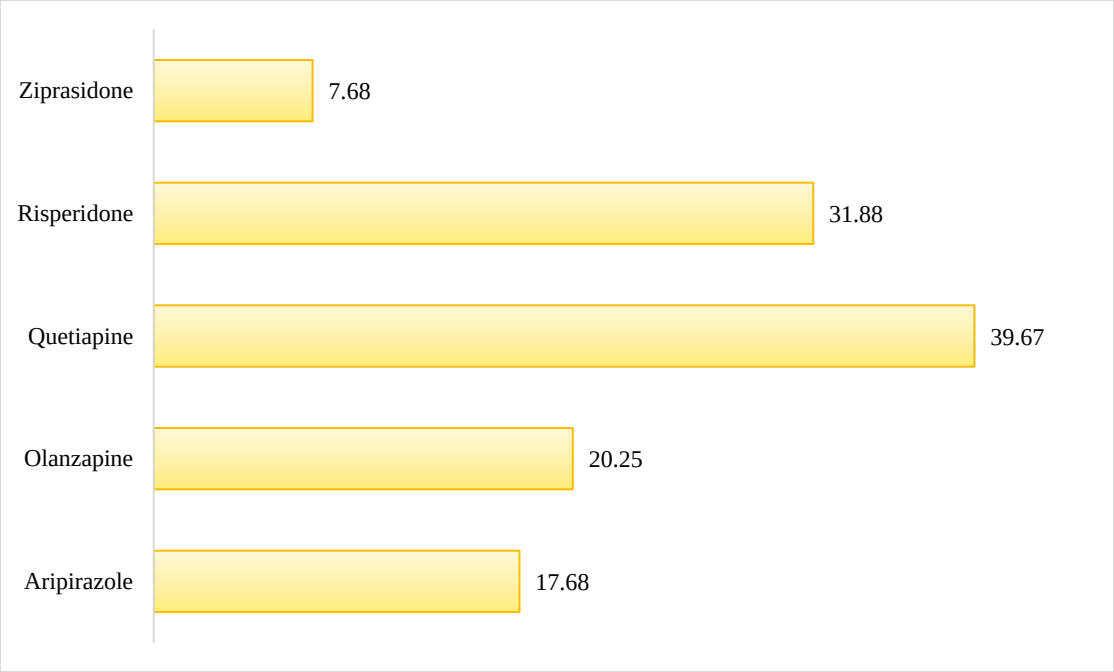


Figure 6: Pattern of AAPs use among mental health beneficiaries in 2009 (%)

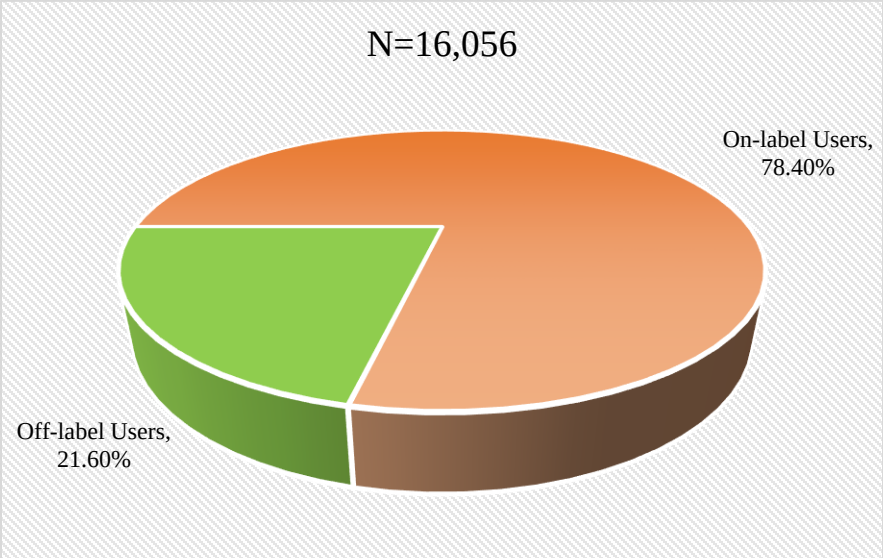


Figure 7: Prevalence of off-label AAPs use among AAPs users in 2009

5.2 Specific Aim III

Specific Aim IIIA: Compare all-cause RU and costs between Medicare beneficiaries using AAPs and those not using AAPs for off-label treatment of mental health conditions.

Pre-match study groups: For this aim, the study groups identified were the off-label AAPs user cohort (N=3,457) and the off-label AAPs non-user cohort (N=74,557) before propensity score matching. Absolute standardized differences were computed to check for differences between the groups (Table 17). The groups differed in their mean age, number of medications used in the previous year, frequency of beneficiaries with disability, and prevalence of certain mental health conditions such as depression and psychoactive substance use. Users were slightly younger than non-users; majority of the users were less than 65 years whereas majority of the non-users were 65 to 84 years. The AAPs users took more medications compared to non-users but did not differ from non-users in their inpatient and outpatient utilization rates.

Table 17: Baseline characteristics of off-label cohort pre-matching

Variable	AAPs User (N=3,457)	AAPs Non-User (N=74,557)	p-value[a]	Standardized Difference (%)
Demographic				
Age (years)	66.19 ± 18.44	69.65 ± 14.89	<0.0001	**20.63**
<65	1494 (43.22%)	20423 (27.39%)		
65-84	1306 (37.78%)	43881 (58.86%)		
>=85	657 (19.00%)	10253 (13.75%)		
Male	1138 (32.92%)	21740 (29.16%)	<0.0001	8.13
Race				
White	2874 (83.14%)	62308 (83.57%)	0.4997	1.17
Black	352 (10.18%)	7582 (10.17%)	0.9805	0.04
Others	231 (6.68%)	4667 (6.26%)	0.3168	1.71
Disease Burden				
CCI	0.90 ± 1.47	1.01 ± 1.60	<0.0001	7.25
No. of medications	12.73 ± 7.51	10.53 ± 6.64	<0.0001	**31.04**
ESRD	16 (0.46%)	947 (1.27%)	<0.0001	8.72
Disability	1517 (43.88%)	20920 (28.06%)	<0.0001	**33.43**
Mental Health Disorders				
Depression	2528 (73.13%)	45320 (60.79%)	<0.0001	**26.47**
Anxiety and Neurotic d/o	1818 (52.59%)	36749 (49.29%)	<0.0001	6.60
Psychoactive Substance Use	376 (10.88%)	12231 (16.40%)	<0.0001	**16.16**
Mental Retardation	589 (17.04%)	4601 (6.17%)	<0.0001	**34.43**
Other Organic Psychoses	935 (27.05%)	7177 (9.63%)	<0.0001	**46.20**
Other Mental Disorders	277 (8.01%)	2887 (3.87%)	<0.0001	**17.58**
Personality	201 (5.81%)	915 (1.23%)	<0.0001	**25.08**
Dementia	294 (8.50%)	1812 (2.43%)	<0.0001	**26.96**
Child and Adolescent d/o	161 (4.66%)	807 (1.08%)	<0.0001	**21.53**
Child Organic Psychoses	161 (4.66%)	279 (0.37%)	<0.0001	**27.61**
Transient Organic Psychoses	95 (2.75%)	1144 (1.53%)	<0.0001	8.39
Psychosexual d/o	6 (0.17%)	132 (0.18%)	0.9620	0.08
Drug Psychoses	25 (0.72%)	627 (0.84%)	0.4570	1.34
Alcoholic Psychoses	22 (0.64%)	409 (0.55%)	0.4959	1.14
Non-Organic Psychoses	2 (0.06%)	40 (0.05%)	0.9170	0.18
Paranoia[b]	0	1 (0%)	0.8295	0.52
Resource Utilization				
Inpatient	0.36 ± 0.98	0.39 ± 0.93	0.0270	3.93
Outpatient	5.02 ± 6.93	5.48 ± 5.43	<0.0001	6.46

[a]Pooled or Satterthwaite p-value for t-test based on test of equal variances
[b]Not included in the propensity score model since there are zero cases
Abbreviation used: d/o; disorder

Propensity scores for off-label users and non-users were computed using logistic regression. Figures 8a and 9a illustrate the distribution of the propensity scores in the two groups before matching using the box-plot and histogram techniques and show overlapping distributions indicating that the common support assumption holds true. The mean scores are significantly different among users and non-users as seen by the Kolmogorov-Smirnov two sample test ($p<0.0001$) and hence matching between the groups was done to remove baseline differences.

1: AAPs Users; 0: Non-Users

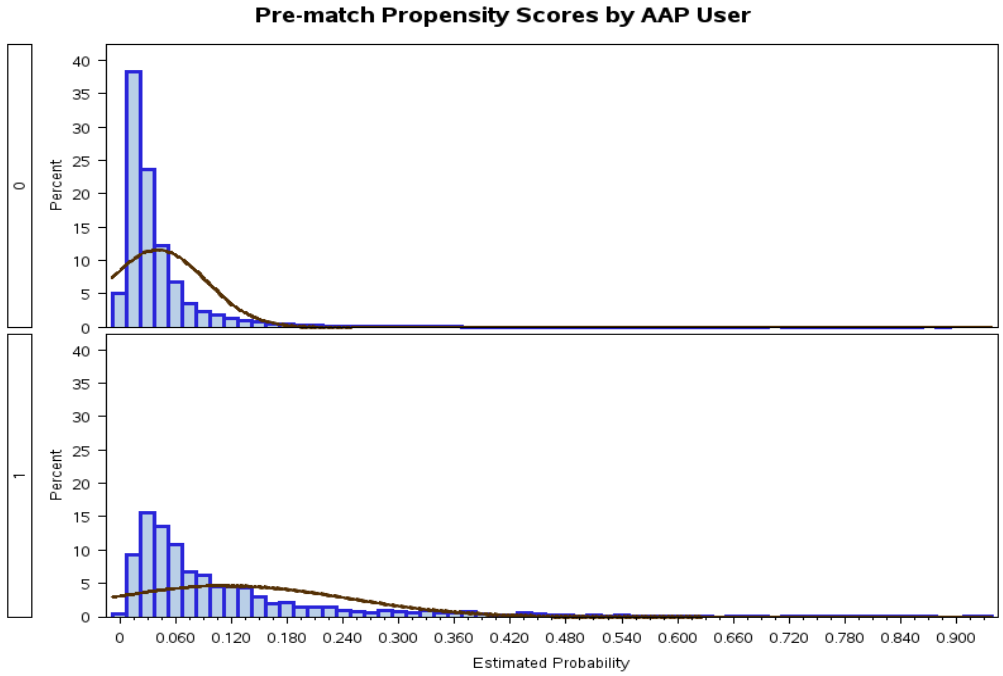


Figure 8a: Distribution of propensity scores before matching

1: AAPs Users; 0: Non-Users

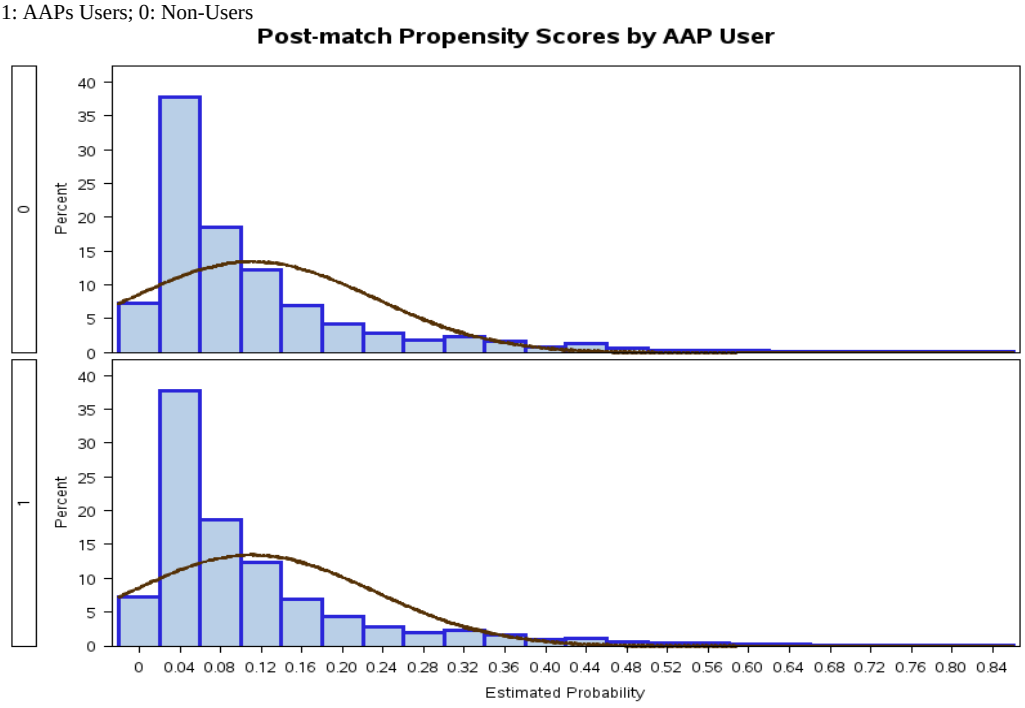


Figure 8b: Distribution of propensity scores after matching

1: AAPs Users; 0: Non-Users

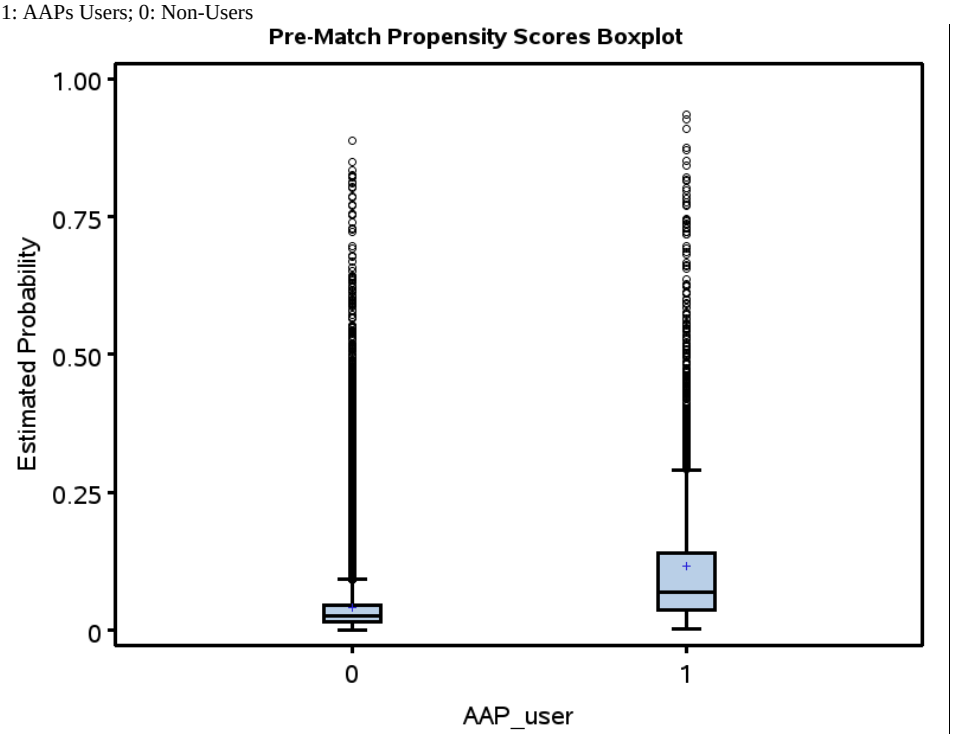


Figure 9a: Distribution of propensity scores before matching – Boxplot

1: AAPs Users; 0: Non-Users

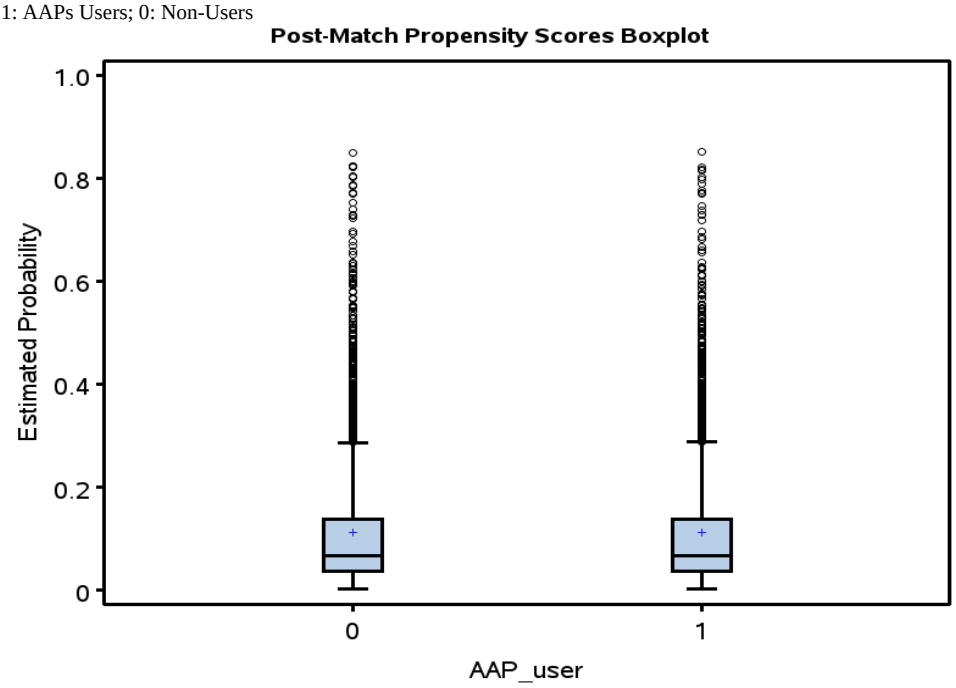


Figure 9b: Distribution of propensity scores after matching – Boxplot

Post-match study groups: After matching, no difference was found among the means of the propensity scores between the cohorts (p=1.0000). Figures 8b and 9b also visually illustrate that the distribution of scores were very similar across the two groups after matching. The number of beneficiaries in the AAPs user and non-user cohort before and after matching is reported in Table 18.

Table 18. Pre and post-match cohort counts

	Frequency	Percent	Cumulative Frequency	Cumulative percent
Pre				
Control	74557	95.57	74557	95.57
Case	3457	4.43	78014	100.00
Post				
Control	3438	50.00	3438	50.00
Case	3438	50.00	6876	100.00

To assess if the propensity score matching process balanced the covariates across the two groups, absolute standardized differences were calculated (Table 19). All standardized differences are less than 10%; hence good matches with balanced observed covariates were obtained. The groups had a mean age of 66 years, comprised mostly white females an average of 13 unique medications. In addition, majority of beneficiaries had a diagnosis for depression or neurotic disorders.

Table 19: Baseline characteristics of off-label cohort post-matching

Variable	AAPs User (N=3,438)	AAPs Non-User (N=3,438)	Standardized Difference (%)
Demographic			
Age (years)	66.29±18.42 (20-101)	66.01±17.44 (21-104)	1.53
<65	1477 (42.96%)	1516 (44.10%)	
65-84	1304 (37.93%)	1368 (39.79%)	
>=85	657 (19.11%)	554 (16.11%)	
Male	1130 (32.87%)	1123 (32.66%)	0.43
Race			
White	2858 (83.13%)	2794 (81.27%)	4.87
Black	350 (10.18%)	380 (11.05%)	2.83
Others	230 (6.69%)	264 (7.68%)	3.83
Disease Burden			
CCI	0.90±1.48	0.98±1.51	4.88
No. of medications	12.70±7.39	13.13±8.04	5.54
ESRD	16 (0.47%)	20 (0.58%)	1.61
Disability	1500 (43.63%)	1549 (45.06%)	2.87
Mental Health Disorders			
Depression	2516 (73.18%)	2561 (74.49%)	2.98
Neurotic	1804 (52.47%)	1771 (51.51%)	1.92
Psychoactive Substance	376 (10.94%)	375 (10.91%)	0.09
Mental Retardation	572 (16.64%)	548 (15.94%)	1.89
Other Organic Psychoses	925 (26.91%)	974 (28.33%)	3.19
Other Mental Disorders	273 (7.94%)	274 (7.97%)	0.11
Personality	199 (5.79%)	187 (5.44%)	1.52
Dementia	290 (8.44%)	269 (7.82%)	2.23
Child and Adolescent	150 (4.36%)	136 (3.96%)	2.04
Child Organic Psychoses	151 (4.39%)	99 (2.88%)	8.09
Transient Organic Psychoses	92 (2.68%)	94 (2.73%)	0.36
Drug Psychoses	25 (0.73%)	22 (0.64%)	1.06
Alcoholic Psychoses	22 (0.64%)	18 (0.52%)	1.53
Psychosexual	6 (0.17%)	6 (0.17%)	0
Non-Organic Psychoses	2 (0.06%)	0	3.41
Resource Utilization			
Inpatient	0.36±0.98	0.38±0.88	2.71
Outpatient	5.02±6.94	5.34±6.67	4.69

Costs: Table 20 presents direct all-cause health care costs for beneficiaries by AAPs use to treat off-label mental health conditions during the follow-up period. Costs were broken down based on payers; Medicare costs, out-of-pocket costs by the beneficiary and other payers such as a private insurance. Medicare followed by beneficiaries paying out-of-pocket paid the largest share of costs. Beneficiaries had to pay the highest share out-of-pocket for prescriptions and these costs were higher among the AAPs users as compared to the non-users. Among the total health care costs, the major cost component among non-users was inpatient (IP) cost but among the AAPs users it was prescription cost (RX) (Figure 10). Outpatient (OP) costs remained similar in both cohorts.

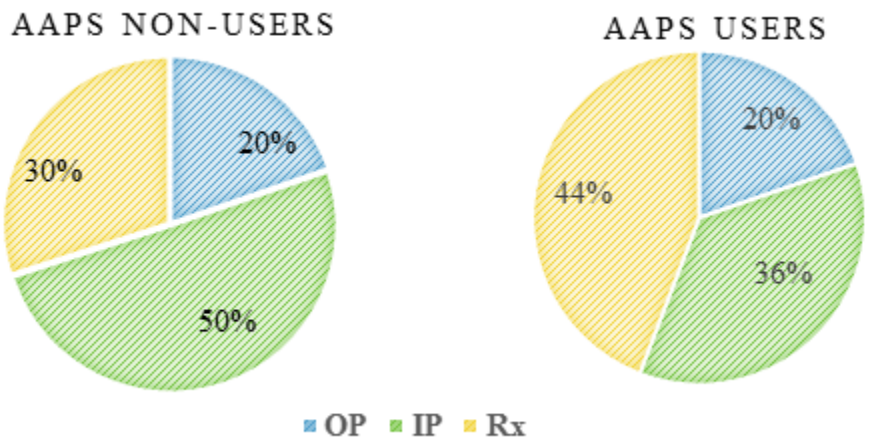


Figure 10: Breakdown of direct health care costs through the follow-up period

Out of the 6,876 beneficiaries after matching only 29 beneficiaries (0.4%) had zero total costs and therefore no measures were undertaken to account for a high number of zero costs in the analyses. Univariate analyses of total costs showed a right skew distribution with a maximum cost of $455,000 (Figure 11) and hence both total mean (paired t-test) and median (Wilcoxon Sign-Rank test) costs were reported in Table 20. Of the total beneficiaries, 69 had costs greater than

$92,500 (99% quantile). Due to the presence of some extreme observations the Sign test was also reported in Table 21. The Sign test assessed differences in median cost in the absence of extreme observations. Even though there were no differences in the total mean costs between AAPs users and non-users (p=0.6112), AAPs non-users had significantly higher inpatient costs of $6,945 per person versus the $4,841 per person among users (p <0.0001). On the other hand, prescription costs were significantly higher among the users by approximately $1,700 which would also include the cost of AAPs. Since the cost data is not normally distributed and may be sensitive to extreme observations, medians were also reported. Median outpatient costs among non-users were significantly higher than among users even though no differences were found between mean outpatient costs.

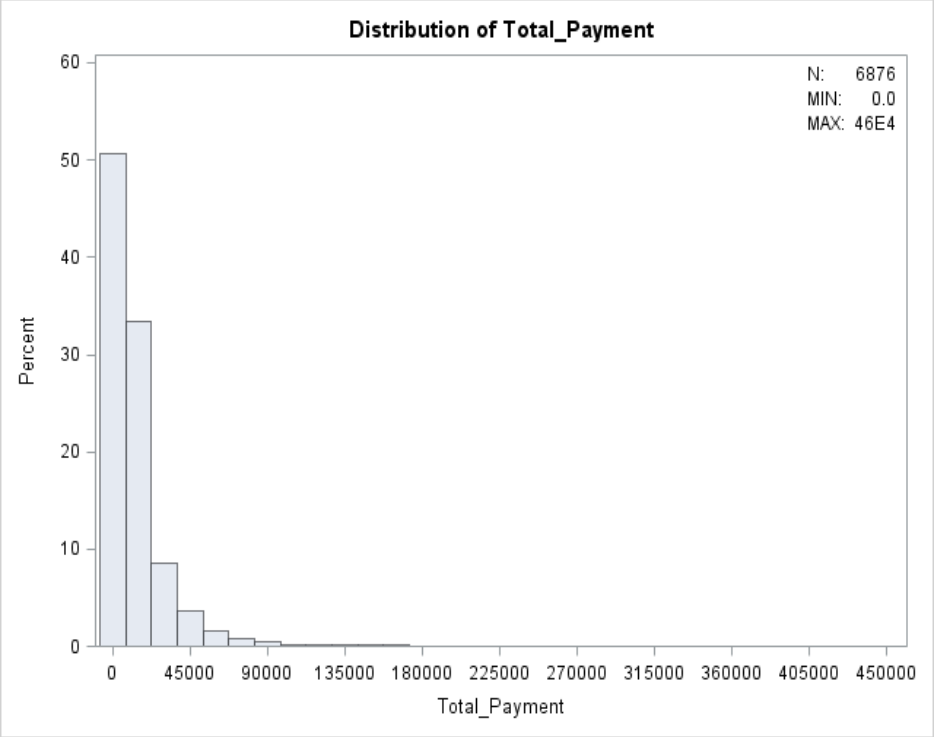


Figure 11: Distribution of total costs in off-label cohort

Table 20: Direct all-cause health care costs by payer

Variable	Mean ($)	Lower 95% CI	Upper 95% CI	Median ($)	Minimum ($)	Maximum ($)
AAPs Non-Users						
Outpatient						
Medicare	2,117	1,953	2,282	683	0	89,071
Beneficiary	588	546	629	206	0	17,595
Other payers	15	3	27	0	0	12,744
Inpatient						
Medicare	6,295	5,678	6,912	0	0	358,363
Beneficiary	539	494	583	0	0	51,147
Other payers	111	-80	303	0	0	335,446
Prescription						
Medicare	3,256	3,059	3,454	1,915	0	125,953
Beneficiary	880	854	906	687	0	5,548
AAPs Users						
Outpatient						
Medicare	2,056	1,893	2,219	620	0	61,586
Beneficiary	574	531	617	182	0	16,608
Other payers	14	2	26	0	0	18,796
Inpatient						
Medicare	4,412	3,954	4,869	0	0	218,776
Beneficiary	395	358	432	0	0	44,667
Other payers	34	4	65	0	0	38,259
Prescription						
Medicare	4,855	4,695	5,015	3,739	25	86,396
Beneficiary	1,066	1,040	1,092	896	12	6,378

Abbreviation used: CI, Confidence interval

Table 21: Mean all-cause health care costs for AAPs users and non-users

Variable	Non-Users			Users			p-value		
	Mean ($)	Median ($)	SD	Mean ($)	Median ($)	SD	Paired t-test	Sign	WSR
Outpatient	2,720	897	6,129	2,644	837	6,159	0.6112	0.0013	0.0181
Inpatient	6,945	0	20,238	4,841	0	14,389	<0.0001	<0.0001	<0.0001
Prescription	4,137	2,630	6,442	5,921	4,742	5,310	<0.0001	<0.0001	<0.0001
Total	13,801	6,389	23,704	13,407	7,979	18,130	0.4373	<0.0001	0.0002
- Medicare	11,669	4,788	21,335	11,323	6,283	16,614	0.4536	<0.0001	<0.0001

Abbreviation used: SD, Standard Deviation; WSR, Wilcoxon Sign-Rank

Resource Utilization: The descriptive statistics and patterns of RU by beneficiaries using and those not using AAPs off-label to treat their mental health conditions are reported in Table 22. In the 12 month follow-up period both users and non-users had an average of six outpatient visits per year and 13 medications per year with no significant differences among the cohorts (Table 23) except for the number of medication claims. On the other hand beneficiaries who used AAPs for off-label treatment had significantly lower number of inpatient visits ($p < 0.0001$) during the follow-up period. The maximum number of times an AAPs user used an inpatient service was 10 times a year in comparison to the 14 visits by a non-user.

Table 22: Annual health care RU among off-label AAPs users and non-users

Variable	Mean	Lower 95% CI	Upper 95% CI	Min	Max
AAPs Non-Users					
Outpatient visits	6.39	6.12	6.66	0	103
Inpatient visits	0.58	0.54	0.61	0	14
Medication claims	67.50	65.85	69.14	0	428
Unique medications	13.08	12.82	13.34	0	51
AAPs Users					
Outpatient visits	6.41	6.11	6.71	0	128
Inpatient visits	0.41	0.38	0.45	0	10
Medication claims	84.78	83.10	86.46	2	596
Unique medications	13.22	12.97	13.46	1	54

Abbreviation used: CI, Confidence interval; Min, Minimum; Max, Maximum

Table 23: Differences in RU between off-label AAPs users and non-users

Variable	Difference (Non-Users-Users)	SD	Lower 95% CI	Upper 95% CI	p-value
Outpatient visits	-0.02	12.06	-0.42	0.38	0.2106
Inpatient visits	0.16	1.47	0.11	0.21	<0.0001
Medication claims	-17.28	67.74	-19.55	-15.02	<0.0001
Unique medications	-0.14	10.46	-0.49	0.21	0.4445

Abbreviation used: CI, Confidence interval; SD, Standard Deviation

Logistic regression analyses reported in Table 24 showed that AAPs users had 34% lower odds than non-users to have an inpatient visit ($p < 0.0001$). Among the AAPs users only 24% had at least one inpatient visit while at least 32% had an inpatient visit among the non-users. More than 80% of both users and non-users had at least one outpatient visit during the follow-up period.

Table 24: Odds ratios of RU between off-label AAPs users and non-users

Variable	**Non-User (%)**	**User (%)**	**OR Non-User=Ref**	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Outpatient visits	2869 (83.4)	2816 (81.91)	0.896	0.79	1.017	0.0891
Inpatient visits	1101 (32.02)	831 (24.17)	0.661	0.592	0.738	<0.0001
Medication use	3388 (98.55)	3438 (100.00)	*			

Abbreviation used: CI, Confidence interval; OR, Odds Ratio
* Regression not done since 100% medication use in user cohort

Specific Aim IIIB: Compare mental health RU and costs between Medicare beneficiaries using AAPs and those not using AAPs for off-label treatment of mental health conditions.

Costs: Beneficiaries in the AAPs user cohort had higher total mental health costs during the follow-up period (Table 25). The mean total costs among AAPs users were $3,665 versus $1,297 among the non-users (p <0.0001). Prescription costs and outpatient costs were higher among the AAPs users as compared to non-users but no differences were seen among inpatient costs. Majority of the costs were attributed to prescription costs which were $2,349 per AAPs user and $282 per non-user (p<0.0001). Of the five AAPs of interest, risperidone contributed least to the prescription costs ($397 per beneficiary) while quetiapine contributed the most ($3562 per beneficiary) followed by aripiprazole and olanzapine ($2,769 per beneficiary and $2,478 per beneficiary respectively).

Table 25: Mean mental health costs among AAPs users and non-users

Variable	Non-Users		Users		Difference ($)	p-value
	Mean ($)	SD	Mean ($)	SD		
Outpatient	297	1,917	461	2,378	-165	0.0017
Inpatient	719	3,596	854	4,019	-135	0.1314
Prescription	282	542	2,349	2,311	-2,068	<0.0001
Total	1,297	4,278	3,665	5,211	-2,368	<0.0001
- Medicare	1,086	3,838	3,162	4,655	-2,076	<0.0001

Abbreviation used: SD, Standard Deviation

Resource Utilization: The mean number of outpatient and inpatient visits and medications used are described in Table 26. In the 12 month follow-up period users had an average of more than one outpatient visit per year. About 30% of AAPs users had at least one outpatient visit during the year versus only 23% of non-users (Table 27). Regression analyses showed that the odds of having an outpatient visit among AAPs users was significantly higher as compared to non-users

(OR = 1.55, p <0.0001). No difference was found in the mean number of mental health inpatient visits between the groups (Table 26) and approximately 7% of beneficiaries had at least one inpatient visit over the period of one year (Table 27). AAPs users also had significantly higher number of medications and medication claims compared to non-users (p<0.0001).

Table 26: Mean annual mental health RU

Variable	Non-Users			Users			p-value
	Mean	Lower 95% CI	Upper 95% CI	Mean	Lower 95% CI	Upper 95% CI	
Outpatient visits	0.61	0.54	0.67	1.06	0.94	1.17	<0.0001
Inpatient visits	0.08	0.07	0.09	0.09	0.08	0.11	0.0769
Medication claims	6.97	6.68	7.25	21.89	21.47	22.31	<0.0001
Unique medications	1.05	1.01	1.08	2.48	2.44	2.52	<0.0001

Abbreviation used: CI, Confidence interval

Table 27: Odds ratios of mental health RU

Variable	Non-User (%)	User (%)	OR Non-User=Ref	Lower 95% CI	Upper 95% CI	p-value
Outpatient visits	775 (22.54)	1059 (30.80)	1.553	1.39	1.735	<0.0001
Inpatient visits	226 (6.57)	257 (7.48)	1.156	0.956	1.397	0.1348
Medication use	2202 (64.05)	3438 (100.00)	*			

Abbreviation used: CI, Confidence interval; OR, Odds Ratio
* Regression not done since 100% medication use in user cohort

5.3 Specific Aim IV

Specific Aim IV A: To compare all-cause resource utilization and costs between Medicare beneficiaries using AAPs and those not using AAPs for on-label treatment of mental health conditions.

Pre-match study groups: For this aim, the study groups identified before matching were on-label AAPs user cohort (N=1,219) and on-label AAPs non-user cohort (N=2,442). The characteristics of these beneficiaries are described in Table 28 and the cohorts were different across multiple covariates. The typical AAPs user was a younger white male with fewer comorbid conditions but higher chances of disability and having a diagnosis for schizophrenia or bipolar disorder as compared to the typical non-user. The cohorts also differed in their RU with AAPs users having lower numbers of inpatient and outpatient visits the prior year.

After the propensity scores were computed using logistic regression model, the scores were plotted and the overlapping graphs indicated that the common support assumption held true (Figures 10a and 11a). The Kolmogorov-Smirnov two sample test showed that the propensity scores were significantly different among the users and non-users ($p<0.0001$).

Table 28: Baseline characteristics of on-label cohort pre-matching

Variable	AAPs User (N=1,219)	AAPs Non-User (N=2,442)	p-value[a]	Standardized Difference (%)
Demographic				
Age (years)	51.70 ±15.70	66.14±17.78	<0.0001	**86.07**
Male	763 (62.59%)	1160 (47.50%)	<0.0001	**30.69**
Race				
White	833 (68.33%)	1839 (75.31%)	<0.0001	**15.55**
Black	269 (22.07%)	428 (17.53%)	0.0010	**11.41**
Others	117 (9.60%)	175 (7.17%)	0.0105	8.78
Disease Burden				
CCI	0.32±0.91	0.74±1.41	<0.0001	**34.90**
No. of medications	7.17±4.96	7.64±5.97	0.0108	8.67
ESRD	3 (0.25%)	28 (1.15%)	0.00051	**10.84**
Disability	960 (78.75%)	1018 (41.69%)	<0.0001	**81.82**
Mental Health Disorders				
Schizophrenia	1024 (84.00%)	1836 (75.18%)	0.0011	**22.01**
Bipolar Disorder	454 (37.24%)	777 (31.82%)	<0.0001	**11.43**
Resource Utilization				
Inpatient	0.05±0.29	0.23±0.70	<0.0001	**32.40**
Outpatient	2.25±4.35	3.87±6.30	<0.0001	**29.93**

[a]Pooled or Satterthwaite p-value for t-test based on test of equal variances

Post-match study groups: After the user and non-user cohorts were matched no difference was found in the means of the propensity scores (p=1.0000). Figures 12b and 13b illustrate that the distribution of the scores are very similar between the two groups after matching. The total numbers of matched pairs are reported in Table 29. A total of 981 matched pairs were obtained for this aim.

Table 29: Pre and post-match cohort counts

	Frequency	Percent	Cumulative Frequency	Cumulative percent
Pre				
Control	2442	66.70	2442	66.70
Case	1219	33.30	3661	100.00
Post				
Control	981	50.00	981	50.00
Case	981	50.00	1962	100.00

1: AAPs Users; 0: Non-Users

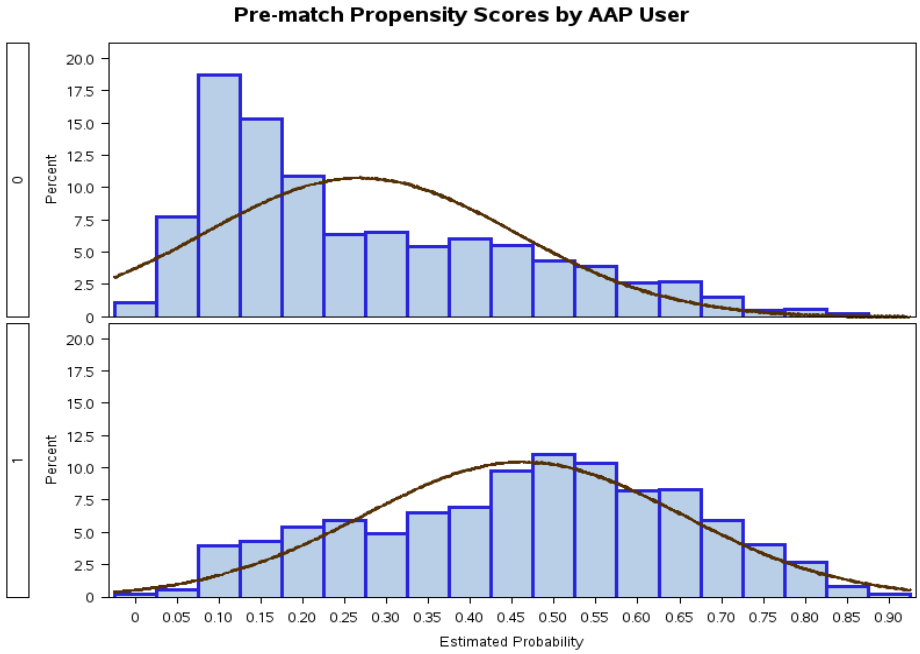


Figure 12a: Distribution of propensity scores before matching

1: AAPs Users; 0: Non-Users

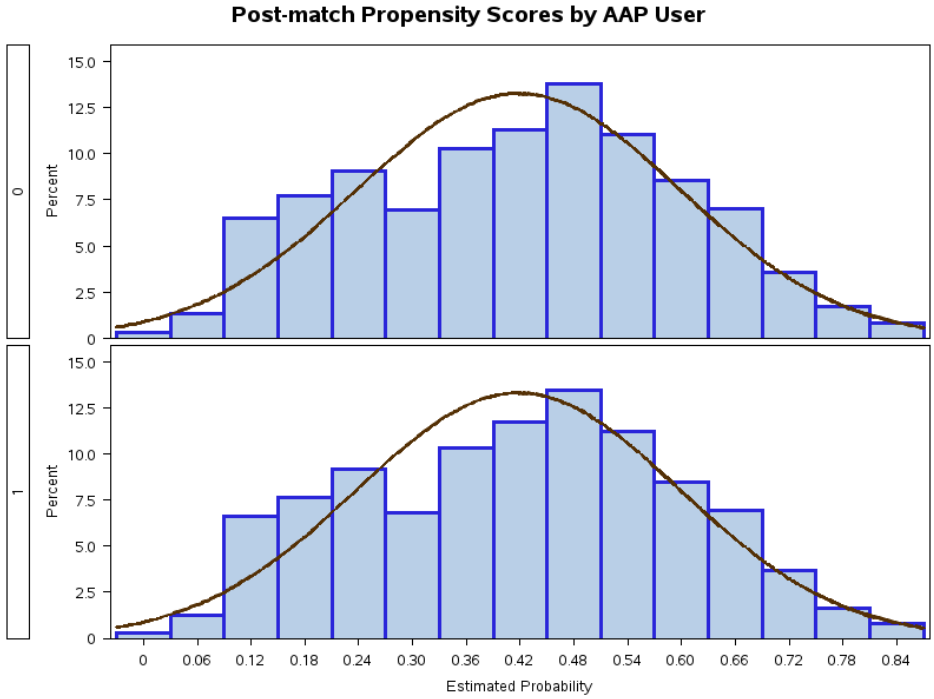


Figure 12b: Distribution of propensity scores after matching

1: AAPs Users; 0: Non-Users

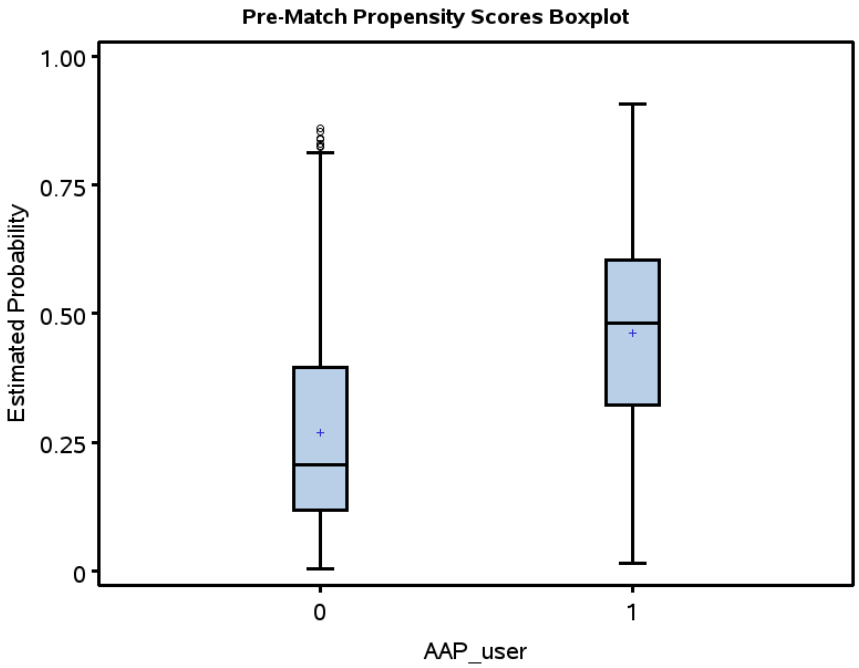


Figure 13a: Distribution of propensity scores before matching – Boxplot

1: AAPs Users; 0: Non-Users

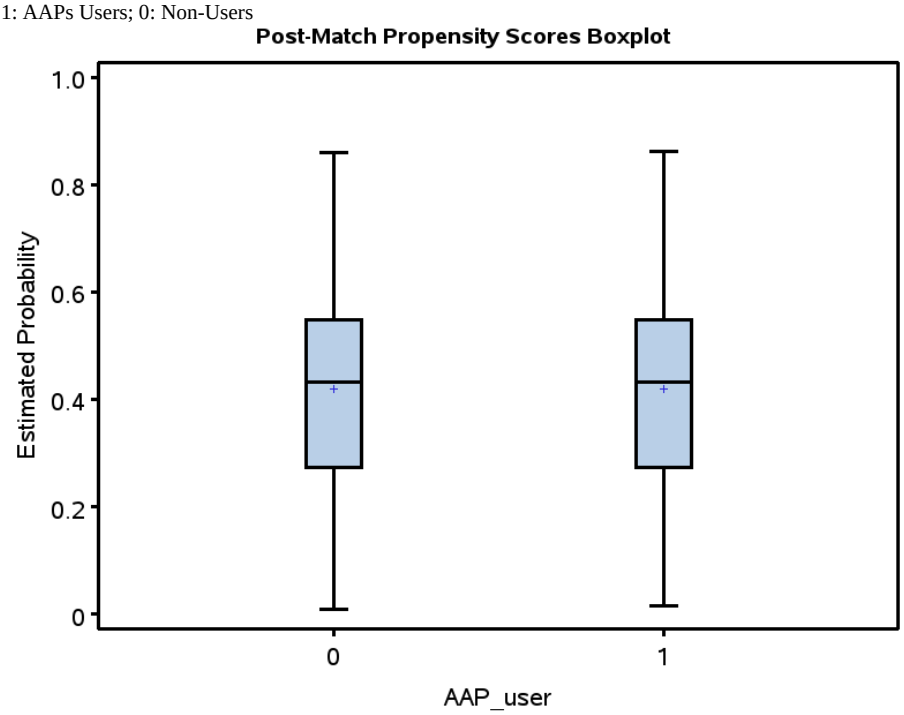


Figure 13b: Distribution of propensity scores after matching – Boxplot

The absolute standardized differences after matching were calculated and reported in Table 30. All the differences were less than 10% and hence all the covariates were appropriately balanced across the user and non-user cohort. The groups had a mean age of 54 years, comprised mostly of white males with disability and approximately seven unique medications the previous year with majority of beneficiaries having a diagnosis for schizophrenia and two outpatient visits per year.

Table 30: Baseline characteristics of on-label cohort post-matching

Variable	**AAPs User (N=981)**	**AAPs Non-User (N=981)**	**Standardized Difference (%)**
Demographic			
Age (years)	54.47±15.53 (21-98)	54.17±16.68 (21-102)	1.85
Male	589 (60.04%)	573 (58.41%)	3.32
Race			
White	677 (69.01%)	658 (67.07%)	4.15
Black	217 (22.12%)	223 (22.73%)	1.47
Others	87 (8.87%)	100 (10.19%)	4.51
Disease Burden			
CCI	0.36±0.98	0.32±0.83	4.83
No. of medications	7.02±4.79	6.83±6.14	3.46
ESRD	3 (0.31%)	2 (0.20%)	2.02
Disability	722 (73.60%)	728 (74.21%)	1.39
Mental Health Disorders			
Schizophrenia	797 (81.24%)	789 (80.43%)	2.07
Bipolar Disorder	345 (35.17%)	345 (35.17%)	0
Resource Utilization			
Inpatient	0.06±0.30	0.07±0.38	2.37
Outpatient	2.45±4.69	2.24±3.86	4.79

Costs: The descriptive statistics of all-cause health care costs of beneficiaries using and not using AAPs to treat FDA approved conditions are reported in Table 31. Among non-users the highest cost component was inpatient (IP) costs but among AAPs users it was prescription (Rx) costs (Figure 14). Outpatient (OP) costs were consistent across the groups with non-users having 22% of their costs coming from outpatient services. Among users, Medicare paid a mean of $5,052 per beneficiary in a year and beneficiaries paid an average of $557 per person out-of-pocket. As with the off-label cohort, prescription costs were the major out-of-pocket costs for beneficiaries.

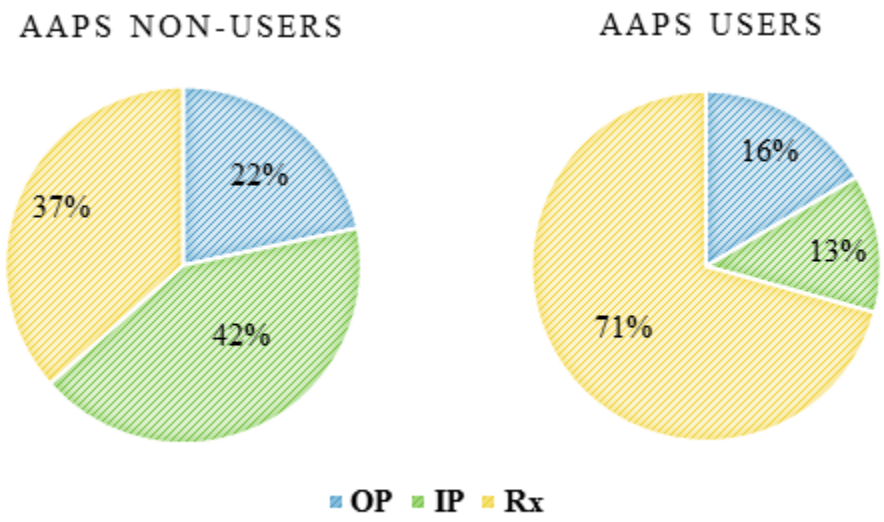


Figure 14: Breakdown of health care costs by component

Only 113 (5%) of the 1,962 beneficiaries had zero total costs and the cost distribution had a right skew distribution. The maximum total cost per beneficiary for the year was $227,900 (Figure 15) but 99% of beneficiaries had a mean total cost less than $53,000 per beneficiary. The mean and median total costs are reported in Table 32. Mean total costs were found to be significantly higher in AAPs users ($7,929) as compared to non-users ($5,402) with a $p < 0.0001$.

Even though users had higher mean prescription costs, they had a significantly lower mean inpatient cost of $1,012 per beneficiary versus $2,257 per beneficiary among non-users (p=0.0019). No differences were found in outpatient costs and these results were robust even in the absence of extreme observations (Table 32).

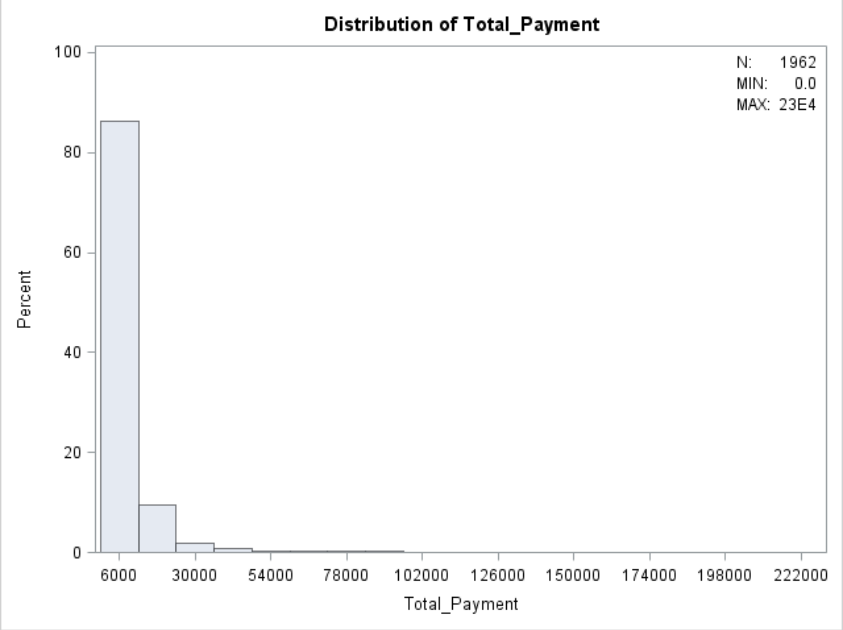


Figure 15: Distribution of total costs among beneficiaries in on-label cohort

Table 31: Direct all-cause health care costs by payer

Variable	Mean ($)	Lower 95% CI	Upper 95% CI	Median ($)	Minimum ($)	Maximum ($)
AAPs Non-Users						
Outpatient						
Medicare	881	679	1,083	131	0	51,434
Beneficiary	282	207	357	24	0	24,101
Other payers	7	-4	17	0	0	4,883
Inpatient						
Medicare	2,083	1,412	2,754	0	0	212,141
Beneficiary	159	124	193	0	0	8,781
Other payers	16	-15	46	0	0	15,258
Prescription						
Medicare	1,582	1,388	1,777	696	0	51,051
Beneficiary	392	358	426	185	0	4,282
AAPs Users						
Outpatient						
Medicare	993	730	1,256	116	0	68,032
Beneficiary	282	212	353	20	0	19,084
Other payers	33	-5	71	0	0	17,069
Inpatient						
Medicare	913	596	1,231	0	0	86,806
Beneficiary	87	66	109	0	0	2,602
Other payers	11	-11	33	0	0	11,021
Prescription						
Medicare	5,052	4,794	5,309	3,938	63	26,055
Beneficiary	557	525	589	411	3	4,558

Abbreviation used: CI, Confidence interval

Table 32: Mean all-cause health care costs for on-label AAPs users and non-users

Variable	Non-Users			Users			p-value		
	Mean ($)	Median ($)	SD	Mean ($)	Median ($)	SD	Paired t-test	Sign	WSR
Outpatient	1,170	171	4,356	1,308	164	5,350	0.5311	0.5803	0.6459
Inpatient	2,257	0	11,160	1,012	0	5,338	0.0019	0.0109	0.001
Prescription	1,975	953	3,448	5,609	4,519	4,324	<0.0001	<0.0001	<0.0001
Total	5,402	1,858	13,420	7,929	5,660	9,073	<0.0001	<0.0001	<0.0001
- Medicare	4,547	1,407	12,307	6,958	4,784	8,011	<0.0001	<0.0001	<0.0001

Abbreviation used: SD, Standard Deviation; WSR, Wilcoxon Sign-Rank

Resource utilization: The pattern of RU by beneficiaries using AAPs in the presence of schizophrenia and bipolar conditions have been described in Table 33. Both users and non-users had an average of almost four outpatient visits during the year and did not differ significantly (p=0.4826) (Table 34). Users had a significantly fewer inpatient visits during the year (p=0.0008). There were non-users who had to use the inpatient services up to nine times during the year while the maximum number of inpatient stays a AAPs user had was only four times in the year. Users were prescribed more medications during the year in comparison to their non-user counterparts (7 vs 6 respectively) and also had higher number of medication claims.

Table 33: Annual health care RU among on-label AAPs users and non-users

Variable	Mean	Lower 95% CI	Upper 95% CI	Min	Max
AAPs Non-Users					
Outpatient visits	3.80	3.40	4.19	0	64
Inpatient visits	0.17	0.13	0.21	0	9
Medication claims	37.89	35.61	40.17	0	221
Unique medications	6.86	6.47	7.26	0	37
AAPs Users					
Outpatient visits	3.85	3.46	4.23	0	58
Inpatient visits	0.09	0.07	0.11	0	4
Medication claims	54.99	52.59	57.38	1	245
Unique medications	7.60	7.28	7.92	1	30

Abbreviation used: CI, Confidence interval; Min, Minimum; Max, Maximum

Table 34: Differences in RU between on-label AAPs users and non-users

Variable	Difference (Users-Non Users)	SD	Lower 95% CI	Upper 95% CI	p-value
Outpatient visits	-0.05	8.58	-0.5906	0.4846	0.4826
Inpatient visits	0.08	0.75	0.0333	0.1277	0.0008
Medication claims	-17.10	51.06	-20.2963	-13.8974	<0.0001
Unique medications	-0.73	7.82	-1.2249	-0.2451	0.0033

Abbreviation used: CI, Confidence interval; SD, Standard Deviation

Results of the conditional logistic regression models are reported in Table 35. AAPs users had 36% lower odds of having an inpatient visit during the year compared to non-users (p=0.0069) and had the same odds as a non-user for having an outpatient visit (p=0.1249). More than 10% of non-users had at least one inpatient visit during the year versus only 7% of the AAPs users. Even though no differences were found in the mean number of outpatient visits between the groups, there was a slightly higher number of users (65%) who had at least one outpatient visit when compared to the non-users (62%).

Table 35: Adjusted odds ratios of RU between on-label AAPs users and non-users

Variable	**Non-User (%)**	**User (%)**	**OR Non-User=Ref**	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Outpatient visits	606 (61.77)	638 (65.04)	1.159	0.96	1.4	0.1249
Inpatient visits	102 (10.40)	68 (6.93)	0.642	0.466	0.886	0.0069
Medication use	842 (85.83)	*				

Abbreviation used: CI, Confidence interval; OR, Odds Ratio
* Regression not done since 100% medication use in user cohort

Specific Aim IVB: Compare mental health RU and costs between Medicare beneficiaries using AAPs and those not using AAPs for on-label treatment of mental health conditions.

Costs: AAPs users were found to have significantly higher mean total, prescription and inpatient costs (Table 36). The mean total costs among AAPs users were $4,959 versus only $744 among non-users (p <0.0001). Medicare was paying an average of $4,605 per AAPs user per year to cover mental health costs versus only paying $640 per non-user per year. Inpatient and prescription costs were also found to be higher among AAPs users as compared to non-users but no differences were found for outpatient costs. Prescription cost was the major cost component among the users. Among the AAPs agents, risperidone cost the least at approximately $613 per beneficiary, while quetiapine cost $6,434 per beneficiary followed by olanzapine and aripiprazole at $5,644 per beneficiary and $3,402 per beneficiary respectively.

Table 36: Mean mental health costs among AAPs users and non-users

Variable	**Non-Users**		**Users**		**Difference ($)**	**p-value**
	Mean ($)	**SD**	**Mean ($)**	**SD**		
Outpatient	197	1,649	369	2,563	-172	0.0782
Inpatient	129	1,650	370	2,478	-241	0.0117
Prescription	418	931	4,221	3,999	-3,802	<0.0001
Total	744	2,539	4,959	5,555	-4,215	<0.0001
- Medicare	640	2,154	4,605	5,129	-3,966	<0.0001

Abbreviation used: SD, Standard Deviation

Resource Utilization: The pattern of mental health RU is described in Table 37. AAPs users had significantly higher RU as compared to non-users. Users were prescribed an average of two psychotherapeutic medications and filled approximately 21 prescriptions in the year while non-users had an average of one medication per year and had an average of only seven claims per year. Approximately 27% of users had at least one outpatient visit during the year as compared with only 18% of non-users (Table 38). Users had 1.68 times and 2.75 times the odds of non-users to have an outpatient and inpatient visit respectively during the follow-up period.

Table 37: Mean annual mental health RU among AAPs users and non-users

Variable	Non-Users			Users			p-value
	Mean	Lower 95% CI	Upper 95% CI	Mean	Lower 95% CI	Upper 95% CI	
Outpatient visits	1.09	0.83	1.34	1.20	0.98	1.42	0.0105
Inpatient visits	0.01	0.01	0.02	0.04	0.03	0.06	0.0009
Medication claims	7.74	7.04	8.43	21.41	20.56	22.26	<0.0001
Unique medications	0.88	0.82	0.94	2.12	2.05	2.19	<0.0001

Abbreviation used: CI, Confidence interval

Table 38: Adjusted odds ratios of mental health RU

Variable	Non-User (%)	User (%)	OR Non-User=Ref	Lower 95% CI	Upper 95% CI	p-value
Outpatient visits	177 (18.04)	263 (26.81)	1.683	1.35	2.098	<0.0001
Inpatient visits	12 (1.22)	33 (3.36)	2.75	1.42	5.324	0.0027
Medication use	536 (54.64)	981 (100.00)	*			

Abbreviation used: CI, Confidence interval; OR, Odds Ratio

* Regression not done since 100% medication use in user cohort

5.4 Specific Aim V

Specific Aim V: Evaluate differences in RU and associated costs in Medicare beneficiaries using AAPs and those not using AAPs to treat specific mental health conditions.

Depression: Beneficiaries with a diagnosis of depression and no other mental health conditions were identified. Before matching the beneficiaries with depression who used AAPs in their treatment and those who did not differed on all baseline characteristics. After matching, 544 pairs with balanced covariates were obtained as reported in Table 39. The typical beneficiary with depression was a 67 year old white female prescribed 13 medications with less than one inpatient and four outpatient visits during the year.

Table 39: Characteristics of beneficiaries with depression before and after matching

Variable	**Pre-match**			**Post-match**		
	User N=545	**Non-User N=18,995**	**ASD (%)**	**User N=544**	**Non-User N=544**	**ASD (%)**
Demographic						
Age (%)						
Mean (years)	67.93±16.67	71.17±13.32	**21.47**	67.95±16.68	67.28±14.89	4.24
<65	37.80	21.67		37.68	38.60	
65-84	46.42	65.18		46.51	49.63	
>=85	15.78	13.15		15.81	11.76	
Sex (%)						
Male	32.84	26.46	**14.01**	32.72	34.19	3.12
Race (%)						
White	75.96	83.97	**20.12**	75.92	75.55	0.86
Black	13.21	8.87	**13.88**	13.24	11.95	3.88
Others	10.83	7.15	**12.86**	10.85	12.50	5.15
Disease Burden						
CCI (mean)	0.69±1.40	0.97±1.60	**18.32**	0.69±1.40	0.82±1.30	9.91
No. of meds (mean)	12.39±7.28	10.69±6.30	**25.1**	12.33±7.11	12.87±7.03	7.64
ESRD (%)	0.18	1.35	**13.42**	0.18	0.74	8.16
Disability (%)	39.08	22.45	**36.64**	38.97	40.81	3.75
RU						
Inpatient (mean)	0.17±0.60	0.31±0.78	**19.79**	0.17±0.60	0.23±0.61	9.83
Outpatient (mean)	4.00±7.02	5.29±7.22	**17.78**	4.01±7.03	4.07±5.27	0.98

Abbreviation used: No. of meds, Number of medications; CCI, Charlson Comorbidity Index; ESRD, End-Stage Renal Disease; RU, Resource Utilization; ASD, Absolute Standardized Difference

Among the 544 patients on AAPs, 433 (80%) had claims for antidepressants in the previous year. This could be indicative of patients who are resistant to treatment or relapsing after a successful course on antidepressants. In beneficiaries with a diagnosis for depression the mean total direct costs were $11,545 among AAPs non-users which was significantly higher than the mean costs of $10,804 among AAPs users (p=0.0173) (Table 40). Non-users had a greater number of inpatient visits during the year and also had higher inpatient costs compared to AAPs users. On the other hand there were no differences in mean number of outpatient visits and mean outpatient costs by AAPs use (Table 41). Even though it was expected that users would be prescribed more medications, both groups were using an average of 13 medications during the follow up year but the costs were significantly greater among the users ($6,152 vs $4,145).

Table 40: Mean all-cause health care costs of beneficiaries with depression

Variable	**AAPs Non-Users**		**AAPs Users**		**p-value**
	Mean ($)	**SD**	**Mean ($)**	**SD**	
Outpatient	2,145	5,020	2,123	5,699	0.9442
Inpatient	5,255	23,847	2,528	12,951	0.0201
Prescription	4,145	7,511	6,152	6,550	<0.0001
Total	11,545	26,485	10,804	17,376	0.0173

Abbreviation used: SD, Standard Deviation

Table 41: Mean all-cause RU in beneficiaries with depression

Variable	**AAPs Non-Users**		**AAPs Users**		**p-value**
	Mean	**SD**	**Mean**	**SD**	
Outpatient visits	4.84	6.34	5.18	9.01	0.4452
Inpatient visits	0.32	0.78	0.17	0.58	0.0005
Medication claims	61.99	45.85	82.29	55.01	<0.0001
Unique medications	12.64	7.09	12.80	7.36	0.6727

Abbreviation used: SD, Standard Deviation

Anxiety and other neurotic disorders: Beneficiaries with ICD-9-CM diagnosis code 300 including disorders such as anxiety, phobias and obsessive compulsive disorder were identified. The balance between the covariates before and after matching are reported in Table 42. After matching 126 pairs were identified with balanced covariates. Beneficiaries with anxiety or other neurotic disorders were typically 65 years, white, female with mean CCI score of 0.6, 11 unique medications and three outpatient visits in a year.

Table 42: Characteristics of beneficiaries with anxiety and neurotic disorders before and after matching

Variable	**Pre-match**			**Post-match**		
	User N=126	**Non-User N=12,812**	**ASD (%)**	**User N=126**	**Non-User N=126**	**ASD (%)**
Demographic						
Age (%)						
Mean (years)	65.38±18.02	73.16±11.86	**51.01**	65.38±18.02	65.53±15.80	0.89
<65	43.65	13.98		43.65	40.48	
65-84	41.27	72.31		41.27	50.00	
>=85	15.08	13.71		15.08	9.52	
Sex (%)						
Male	36.51	23.24	**29.29**	36.51	33.33	6.66
Race (%)						
White	84.13	85.47	3.75	84.13	84.92	2.19
Black	6.35	8.35	7.68	6.35	4.76	6.93
Others	9.52	6.17	**12.48**	9.52	10.32	2.65
Disease Burden						
CCI (mean)	0.67±1.48	0.77±1.37	6.76	0.67±1.48	0.63±1.20	2.93
No. of meds (mean)	11.43±6.98	9.56±5.89	**28.88**	11.43±6.98	11.37±7.18	0.78
ESRD (%)	0	0.69	**11.76**	0	0	0
Disability (%)	43.65	14.59	**67.52**	43.65	42.86	1.60
RU						
Inpatient (mean)	0.21±0.73	0.27±0.70	8.29	0.21±0.73	0.26±0.62	7.00
Outpatient (mean)	3.23±4.32	4.60±6.34	**25.22**	3.23±4.32	3.03±3.89	4.83

Abbreviation used: No. of meds, Number of medications; CCI, Charlson Comorbidity Index; ESRD, End-Stage Renal Disease; RU, Resource Utilization; ASD, Absolute Standardized Difference

In beneficiaries with diagnosis for anxiety or other neurotic disorders the mean total direct costs were $7,250 among AAPs users which was significantly higher than the mean costs of $5,966 among the AAPs non-users (p=0.0397) as shown in Table 43. Unlike in depression, non-users did not differ in their mean inpatient visits or inpatient costs from users. Even though the groups did not differ significantly in their mean outpatient visits or number of medications in the follow up period (Table 44), the costs did differ significantly. AAPs users had higher prescription costs ($5,474) in comparison to non-users ($3,030) but had significantly lower outpatient costs ($947 vs $1,548).

Table 43: Mean all-cause costs of beneficiaries with anxiety and neurotic disorders

Variable	AAPs Non-Users		AAPs Users		p-value
	Mean ($)	SD	Mean ($)	SD	
Outpatient	1,548	2,560	947	1,967	0.0253
Inpatient	1,388	3,963	828	4,087	0.2083
Prescription	3,030	4,348	5,474	7,429	0.0011
Total	5,966	7,480	7,250	8,514	0.0397

Abbreviation used: SD, Standard Deviation

Table 44: Mean all-cause RU in beneficiaries with anxiety and neurotic disorders

Variable	AAPs Non-Users		AAPs Users		p-value
	Mean	SD	Mean	SD	
Outpatient visits	3.86	4.70	3.17	4.95	0.2105
Inpatient visits	0.16	0.41	0.09	0.44	0.1503
Medication claims	50.48	36.01	71.02	47.23	<0.0001
Unique medications	10.85	7.23	11.52	6.18	0.4252

Abbreviation used: SD, Standard Deviation

Dementia: Since there were very few beneficiaries who had dementia in the absence of other mental health conditions, all beneficiaries who had a diagnosis for dementia were included even if they had other mental health conditions. In order to account for the presence of other mental health conditions, was controlled for in the matching. After matching, 279 pairs were identified but the groups were not balanced across all covariates (Table 45). Baseline inpatient RU and the presence of other mental disorders were not balanced across groups and hence these variables were further controlled using GLM regression analyses.

Table 45: Characteristics of beneficiaries with dementia before and after matching

Variable	Pre-match			Post-match		
	User N=294	Non-User N=1,812	ASD (%)	User N=279	Non-User N=279	ASD (%)
Demographic						
Age (%)						
Mean (Years)	81.79±9.5	82.95±8.5	**12.88**	82.38±8.7	82.32±8.4	0.66
<65 (%)	4.76	2.98		3.58	3.23	
65-84	50.68	50.72		50.18	56.99	
>=85	44.56	46.30		46.24	39.78	
Sex (%)						
Male	20.75	21.58	2.03	20.79	22.58	4.35
Race (%)						
White	82.99	80.35	6.83	82.80	82.80	0
Black	12.24	13.52	3.81	12.19	12.54	1.09
Others	4.76	6.13	6.01	5.02	4.66	1.67
Disease Burden						
CCI (mean)	1.74±1.73	1.48±1.70	**15.40**	1.70±1.71	1.81±1.81	6.30
No. of meds (mean)	12.82±6.4	10.45±6.3	**37.35**	12.52±6.1	12.56±7.2	0.59
ESRD (%)	0.34	1.21	9.96	0.36	0.36	0
Disability (%)	4.76	3.04	8.93	3.58	3.58	0
Resource Utilization						
Inpatient (mean)	0.58±1.15	0.52±1.02	5.62	0.57±1.16	0.71±1.13	**12.22**
Outpatient (mean)	6.07±7.99	6.53±9.23	5.41	6.07±8.10	5.75±6.84	4.25
Mental Health Disorders (%)						
Depression	67.69	49.94	**36.65**	66.67	67.03	0.76
Neurotic	42.86	33.55	**19.23**	41.22	41.94	1.45
Psychoactive Substance	5.44	5.30	0.64	5.02	4.30	3.40
Mental Retardation	2.72	1.32	9.93	1.43	1.43	0
Other Organic Psychoses	69.39	49.83	**40.67**	68.1	70.25	4.66
Other Mental Disorders	10.20	4.91	**20.12**	9.68	6.45	**11.87**
Personality	3.40	1.05	16	2.15	1.08	8.54
Child and Adolescent	4.42	0.77	**23.1**	2.15	2.51	2.38
Child Organic Psychoses	0.34	0.06	6.42	0.36	0	8.48
Transient Organic Psychoses	4.76	3.97	3.86	4.30	3.58	3.68
Psychosexual	0	0.06	3.32	0	0	0
Drug Psychoses	0.34	0.77	5.82	0.36	0	8.48
Alcoholic Psychoses	0.68	0.77	1.09	0.72	0.36	4.90
Non-Organic Psychoses	0.34	0.17	3.48	0.36	0.36	0

Abbreviation used: No. of meds, Number of medications; CCI, Charlson Comorbidity Index; ESRD, End-Stage Renal Disease; RU, Resource Utilization; ASD, Absolute Standardized Difference

In beneficiaries with diagnosis for dementia in the presence of other mental health conditions the mean total direct costs were not significantly different among AAPs non-users ($18,803) and AAPs users ($16,873) (Table 46). Non-users had a significantly greater number of inpatient visits during the year (p=0.0490) and had higher inpatient costs ($11,613 for non-users vs. $8,254 for users). On the other hand there were no differences in mean number of outpatient visits (Table 47) and mean outpatient costs by AAPs use. On average beneficiaries with dementia were prescribed 13 medications per year but AAPs users ($5,018) had significantly higher prescription costs than non-users ($3,601).

Table 46: Mean all-cause health care costs of beneficiaries with dementia

Variable	AAPs Non-Users		AAPs Users		p-value
	Mean ($)	SE	Mean ($)	SE	
Outpatient	3,648	348	3,528	344	0.8050
Inpatient	11,613	1,322	8,254	1,153	0.0490
Prescription	3,601	161	5,018	224	<0.0001
Total	18,803	1,335	16,873	1,265	0.2880

Abbreviation used: SD, Standard Deviation

Table 47: Mean all-cause RU in beneficiaries with dementia

Variable	AAPs Non-Users		AAPs Users		p-value
	Mean	SE	Mean	SE	
Outpatient visits	8.32	0.57	8.21	0.57	0.887
Inpatient visits	0.99	0.08	0.72	0.07	0.0170
Medication claims	75.31	2.44	88.60	2.89	<0.0001
Unique medications	13.02	0.36	13.36	0.37	0.5170

Abbreviation used: SD, Standard Deviation

Schizophrenia: Beneficiaries with a diagnosis of schizophrenia and no other mental health conditions were identified. Before matching the beneficiaries with a schizophrenia diagnosis had different baseline characteristics based on their AAPs use. Beneficiaries prescribed AAPs were a younger cohort with mean age of 53 years as compared to the non-users with a mean age of 70 years. After matching, 622 pairs of beneficiaries with schizophrenia and no other mental health conditions were identified (Table 48). The typical beneficiary with schizophrenia was a 56-year-old white male with a mean CCI score of 0.32, prescribed six medications and an average of two outpatient visits during the year.

Table 48: Characteristics of beneficiaries with schizophrenia before and after matching

Variable	**Pre-match**			**Post-match**		
	User N=765	**Non-User N=1,665**	**ASD (%)**	**User N=622**	**Non-User N=622**	**ASD (%)**
Demographic						
Age (%)						
Mean (years)	52.90±16.02	69.81±17.10	**102.04**	56.10±15.52	55.89±16.29	1.31
<65	75.56	33.27		70.10	69.94	
65-84	21.05	45.11		25.72	25.56	
>=85	3.40	21.62		4.18	4.50	
Sex (%)						
Male	67.97	47.21	**42.98**	64.15	65.27	2.35
Race (%)						
White	64.44	72.13	**16.58**	64.47	63.67	1.67
Black	25.23	19.58	**13.58**	25.40	25.88	1.1
Others	10.33	8.29	7.02	10.13	10.45	1.06
Disease Burden						
CCI (mean)	0.27±0.77	0.85±1.53	**48.12**	0.32±0.83	0.32±0.78	0.20
No. of meds (mean)	6.55±4.63	7.76±6.04	**22.53**	6.56±4.64	6.40±6.01	3.08
ESRD (%)	0.26	1.62	**14.12**	0.32	0.32	0
Disability (%)	76.21	33.63	**94.67**	70.74	70.26	1.06
RU						
Inpatient (mean)	0.05±0.28	0.27±0.78	**38.70**	0.06±0.31	0.05±0.29	3.75
Outpatient (mean)	2.11±4.46	4.24±6.89	**36.73**	2.35±4.86	2.42±5.36	1.38

Abbreviation used: No. of meds, Number of medications; CCI, Charlson Comorbidity Index; ESRD, End-Stage Renal Disease; RU, Resource Utilization; ASD, Absolute Standardized Difference

In beneficiaries with diagnosis for schizophrenia the mean total direct costs were $4,999 among AAPs non-users which was significantly lower than the mean costs of $7,989 among the AAPs users (p<0.0001) (Table 49). Even though the groups did not differ in their outpatient and inpatient costs AAPs users had a significantly higher prescription costs ($5,753) which was the major component of total all-cause health care costs. Even though the AAPs users had higher prescription costs they were prescribed on average seven medications during the year which was not significantly different from the number of medications non-users were prescribed (p=0.1244) (Table 50).

Table 49: Mean all-cause health care costs of beneficiaries with schizophrenia

Variable	AAPs Non-Users		AAPs Users		p-value
	Mean ($)	SD	Mean ($)	SD	
Outpatient	1,078	4,011	1,227	5,323	0.5788
Inpatient	2,016	12,784	1,009	5,780	0.068
Prescription	1,905	2,888	5,753	4,542	<0.0001
Total	4,999	14,452	7,989	9,345	<0.0001

Abbreviation used: SD, Standard Deviation

Table 50: Mean all-cause RU in beneficiaries with bipolar disorder

Variable	AAPs Non-Users		AAPs Users		p-value
	Mean	SD	Mean	SD	
Outpatient visits	3.64	6.35	3.81	6.10	0.6227
Inpatient visits	0.13	0.55	0.09	0.41	0.1727
Medication claims	36.73	36.17	53.69	37.87	<0.0001
Unique medications	6.40	5.81	6.84	4.68	0.1244

Abbreviation used: SD, Standard Deviation

Bipolar disorder: Beneficiaries with a diagnosis of bipolar disorder and no other mental health conditions were identified from the population of interest. The AAPs users and non-users differed significantly in their mean age, mean CCI score, mean number of medications, outpatient and inpatient visits among others (Table 51). A total of 176 pairs of bipolar patients were identified after matching and all covariates except race were balanced at baseline, hence race was controlled for in the regression. The typical beneficiary with bipolar disorder was a 52-year-old white female with a mean CCI score of 0.4, eight unique medications and two outpatient visits over the baseline period.

Table 51: Characteristics of beneficiaries with bipolar disorder before and after matching

Variable	**Pre-match**			**Post-match**		
	User N=195	**Non-User N=606**	**ASD (%)**	**User N=176**	**Non-User N=176**	**User N=195**
Demographic						
Age (%)						
Mean (Years)	50.00±15.54	59.94±16.59	**61.78**	51.68±14.96	51.94±16.75	1.65
<65 (%)	78.46	51.16		76.14	76.14	
65-84	18.97	45.54		21.02	21.59	
>=85	2.56	3.3		2.84	2.27	
Sex (%)						
Male	43.59	45.54	3.93	46.59	47.73	2.28
Race (%)						
White	82.05	85.48	9.3	82.39	86.93	**12.64**
Black	9.23	10.07	2.83	10.23	6.25	14.5
Others	8.72	4.46	**17.25**	7.39	6.82	2.21
Disease Burden						
CCI (mean)	0.39±0.97	0.55±1.15	**15.27**	0.39±1.00	0.40±0.98	1.72
No. of medications (mean)	8.54±5.42	7.74±5.80	**14.27**	7.82±4.80	7.75±6.45	1.2
ESRD (%)	0	0.17	5.75	0	0	0
Disability (%)	78.97	52.81	**57.43**	76.7	77.27	1.35
Resource Utilization						
Inpatient (mean)	0.09±0.32	0.15±0.53	**13.73**	0.09±0.33	0.09±0.36	0
Outpatient (mean)	2.53±3.76	3.23±4.83	**16.23**	2.51±3.83	2.45±3.51	1.54

Abbreviation used: No. of meds, Number of medications; CCI, Charlson Comorbidity Index; ESRD, End-Stage Renal Disease; RU, Resource Utilization; ASD, Absolute Standardized Difference

In beneficiaries with diagnosis for bipolar disorder with no other mental health conditions the mean total direct costs were significantly higher among the AAPs users ($7,673) as compared to the non-users ($4,477) (Table 52). This difference in cost was mainly driven by prescription costs since the inpatient and outpatient costs did not differ by AAPs use. AAPs users had a mean prescription cost of $5,011 per beneficiary in comparison to $2,321 per non-user (p<0.0001). The beneficiaries did not differ in their outpatient and inpatient visits (Table 53) but AAPs users were prescribed on average more unique medications in the follow up period as compared to the non-users (p<0.0001).

Table 52: Mean all-cause health care costs of beneficiaries with bipolar disorder by AAPs use

Variable	AAPs Non-Users		AAPs Users		p-value
	Mean ($)	SE	Mean ($)	SE	
Outpatient	1,467	283	1,297	244	0.6460
Inpatient	737	324	1,328	458	0.2960
Prescription	2,321	314	5,011	683	<0.0001
Total	4,477	503	7,673	865	0.0010

Abbreviation used: SD, Standard Deviation

Table 53: Mean all-cause RU in beneficiaries with bipolar disorder

Variable	AAPs Non-Users		AAPs Users		p-value
	Mean	SE	Mean	SE	
Outpatient visits	3.22	0.34	3.52	0.37	0.5530
Inpatient visits	0.07	0.02	0.11	0.02	0.2260
Medication claims	36.00	2.40	56.00	3.72	<0.0001
Unique medications	7.72	0.42	9.38	0.51	0.0130

Abbreviation used: SD, Standard Deviation

5.5 Sensitivity Analyses

1) In Specific Aim III, AAPs users included both existing users and new users of AAPs since sample size of using only new AAPs users was a concern. In this sensitivity analysis, only beneficiaries who were new AAPs users were included; that is, any beneficiary with AAPs prescriptions in 2008 were excluded. The users and non-users were matched and all covariates were balanced across the two groups. Even though mental health visits and costs remained robust with AAPs users having more outpatient, prescription and total costs (Table 55), there were some changes in all-cause costs. Outpatient costs and visits, which were not significantly different among users and non-users in Specific Aim IIIA, showed that AAPs users had significantly higher outpatient costs and visits (Table 54). Similarly, inpatient costs between the users and non-users had no significant differences, which was a change from non-users having more inpatient costs in Specific Aim IIIA. These results in combination with the mental-health visits may be indicative of higher RU and costs among new AAPs users.

Table 54: All-cause costs and RU among new off-label AAPs users and non-users

Variable	**AAPs Non-Users**		**AAPs Users**		**p-value**
	Mean	**SD**	**Mean**	**SD**	
Cost ($)					
Outpatient	2,945	6,813	3,675	7,582	0.0010
Inpatient	8,870	26,197	6,969	16,129	0.1448
Prescription	3,798	5,549	5,890	5,659	<0.0001
Total	15,613	29,917	16,534	20,756	0.4099
RU					
Outpatient visits	6.39	8.16	6.41	8.90	0.0132
Inpatient visits	0.58	1.15	0.41	0.96	0.0390
Medication claims	67.50	49.14	84.78	50.27	<0.0001
Unique medications	13.08	7.82	13.22	7.27	<0.0001

Table 55: Mental health costs and RU among new off-label AAPs users and non-users

Variable	AAPs Non-Users		AAPs Users		p-value
	Mean	SD	Mean	SD	
Cost ($)					
Outpatient	183	777	663	3,143	<0.0001
Inpatient	771	3,113	1,149	4,326	0.0226
Prescription	45	93	233	220	<0.0001
Total	1,000	3,276	2,045	5,323	<0.0001
RU					
Outpatient visits	0.53	1.51	1.36	4.20	<0.0001
Inpatient visits	0.09	0.33	0.12	0.44	0.1323
Medication claims	6.88	8.05	18.90	12.44	<0.0001
Unique medications	1.07	1.06	2.61	1.27	<0.0001

2) In this sensitivity analyses all aripiprazole users were excluded so that any depression AAPs users in this cohort is truly an off-label user. The users and non-users were matched and all covariates were balanced across the two groups. As in the previous sensitivity analysis, the mental health costs and RU remained robust despite the change in the included cohort (Table 57). Interestingly, in all-cause costs, outpatient, inpatient, prescription, and total costs were now significantly higher among AAPs non-users (Table 56). In Specific Aim IIIA, only inpatient costs and prescription costs were higher among non-users while no differences were observed in outpatient and total costs.

Table 56: All-cause costs and RU among off-label AAPs users and non-users excluding aripiprazole users

Variable	**AAPs Non-Users**		**AAPs Users**		**p-value**
	Mean	**SD**	**Mean**	**SD**	
Cost ($)					
Outpatient	2,714	5,559	2,506	5,786	0.0030
Inpatient	7,327	21,752	4,709	13,957	<0.0001
Prescription	3,933	6,654	5,551	4,999	<0.0001
Total	13,975	24,716	12,766	17,483	0.0390
RU					
Outpatient visits	6.39	8.16	6.41	8.90	0.0368
Inpatient visits	0.58	1.15	0.41	0.96	<0.0001
Medication claims	67.50	49.14	84.78	50.27	<0.0001
Unique medications	13.08	7.82	13.22	7.27	0.3937

Table 57: Mental health costs and RU among off-label AAPs users and non-users excluding aripiprazole users

Variable	AAPs Non-Users		AAPs Users		p-value
	Mean	SD	Mean	SD	
Cost ($)					
Outpatient	234	1,362	408	2,142	<0.0001
Inpatient	645	3,135	867	4,134	0.0242
Prescription	41	87	196	198	<0.0001
Total	920	3,475	1,472	4,694	<0.0001
RU					
Outpatient visits	0.58	1.67	0.97	3.06	<0.0001
Inpatient visits	0.08	0.31	0.09	0.39	0.0925
Medication claims	6.79	8.57	21.53	12.59	<0.0001
Unique medications	1.00	1.05	2.41	1.18	<0.0001

Chapter 6: Discussion

This chapter discusses the results of the Medicare study and describes the strengths and limitations of the study.

6.1 Specific Aim II

The sample used in the analysis was Medicare beneficiaries prescribed AAPs in 2008, 2009 and 2010. Approximately 3.2% of the Medicare beneficiaries were prescribed AAPs each year and the prevalence remained constant across the three years. The typical AAPs users were 64-year-old white females, almost half of them had disability and less than 1% had ESRD. Even though the socio-demographic characteristics are similar to published literature in the same population (Driessen et al., 2016) the prevalence of AAPs use in this population (3.2%) is lower than in the published literature (8%), probably because our study used a more conservative definition of AAPs user. We defined a user as a beneficiary who had at least two claims within 60 days for one AAPs agent while Driessen et al. defined it as a beneficiary with one AAPs claim. Majority of the AAPs users were prescribed quetiapine (43%) followed by risperidone (34%) while ziprasidone was the least commonly prescribed AAPs (7%).

The prevalence of off-label use among AAPs users has been persistent across 2008 to 2010. The prevalence was 36.7% in 2008 and 36.5% in 2010. The rate of off-label use is lower than that reported by Driessen et al. in a Medicare population, but our study used the more conservative definition of AAPs use. Driessen et al. reported a decline in off-label use from 51% to 45% from 2008 to 2010. The typical off-label AAPs user was a 70-year-old white female without a disability while the typical on-label AAPs user was 60-year-old white female with disability and the socio-demographic factors are in accordance to published results (Driessen et al., 2016). Driessen et al.

also reported off-label users to be older (mean age = 66 years) compared to on-label users (mean age = 52 years) and were typically white females.

The prevalence of off-label use among 18-64 year old AAPs users is 24% which is almost comparable to the 19.5% prevalence of off-label use in a similar age group reported by Citrome et al. (2013). The prevalence of off-label use among AAPs users greater than 65 years was 49%, this is lower than the estimates reported by Kamble et al. (86%) and Levinson (83%) in nursing home residents (Kamble et al., 2010; Levinson, 2011). The difference in the findings between our study and earlier reports within the same age groups could be explained due to the differences in the health of the population included in the studies. Our study focused on community dwelling Medicare beneficiaries whereas the previous studies reported off-label use in Medicare beneficiaries residing in nursing homes. A majority of these patients were diagnosed with dementia requiring constant care and this could explain the higher rates of off-label use.

Even though the prevalence of off-label use has not dramatically shifted over the three years, there have been noticeable changes in the prevalence of the mental health conditions associated with off-label use. In 2008, 31% of the off-label users had dementia or related other organic psychosis: this decreased to 24.8% by 2010. Similarly, beneficiaries with depression decreased from 53.8% to 48.6% and beneficiaries with neurotic and anxiety disorders decreased slightly from 35.9% to 32.8%. These changes could be reflective of published literature in 2007 by AHRQ on the evidence for safety and efficacy of off-label AAPs use (AHRQ, 2007). Despite the FDA black box warning due to safety issues and only moderate to low evidence for its efficacy in dementia (Schneider et al., 2006); it continues to be one of the top three reasons for off-label use. Similarly, for patients with SSRI resistant depression, there was only modest evidence to support augmentation of antidepressant therapy with AAPs which could be driving the slight

decrease in patients with depression. The updated AHRQ review in 2011 states that there may be new evidence to show that AAPs have efficacy as augmentation therapy in depression and quetiapine may even be effective as monotherapy (Maglione et al., 2011) which could lead to differences in prescribing patterns compared to results observed in this study.

Although off-label prescribing is a prevalent and common practice, it is particularly prevalent in the AAPs class of drugs. Our study found that 37% of AAPs use is in the complete absence of an FDA approved indication; that is a lower estimate than previously published. This could be due to federal steps such as the black box warning and the litigations. Even though this estimate is lower than expected, it is still of concern due to the presence of risk of adverse events and lack of evidence of effectiveness. Often physicians are faced with no other choice than to prescribe AAPs due to the patient's perceived need for treatment and in the face of treatment resistant patients. It also poses a dilemma to the payers since they have to balance the needs of the prescriber and patients, with safety concerns and cost issues. It may be worthwhile to educate patients and physicians in order to change their beliefs about the efficacy of AAPs in off-label treatment. Patients may also need to be educated about expected signs and symptoms of certain conditions such as neuropsychiatric symptoms of dementia to help them differentiate abnormal versus expected symptoms. Educating patients about what is expected could better help them prepare for these conditions rather than resorting to pharmacotherapy at the onset.

6.2 Specific Aim III

The purpose of this aim was to compare health care RU and costs between off-label AAPs users and non-users with mental health diagnoses in a Medicare population. The study results found that AAPs users were more likely than non-users to use an outpatient facility for mental health visits. AAPs users were also more likely to have mental health medications and claims. Total mental health costs were significantly higher among AAPs users ($1,545) in the 12-month follow up as compared to non-users ($1,057). Medicare paid an additional $396 per beneficiary per year for mental health costs for off-label users. These findings are similar to the study by Del Paggio et al.which reported an increase in mental health medication and outpatient costs after initiation with olanzapine but also reported a decrease in inpatient and emergency costs (Del Paggio et al., 2002). This difference from our study could be due to the indigent population in the Del Paggio study who had to be severely and persistently ill to qualify for the publicly funded program whereas our study population was community dwelling patients.

Upon examining all-cause RU and costs, AAPs users had a significantly lower number of inpatient visits and costs. AAPs users had 34% lower odds of having an inpatient visit in comparison to non-users and AAPs non-users incurred an incremental cost of $2,104 per beneficiary per year for inpatient visits. These findings are similar to the results reported by Al-Zakwani et al. using data from a private health plan which reported that AAPs users had fewer inpatient admissions after initiation of AAPs as compared to baseline (Al-Zakwani et al., 2003).

Al-Zakwani et al. reported lower outpatient visits in their population but our study failed to show a difference in the number of outpatient visits and costs between AAPs users and non-users. This could be reflective of the different population in the two studies. Our study focused on

a Medicare population that comprised mostly an older population with mean age of 66 years who may have scheduled more outpatient visits for increased monitoring of drug effects and chronic condition treatment but the population in the study was a young cohort form a private health plan. The different reimbursement policies between private plans and Medicare could also affect these differences.

Our results also indicate that the rate of RU is sensitive to whether the AAPs is newly initiated or not. Upon examining RU in off-label AAPs users who had newly initiated the AAPs in 2009, AAPs users had significantly higher outpatient costs compared to non-users which was similar to the results we obtained in the MEPS study which concluded that AAPs users had higher outpatient costs. Inpatient costs had also gone from being higher among non-users to being not different from AAPs users. These results indicate that in new AAPs users, RU is higher among users as compared to non-users.

The Del Paggio et al. study is the only one that assessed mental health prescription costs and our study reflected similar results costs (Del Paggio et al., 2002). Prescription costs were significantly higher among AAPs users than non-users irrespective of whether they were all-cause or mental health. AAPs are generally an expensive class of medications and the average cost of some of the AAPs can be a financial burden on patients. Additionally, during the study period from 2008-2010 all of the AAPs of interest were available only as brand name products except risperidone which became available as generic during the study period. Since some of these agents are now available as generic, AAPs costs may show a downward trend in the future. Prescription costs can be a financial burden on both Medicare and on beneficiaries. Among AAPs users the highest share of costs for Medicare (average $4,855 per person per year) and beneficiaries (average $1,066 per person per year) was attributed to prescription costs. The additional prescription costs

can be considered cost-effective if treatment with AAPs adequately decreases other health care costs such as inpatient and emergency costs or if they are clinically effective. In this study, inpatient costs were found to be the major contributing factor towards total costs among non-users and a smaller component of total costs in AAPs users. This seems to indicate an association between AAPs use and lower inpatient costs.

6.3 Specific Aim IV

The objective of this aim was to compare RU and costs associated with Medicare beneficiaries who are using AAPs for on-label treatment of schizophrenia and bipolar disorder to non-users with the same indications. The study results show AAPs users to have significantly higher mental health inpatient, prescription and total costs in comparison to their AAPs non-user counterparts. There was an additional cost of $718 per beneficiary for total mental health costs and Medicare spent three times the amount on a beneficiary using AAPs than a non-user during the follow up period. AAPs users also had significantly higher mental health RU. The odds of having at least one mental health outpatient and inpatient visit were 68% and 175% higher for AAPs users than non-users. Revicki et al. reported higher mental health outpatient costs among AAPs users in a bipolar population and He et al. reported higher number of psychiatric outpatient visits among AAPs users in a schizophrenic population, which are similar trends to our study results (Revicki et al., 2003, He et al., 2015).

Prescription costs continue to be the major factor driving total costs among users. It was the main cost component among on-label AAPs users during the follow-up period while inpatient costs are the main component among non-users. AAPs users had higher all-cause and mental health

prescription costs which was similar to the findings by He et al. (He et al., 2015). He et al. reported AAPs users had a mean cost of $438 per beneficiary which is slightly higher than our findings of $356 per beneficiary. Inpatient costs follow a different pattern from what is reported by Guo et al. (Guo et al., 2007). Our study findings show all-cause inpatient costs to be significantly lower among AAPs users compared to non-users. This finding was robust even after accounting for skewed distribution or exceptionally high inpatient costs for a few beneficiaries. Guo et al. reported that AAPs users had higher inpatient and emergency costs but their comparison group was beneficiaries using mood stabilizers for the treatment of bipolar disorder unlike our comparison group that included beneficiaries who may have had non-antipsychotic treatment but also includes those with no treatment at all.

An interesting pattern also exists among the mental health costs between off-label and on-label AAPs user cohort from Specific Aim III and IV. Off-label users had comparatively higher inpatient, outpatient and total costs even though both cohorts were using AAPs to treat mental health conditions. The major difference between the treatments in the two groups is the level of evidence. While on-label use is supported in literature by strong to moderate evidence, most off-label use only has moderate to low evidence (Maglione et al., 2011). This could be further reason to believe that off-label use of AAPs in the treatment of mental health conditions that is not supported by evidence does not benefit the health care system from a payer perspective because of increased RU and from a patient perspective since they are exposed to the adverse effects of these agents. Therefore, the benefit of initiating these agents for off-label treatment should be weighed against the risks and should be reserved only if no other options are viable.

The typical off-label user is a 66-year-old white female in contrast to a typical on-label user who is a 52-year-old white male. It is an interesting phenomenon that older patients are more

likely to be prescribed AAPs in the absence of an FDA approved indication and without strong clinical evidence to support the use. This is of concern since elderly patients are more susceptible to the adverse effects of these agents. Off-label AAPs users also had higher number of comorbid conditions as seen by an average CCI of 0.9 whereas the CCI is only 0.32 among on-label users which could also explain the higher health care costs among off-label users. Off-label users also have higher medication burden with an average of 13 medications per beneficiary in comparison to the 7 medications per on-label user.

6.4 Specific Aim V

In this aim the RU and costs of AAPs users treated for specific mental health conditions were compared to their non-user counterparts.

Depression: Among patients with depression, the mean number of all-cause inpatient visits and costs were significantly lower in AAPs users than non-users. The higher prescription costs among users were offset by their lower inpatient costs leading to a significantly lower total health care costs. Interestingly both users and non-users had similar medication burden of approximately 13 medications per beneficiary but users had significantly higher costs compared to non-users. AAPs are increasingly used to treat patients with depression over the years especially with some of AAPs receiving FDA approval for the same. There is moderate evidence to support the use of aripiprazole, quetiapine and risperidone as augmentation therapy and quetiapine as monotherapy therefore treatment with these agents should only be considered in anti-depressant treatment resistant patients (Maglione et al., 2011).

Anxiety and neurotic disorder: In patients with anxiety, neurotic and other somatoform disorders AAPs users had numerically lower inpatient and outpatient costs but it did not achieve significance. Due to the significantly large prescription costs, total health care costs were significantly higher in AAPs users compared to non-users. This pattern could be of key interest to payers such as Medicare and private health plans since they have to incur additional costs on AAPs users but it could potentially increase the patients' quality of life and decrease downstream costs if they are able to avoid multiple inpatient and outpatient visits. The presence of moderate to strong evidence for the use of risperidone and quetiapine in OCD and anxiety respectively, warrants the consideration of use of AAPs in this population. Even though use of AAPs in this cohort is off-label, it could be cost-effective to treat these patients with AAPs if the excess prescription costs are accompanied by positive clinical changes. Due to the nature of our data, we were unable to capture clinical effectiveness in our study but future research can focus on examining the relation between costs and clinical effectiveness.

Dementia: Off-label use of AAPs in elderly patients with dementia is controversial due to the increased risk of mortality. Despite significantly higher prescription costs in AAPs users, non-users had higher total costs ($18,803 vs $16,873) than users. Even though this failed to show any statistical significance, non-users incurred approximately $2,000 additional per person not treated with AAPs. This might reflect the severity of patients with no other treatment options. There could be non-users who are severely ill but not prescribed medications due to the risk profile or lack of evidence of efficacy and who seek emergent or inpatient care for their medication needs. Strong evidence for the efficacy of AAPs in the treatment of behavioral symptoms of dementia might explain the practice of prescribing AAPs to patients with dementia despite the associated risks (Maglione et al., 2011). Therefore, it is once again imperative to consider not only the costs

associated with AAPs user but also clinical changes in the patients. Patients who have no other treatment options may very well respond to AAPs under careful monitoring and supervision of practitioners. *Schizophrenia:* Patients with schizophrenia using AAPs had significantly higher prescription and total costs compared to patients not treated with AAPs. AAPs are the first line of treatment for patients with schizophrenia and all the agents have been FDA approved for this indication. Since there are no other treatment options, the higher costs of the drugs can still be cost-effective as patients achieve clinical stability.

Bipolar disorder: Beneficiaries with bipolar disorder showed very similar trends wherein AAPs users had higher prescription and total costs compared to non-users but no differences were observed in outpatient and inpatient costs. Guo et al. (2007) discussed in their study about how despite sufficient evidence to support the use of AAPs in bipolar patients it might be worthwhile to consider initiating other therapies such as mood stabilizers which are associated with lower RU and costs. Since our study did not show either cohort to have significantly higher inpatient or outpatient costs, but showed significantly higher prescription costs, it may be of economic value to consider other pharmacotherapy which are shown to be equally effective but cheaper in this population.

6.5 Strengths and Limitations

To the best of our knowledge, this is the first study that has evaluated RU and costs associated with off-label use of AAPs in a Medicare population. Published literature has primarily studied the effects on a younger population even though there is evidence of adverse effects of AAPs in the elderly population. Further, ours is the first study to use Medicare claims data, which is a public payer, to evaluate off-label use. Studies have mostly evaluated costs from a private payer perspective and this study provides estimates of RU and costs from the perspective of a public payer. In addition, recall and self-report bias was reduced since administrative claims data was used instead of other sources like self-reported surveys.

The study also used sound methodologic design to control for observed variables. We identified a control group and used propensity score matching to balance covariates across the study groups. This reduced the potential for bias. In groups where propensity score matching did not balance all covariates between the two groups, generalized linear models were used to control for any unbalanced covariate. Having three years of data also enabled a longer duration of baseline and follow-up (12 months). The study also used conservative methods when possible to capture the true effects. For example, to be diagnosed with a medical condition, the beneficiary had to have two outpatient claims instead of just one claim. Similarly, to be defined as AAPs user, the beneficiary had to have at least two claims one to 60 days apart for the same antipsychotic.

The study, however, has several limitations. First, the secondary nature of the dataset imposes certain assumptions. We assume that patients with claims for AAPs are taking the medication as prescribed. We also assume that the information recorded in the claims dataset is accurate. Databases may be subject to miscoding which could lead to inaccurate and biased results. There may also be underrepresentation of certain diagnoses since diseases with greater severity

could be listed under primary diagnosis (Brookhart, 2014). For example, a patient's primary diagnosis code reports myocardial infarction but his depression diagnosis is not coded. Second, we cannot determine which medical condition the prescribed drug is treating. Therefore, we were unable to determine if AAPs were used in off-label or on-label treatment in beneficiaries with multiple mental health conditions. We addressed this limitation by creating mutually exclusive groups of beneficiaries who were using AAPs for off-label treatment or on-label treatment by excluding those beneficiaries who had indications for both an off-label and on-label condition. By creating mutually exclusive groups, we ascertain that the users are using the drug only in the presence of the particular condition even if we cannot ascertain that the drug was used for that condition. In the final Specific Aim we also created mutually exclusive groups by specific disease state to identify beneficiaries who were using AAPs only in the presence of diagnosis claims for depression, anxiety, schizophrenia or bipolar disorder. Third, even though matching was performed to remove differences among the groups due to observed variables, the study was not able to control for unobserved differences such as patient specific factors including patient preferences. These predictors could have influenced the choice of AAPs in the treatment of certain conditions and could be potentially influencing the results. For example, patients intolerable to adverse effects of antidepressants such as decreased libido and disturbed sleep cycles may prefer initiation of AAPs. Fourth, since we used claims data and not electronic health records we were unable to obtain past medical history, which can influence RU and costs. We tried to address this limitation by using 12 months of baseline period to capture comorbid conditions using claims data. Even though we addressed this limitation in the best possible manner using claims data, we have to recognize that only conditions for which the patient had an inpatient or outpatient visit was captured in their baseline. Therefore, any conditions for which the beneficiary did not seek

treatment during the study period were not captured. Fifth, even though we tried to control for severity of disease by including the baseline RU in the propensity model, there may still be underlying differences among the AAPs users and non-users due to the level of severity of disease which is beyond the researcher's control. Sixth, due to limited funding the study was limited to institutional costs which were obtained from inpatient, outpatient and prescription costs. We did not include the carrier file claims in this study therefore the RU and costs estimated in this study do not reflect physician office-based outpatient costs. Similarly, other costs, which may be estimated from other Medicare files such as home health and hospice, were also not included in this study. Due to the lack of these components, we were unable to estimate the total RU associated with off-label use and the study focused only on institutional costs. Additionally, since we did not have the carrier file, we were restricted to identifying chronic health and other mental conditions by only using inpatient and institutional outpatient claims. In order to restrict this limitation, we used the Chronic Conditions and Other Chronic Conditions files to identify diagnoses codes that may not have appeared in the claims during the 3-year study period.

6.6 Conclusions and Future Research

Off-label use of AAPs is an important public health issue that has gained attention the last few years. As a class of drugs, AAPs carry their own adverse risk profile even as they are used to treat mental health conditions for which no other treatments exist or to treat patients who have become resistant to other treatments. To the best of our knowledge no other study has examined the RU and costs in off-label AAPs users using nationally representative data or Medicare data.

The objective of the pilot study was to examine patterns of RU among off-label AAPs users in a nationally representative population. Patients using AAPs for off-label treatment of mental health conditions had higher all-cause utilization of any resource, office-based provider visits, and hospital inpatient visits per year compared to those not using AAPs in off-label treatment and their total costs including prescription and office-based outpatient costs were significantly higher.

The objective of the second study was to evaluate the prevalence of off-label use in Medicare beneficiaries and to compare RU between off-label AAPs users and non-users. Of the total beneficiaries, 3.2% used AAPs and 36% of these were off-label users. Some of the most common indications of off-label use were depression, anxiety and dementia. Total mental health costs, outpatient costs and medication costs were higher among off-label AAPs users but all-cause inpatient costs were higher among non-users.

Off-label prescribing of AAPs continued to be a prevalent practice though it affects less than half of all AAPs users. For all-cause RU and costs, we had different results from the MEPS study and the Medicare study: among MEPS respondents AAPs users had higher RU and costs but Medicare AAPs users had lower RU and costs. This difference in results could be due to the difference in the population (younger vs. older), design (cross-sectional vs. cohort), study methods

(regression vs. matching), or data (self-report vs. administrative claims). Medicare study also showed that AAPs users had higher RU and costs associated with mental health visits and prescription cost was the main factor driving total costs. This study points to some association towards AAPs use and increased costs. If the increased costs from medications can be offset by decreased inpatient or outpatient costs or is accompanied with clinical effectiveness then off-label treatment with AAPs can be recommended as a cost-effective option.

Future research should examine the RU patterns based on the evidence supporting the off-label treatment. Cohorts of patients with off-label but supported use and off-label but unsupported use should be identified and compared. Future research should also focus on examining the association between RU and clinical outcomes. For example, does off-label use of AAPs improve clinical outcomes and improve quality of life despite the higher RU? This would help identify cost-effectiveness of using AAPs for off-label use. Future researchers can also assess the effects of duration of therapy and adherence on long term RU and costs.

As we move forward, it will be interesting to observe the RU pattern in this population in the after-effects of the CMS partnerships. The results of this study will serve as the baseline as we try to identify if utilization and costs have increased or decreased as a direct effect of these changes.

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