THE ECONOMIC AND CLINICAL IMPACTS OF PRESCRIBING ANTIDEPRESSANT, ANTICONVULSANT AND ANTIPSYCHOTIC MEDICATIONS OFF-LABEL FOR PATIENTS WITH SCHIZOPHRENIA, BIPOLAR DISORDERS, DEPRESSION AND ANXIETY

by

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(Under the Direction of Bradley C. Martin)

ABSTRACT

The objective of this study was to 1) estimate the prevalence of using antidepressant, anticonvulsant and antipsychotic medications off-label, 2) explore factors associated with these off-label uses and 3) determine the effects of using these medications off-label on total health expenditures, inpatient hospitalizations and emergency room (ER) visits in Medicaid enrollees with schizophrenia, bipolar disorders, depression, or anxiety.

Georgia Medicaid data (1999-2001) were obtained from the Georgia Department of Community Health. In the outcomes analysis, four disease-specific cohorts were constructed for patients with schizophrenia, bipolar disorders, depression and anxiety disorders. Within each cohort, the treatment group was formed of subjects who received off-label antidepressant, anticonvulsant or antipsychotic medications at the beginning of a 12 months observation period, while the comparison group consisted of subjects who did not receive these off-label medications for the entire observation period. Differences in annual outcomes were estimated between propensity score matched off-label and on-label users. Rosenbaum bounds sensitivity analysis was performed to test the robustness of the outcome estimates against hidden bias.

46,976 (75.42%) antidepressant recipients, 38,497 (80.12%) anticonvulsant recipients and 21,252 (63.62%) antipsychotic recipients received at least one of these medications off-label in

2001. Recipients older than 64 were four to six times more likely to receive an off-label prescription relative to those younger than 40. The off-label users experienced significantly higher per capita annual prescription expenditures across the cohorts (net difference: schizophrenia cohort $892.88; bipolar cohort $555.51; depression cohort: $783.87; anxiety cohort: $640.72). Besides prescription costs, the off-label users in the depression cohort also had higher outpatient, inpatient, long-term care and mental health related expenditures, which in total, resulted in a $2,209.36 average cost difference between the off-label and the on-label groups. The off-label users in the schizophrenia cohort incurred significantly lower hospital utilizations and expenditures.

In conclusion, the off-label use of antidepressant, anticonvulsant and antipsychotic medications is highly prevalent. Using these medications off-label is associated with significantly increased prescription expenditures across all mental disorders under investigation. For other outcome measures including medical expenditures, ER and hospital utilizations, the influences of off-label drug use are heterogeneous in different mental disorders.

INDEX WORDS: Off-label, Antidepressants, Anticonvulsants, Antipsychotics, Schizophrenia, Bipolar Disorders, Depression, Anxiety, Medicaid, Costs, Hospitalizations, Emergency Room Visits

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Antidepressants, anticonvulsants and antipsychotics are the central nervous system (CNS) drugs extensively prescribed for off-label uses. Off-label uses can account for 40% to 70% of the prescriptions filled for these three drug categories, with higher rates found in newer and more expensive agents (Barbui 2004; Chen in press; Fountoulakis 2004; Graves 1998; Kaye 2003; Rosenheck 2001; Streator 1997). In addition to the uses for clinical conditions currently without effective pharmacotherapy, such as dementia and behavior disorders, these drugs are also commonly prescribed for psychiatric conditions that already have multiple FDA approved treatments such as anxiety, depression, bipolar disorders and schizophrenia (Barbui 2004; Chen in press; Fountoulakis 2004; Graves 1998; Hirschfeld 2003; Kaye 2003; Lee 2002; Weiss 2000; Stone 2003). Only a small portion of these off-label uses are supported by substantial scientific evidence (randomized clinical trial) (Chen in press; Thomson Healthcare, Inc 2004). There is a pressing need to rationalize the off-label prescribing of these often-expensive agents with uncertain risk benefit ratios. However, no published study has ever comprehensively examined the economic and clinical impacts of prescribing CNS agents off-label.

The primary objective of this project was to estimate the impact of using antidepressant, anticonvulsant and antipsychotic medications off-label on total health expenditures, hospitalizations and emergency room visits as compared with FDA

approved treatments prescribed for labeled uses. The effects of off-label uses will be evaluated on patients with one of the four psychiatric conditions including schizophrenia, bipolar disorder, depression and anxiety. A retrospective cohort study was performed using Georgia Medicaid claims data for the years 1999 through 2001. Research subjects were hierarchically classified into one of those four disease-specific cohorts according to their diagnoses as described in Figure 2.1 (Kronick 2000). Within each disease-specific cohort, the treatment group was formed of the subjects who were initially treated by off-label antidepressant, anticonvulsant or antipsychotic prescriptions for a new treatment episode, while a comparison group consisted of subjects who received labeled prescriptions only during the entire observation period. A Propensity score matching (Rosenbaum 1984,1985 D'agostino 1998) method was used to eliminate the selection bias due to observed confounding variables between subjects in the treatment (off-label) and the comparison (on-label) groups. The Rosenbaum Bounds method of sensitivity analysis was conducted between matched pairs to determine how strongly an unmeasured confounding variable will affect the treatment selection and therefore affect the outcome measures (DiPrete 2004; Hujer 2003).

The specific aims of the study are to

1. Determine patient characteristics (age, sex, race, comorbidities and prescriptions) and prescriber specialties associated with antidepressants, anticonvulsants, and antipsychotics off-label use.

2. Estimate the effects of using off-label antidepressants, anticonvulsants and antipsychotics alone or as adjunct to labeled pharmacotherapy vs. using only labeled pharmacotherapy for treating schizophrenia, bipolar disorder, depression or anxiety on three main outcome measures: total health expenditures, inpatient hospitalizations and emergency room visits.

This project tested the following hypothesis:

Ha (Alternate hypothesis): Patients who are prescribed antidepressant, anticonvulsant and antipsychotic medications off-label alone or as adjunct to labeled pharmacotherapy vs. patients who are prescribed only labeled pharmacotherapy for schizophrenia, bipolar disorder, depression or anxiety differ significantly in total health care cost, inpatient hospitalizations, and number of emergency room visits.

CHAPTER 2

BACKGROUND AND SIGNIFICANCE

CENTRAL NERVOUS SYSTEM DRUG OFF-LABEL USE

The labeling of a prescription drug is of vital importance to regulators. The drug label presents information about the indications for which a drug is approved by the US Food and Drug Administration (FDA), and summarizes the safety and efficacy information obtained from clinical trials (Landow 1999). The aims of labeling regulation are to improve pharmaceutical quality, provide medical evidence, evaluate the risk benefit ratio of medical products, and therefore enhance the quality of care. However, in actual practice, a great number of drugs are commonly prescribed outside the limits of their labels, which is often referred to as off-label drug use.

Central nervous system (CNS) drugs are one of the drug categories that have been intensively prescribed off-label. Off-label use of CNS drugs can account for 25% to more than 80% of a drug's annual sales (Decision Resources Inc. 2002). In recent years, the research on CNS drugs off-label use has been focused on three CNS drug subcategories: antidepressants, anticonvulsants and antipsychotics. Despite the fact that a large proportion of these agents have been formally evaluated for the treatment of only a few mental and neurological disorders, they are tried on nearly all neuropsychiatric conditions. More than 40% of antidepressant, anticonvulsant or antipsychotic recipients received these agents for off-label purposes with even higher prevalence rates found in

the recipients of new generation agents (Barbui 2004; Chen in press; Fountoulakis 2004; Graves 1998; Kaye 2003; Lee 2002; Rosenheck 2001; Stone 2003).

During the past two decades, several new groups of CNS medications have been introduced for the treatment of seizure disorders (anticonvulsants launched after 1993), depression (Selective Serotonin Reuptake Inhibitor (SSRIs) and Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)) and schizophrenia (atypical antipsychotics). The greatest advantage of these medications is that they reduce the risk of unpleasant or dangerous side effects as compared to older agents, and then improve patient tolerance for long-term drug therapy. For instance, atypical antipsychotics cause substantially fewer extrapyramidal symptoms than conventional antipsychotics. Gabapentin, topiramate and tiagabine are less likely than older anticonvulsants to cause immune-mediated adverse reaction and may be a better choice in patients with a history of drug allergies. In light of their appealing safety profile, these agents have recently gained popularity in treating conditions beyond depression, epilepsy and schizophrenia. Up to 70% of atypical antipsychotics prescribed are for conditions other than schizophrenia and about 50% are for an off-label indication (Barbui 2004, Fountoulakis 2004,). In another study of 1,080 patients who received an SSRI in a network model Health Maintenance Organization (HMO), 56% of medical claims showed such treatment targeted non-FDA approved diagnoses (Streator 1997). Research conducted by Chen et al found that about 81% of recipients prescribed an anticonvulsant marketed after 1993 in Georgia Medicaid received at least one new anticonvulsant off-label in year 2000 (Chen in press).

OFF-LABEL INDICATIONS FOR ANTIDEPRESSANTS, ANTICONVULSANTS AND ANTIPSYCHOTICS

The off-label prescribing of antidepressants, anticonvulsants and antipsychotics covers numerous conditions ranging from common neuropsychiatric disorders with the FDA approved pharmacological therapy to rare conditions without well established treatments, such as hot flashes for breast cancer survivors, substance abuse and stuttering (Fountoulakis 2004; Loprinzi 2000). Among neuropsychiatric conditions with labeled pharmacological treatments, the most recognized off-label indications of these three drug categories include anxiety disorders, neuropathic pain, bipolar disorders, depression and personality disorders (Barbui 2004; Chen in press; Fountoulakis 2004; Graves 1998; Hirschfeld 2004; Kaye 2003; Lee 2002; Weiss 2000; Stone 2003). Antidepressants and anticonvulsants, especially benzodiazapine anticonvulsants, are also often found among the prescriptions for patients with schizophrenia. Because pharmacotherapy is not the main treatment for personality disorders and most neuropathic pain cannot be properly differentiated from other pain problems by ICD9-CM codes used in claims data, only schizophrenia, bipolar disorder, depression or anxiety are considered in this study.

Anxiety disorders

Anxiety disorders (generalized anxiety disorder, panic disorder, phobias and post-traumatic stress disorders) are some of the most prevalent psychotic disorders, affect ingapproximately 19 million American adults (Dickey, 1994). This is a group of disorders that fill people's lives with overwhelming anxiety and fear. Without appropriate treatment, anxiety disorders are chronic, relentless and can grow progressively worse. Benzodiazapine and non-benzodiazapine anxiolytics are the medications approved by

FDA for treating anxiety disorders. However, benzodiazapines such as diazepam, alprazolam, and clonazepam can cause bothersome side effects such as sedation, difficulties concentrating, and dependence. Buspirone, a nonbenzodiazapine anxiolytic that does not lead to dependence, is an effective alternative, but it must be taken three times daily (Stone 2003). Due to those potential disadvantages, the search for new anxiolytics with better tolerance and compliance has never stopped. Almost all antidepressants have been tried on patients with anxiety disorders (Lee 2002, Stone 2003) especially since three new agents (venlafaxine, paroxetine and sertraline) gained the FDA (Food and Drug Administration) approval for treating different types of anxiety disorders. New generation anticonvulsant medications including gabapentin, tiagabine and oxcarbazepine have also been tested as treatments for anxiety disorders, considering that these newer anticonvulsants might possess similar anxiolytic effects as benzodiazapines (Pollack 1998; Rosenthal 2003; Windhaber 1997). Besides antidepressants and anticonvulsants, antipsychotics are also commonly used off-label for anxiety disorders. Weiss et al reported that 20.2% of antipsychotic recipients took the drug as an anxiolytic (Weiss 2000). A British study by Barbui et al showed that anxiety disorders account for 38% of off-label prescriptions of conventional antipsychotics and approximately 10% of off-label prescriptions of olanzapine (Barbui 2004).

Depression

Depression is one of the most common and treatable mental illnesses. In any one-year period, approximately 19 million Americans suffer from this disease (Robins 1990). Depression presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration. These problems can become chronic or recurrent and lead to substantial impairments in an

individual's ability to take care of his or her everyday responsibilities. At its worst, depression can lead to suicide, a tragic fatality associated with the loss of about 850,000 lives every year in the world (WHO 2004). There are several types of antidepressant medications used to treat depressive disorders. These include newer medications—chiefly the SSRIs, the tricyclics (TCAs), and the monoamine oxidase inhibitors (MAOIs). The SSRIs and other newer medications that affect neurotransmitters such as dopamine or norepinephrine generally have fewer side effects than tricyclics. They have become the most commonly prescribed antidepressant for depression. Although there is no clinical trial data to support antipsychotic use for depression and their prescription is not regarded as 'good' practice, clinicians argue that these off-label uses were motivated by the need of tackling psychotic symptoms in the absence of a frank psychotic disorder (Kaye 2003). Based on two European studies, antipsychotic drugs are most frequently prescribed off-label for depressive disorders. Antipsychotic medications account for 51% of off-label prescriptions of conventional antipsychotics and more than 60% of off-label prescriptions of quetiapine (Barbui 2004; Kaye 2003). Another American study by Weiss et al reported 13.3% of the pharmacy customers stated taking antipsychotics for depression (Weiss, 2000).

Bipolar disorder

Bipolar disorder, also known as manic-depressive illness, is a brain disorder that causes dramatic mood swings—from overly "high" and/or irritable to sad and hopeless states, and then back again, often with periods of normal mood in between. Severe changes in energy and behavior go along with these changes in mood. The periods of highs and lows are called episodes of mania and depression. Over the past several decades, substantial progress has been made in the pharmacologic treatment of bipolar disorder. In 1972, lithium was approved by the FDA for the treatment of manic episode of

bipolar disorder and as maintenance treatment. More than 20 years later, divalproex was approved for the treatment of acute manic episodes in patients with bipolar disorder. In 2000, olanzapine, an atypical antipsychotic, was approved for the acute treatment of mania (Hirschfeld 2003). In addition to these examples, a number of other compounds have been investigated and have been prescribed off-label in the treatment of various phases of bipolar disorder. These have included antidepressants (El-Mallakh 1999; Fogelson 1992; Megna 2001; Nemeroff 2001), anticonvulsants (Botts 1999; Benedetti 2004; Denicoff 1997), and, most recently, atypical antipsychotics (Guille 2000). A combination of mood stabilizing agents with antidepressants, anticonvulsants and antipsychotics is becoming the standard regimen to regulate manic and depressive episodes of bipolar disorder.

Schizophrenia

More than two million Americans suffer from schizophrenia every year (Spearing 1999). Schizophrenia is most commonly characterized by both 'positive symptoms' (those additional to normal experience and behavior) and negative symptoms (the lack or decline in normal experience or behavior). Positive symptoms are grouped under the umbrella term psychosis and typically include delusions, hallucinations, and thought disorder. Negative symptoms may include inappropriate or lack of emotion, poverty of speech, and lack of motivation.The severity of the symptoms and long-lasting, chronic pattern of schizophrenia often cause a high degree of disability. The most common medications for schizophrenia are conventional and atypical antipsychotics and when used regularly and as prescribed, can help reduce and control the distressing symptoms of the illness.

Anticonvulsants have been used for treating schizophrenia since the early 1980s (Haas 1982). Carbamazepine and diazepam are the anticonvulsants most commonly seen among the prescriptions for patients with schizophrenia or psychosis disorders. Although both agents have shown some effects on reducing dosages of conventional antipsychotics and preventing symptom progression in schizophrenic patients (Carpenter 1999; Kahn1990), The Cochrane collaboration systematic review, a drug information database that includes rigorous drug evaluation for some specific medical conditions by a panel of experts, does not recommend carbamazepine for routine clinical use for treatment or augmentation of antipsychotic treatment of schizophrenia (Cochrane library 2003). Lamotrigine, a new generation anticonvulsant, has recently been tested for treating clozapine resistant schizophrenia in a double blind, placebo-controlled, 14-week, crossover trial (Tiihonen 2003). Lamotrigine treatment was more effective in reducing positive and general psychopathological symptoms than clozapine alone.

EFFICACY OF USING ANTIDEPRESSANTS, ANTICONVULSANTS AND ANTIPSYCHOTICS OFF-LABEL FOR ANXIETY DISORDERS, BIPOLAR DISORDER AND DEPRESSION

Although the off-label prescribing of antidepressants, anticonvulsants and antipsychotics in persons with schizophrenia, bipolar disorder, depression or anxiety are generally embraced by practitioners, only a few of those uses are supported by randomized clinical trials (Table 2.1), which are so called “evidence based uses”. However, this does not imply that these medications are prescribed without any “evidence”. The majority of off-label uses are supported by varying levels of evidence such as: case reports, case series, small sample size open label studies and retrospective studies (Thomson Healthcare, Inc 2004). Though these types of studies

cannot establish casual inferences, they are often the first reports of such potential uses and encourage physicians to prescribe these drugs for off-label uses.

ISSUES ASSOCIATED WITH OFF-LABEL PRESCRIBING

Safety & efficacy

Successful patient care requires that physicians be free to use drugs according to their best knowledge and judgment. In the opinion of the treating physician who has detailed knowledge of the medical history and clinical status of a given patient, it may be argued that there is possible pharmacological rationale, or certain level of practical evidence obtained by clinical experience for most off-label uses. However, the off-label indication is not subjected to the same level of regulatory examination that the approved indication undergoes. Consequently, the safety and effectiveness of the drug is questionable when prescribed for an off-label indication (Conroy 2002). Many CNS (Central Nervous System) agents have modest effect sizes and dangerous adverse drug reactions. New generation antidepressant, anticonvulsant and antipsychotic medications are regarded as having favorable safety profile over older agents. However, these new agents can still cause very severe adverse drug actions such as seizure (clozapine) and life threatening rashes (lamotrigine). When these agents are prescribed off-label, unexpected adverse drug reaction is always a big concern. Recently, the pooled results of three unpublished trials involving pediatric patients with major depressive disorder failed to show paroxetine to be more efficacious than placebo (GlaxoSmithKline Inc, 2003). In addition, the pooled results showed that suicidal thoughts, suicide attempts and episodes of self-harm were more frequent among the paroxetine users (5.3% of 378 children) than among those in the placebo group (2.8% of 285 children).

Most neurological and psychiatric diseases are chronic. Without appropriate treatments, they could become progressively worse. For episodic conditions such as depression and bipolar disorder, inadequate or inefficient treatments might prolong disease episodes and increase recurrence rates. According to the drug evaluation of Micromedex health care series and Cochrane collaboration systematic review, off-label alternatives often do not show consistent advantages over FDA approved standard regimens for treating neuropsychiatric conditions (Cochrane library 2003; Thomson health care Inc 2004). Although there is no study investigating the general clinical outcomes associated with off-label prescribing, off-label use with uncertain efficacy and side effects might have the potential to increase health resource utilizations and therefore increase health care costs.

Cost & reimbursement

Besides efficacy and safety issues, another concern associated with off-label drug use is prescribing high cost medications off-label and ensuing impact on drug budgets. With the desire to curb costs, the US Centers for Medicare and Medicaid Services (Center for Medicare and Medicaid Services 2004) began to question the off-label use of a number of the newer and more expensive cancer drugs by placing them on coverage review in 2002. For CNS drugs such as antidepressants, anticonvulsants and antipsychotics, new generation agents are prescribed more often for off-label purposes than older agents. The spending on those new drugs, which varies for different conditions, can be up to $500 per month (Drug Topics Red Book 2004). Concern over excessive use and irrational prescribing of these new agents has been voiced for many years. Besides coverage review, numerous government and commercial insurance plans including Medicaid have tried to restrict the off-label uses of these newer more expensive CNS agents in various ways including instituting prescribing guidelines,

formulary restrictions, increased patient co-payments, and drug utilization reviews. However, some people have argued that this action would limit a physician's ability to meet the unique needs of individuals who face the disease and that it would increase morbidity and mortality, and actually increase the costs and complications. With the ever widening range of CNS drugs available, there is a pressing need to rationalize the off-label prescribing of these often expensive and potentially toxic drugs.

RATIONALE AND SIGNIFICANCE

As far as the researchers are aware, this would be the first study aimed at estimating the clinical and economic outcomes associated CNS drug off-label uses, utilizing a large observational database. Insurance plans, as well as the FDA, acknowledge that off-label use of drugs in the practice of medicine may be appropriate, and as such, is not considered illegal or unethical. However, because the risk benefit profile of off-label use has not been demonstrated, it is often associated with "high rates of adverse drug reactions" or "increased costs" (Conroy 2002; Turner 1998; Wilton 1999). Contrarily, because the high prevalence of off-label prescribing is an existing truth, some people and organizations have questioned the FDA's function on protecting American public health (Seavey 2004; Tabarrok 2000). They suggest that the FDA drug evaluation process is overly time-consuming and might delay the public access to new treatments and therefore leave patients untreated or treated by off-label prescriptions. In the past ten years, there have been a few well-publicized lawsuits against either the pharmaceutical industry for illegal off-label promotion (e.g. gabapentin) or against the FDA for denying the industry's First Amendment right by regulating its off-label promotions (US Food and Drug Administration 2004; Hudson 2004). As the consequences of these lawsuits, FDA conceded that it did not have the legal authority to regulate speech of off-label uses in 2000 and Pfizer paid $430 million settlement for

illegally promoting unapproved uses of Neurontin in 2003. After being debated for more than two decades, off-label drug use is still a very controversial issue. There is considerable interest in the off-label prescribing associated with clinical and economic outcomes within governments, health insurance plans and pharmaceutical industries. However, very little information is currently available.

In addition, present studies regarding off-label prescribing associated outcomes often focus on the off-label use of a single drug or a small drug category (e.g. SSRIs) for a specific clinical condition. In this study, three CNS drug categories are under investigation, including more than 80 agents, covering half of all CNS agents and more than two third of all CNS prescriptions written (data on file from our preliminary analysis). The effects of their off-label uses will be investigated on the four most common psychiatric conditions (schizophrenia, bipolar disorder, depression and anxiety). Patient and physician characteristics associated with off-label prescribing will also be identified. The comprehensive information on the effect of prescribing CNS drugs off-label on cost, hospitalization and emergency room visit will especially aid decision making for policy makers in Medicaid administrations and Managed Care Organizations (MCOs) when they consider coverage and reimbursement issues.

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Table 2.1: Off-label uses positively supported by randomized clinical trials (Thomson Healthcare, Inc 2004).

	Anxiety disorders	Depression	Bipolar disorders	Schizophrenia
Antidepressants	citalopram, imipramine, clomipramine			
Anticonvulsants	gabapentin		phenytoin, topiramate	diazepam, topiramate
Antipsychotics		olanzapine		

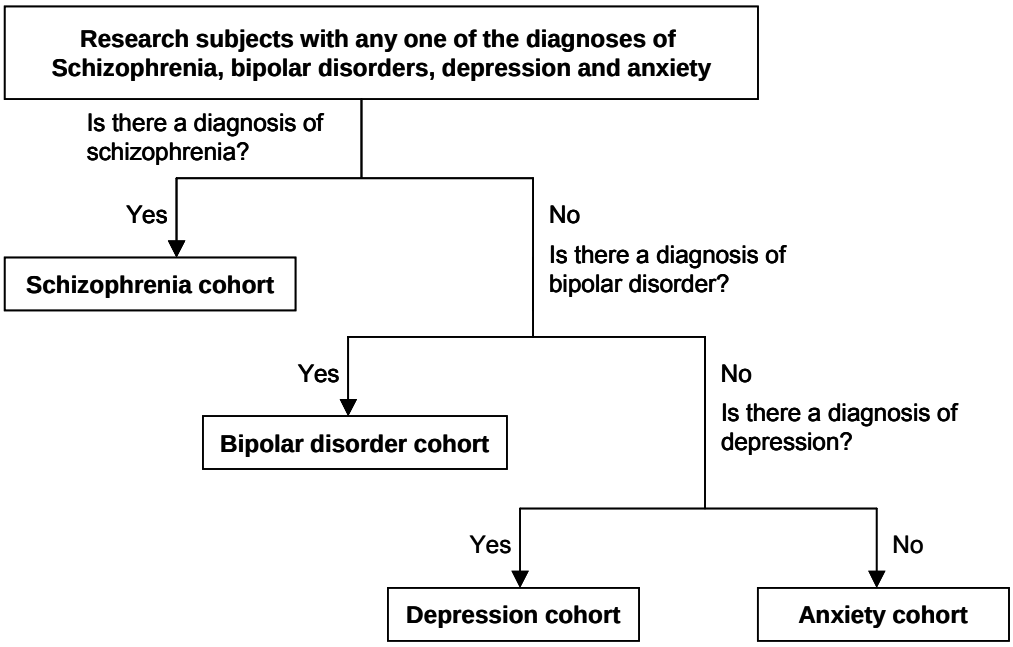

Figure 2.1: Disease-specific cohorts

CHAPTER 3

PREVALENCE AND FACTORS ASSOCIATED WITH THE OFFLABEL USE OF ANTIDEPRESSANT, ANTICONVULSANT AND ANTIPSYCHOTIC MEDICATIONS AMONG GEORGIA MEDICAID ELIGIBLES IN 2001[1]

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ABSTRACT:

Background: Antidepressants, anticonvulsants and antipsychotics are central nervous system (CNS) drugs extensively prescribed for off-label uses. Off-label uses can account for 40% to 70% of the prescriptions filled for these three drug categories with higher rates found in newer and more expensive agents.

Objectives: The objective of this study was to determine the prevalence and factors associated with the off-label use of antidepressant, anticonvulsant and antipsychotic medications.

Methods: A retrospective study of Georgia Medicaid recipients at least 18 years of age who filled at least one antidepressant, anticonvulsant or antipsychotic prescription in 2001 was conducted. Three cohorts were constructed of recipients prescribed antidepressant, anticonvulsant or antipsychotic medications. A prescription was defined as off-label if none of the ICD-9-CM codes received within 2000-2001 matched the labeled indications of the study prescription(s). A stepwise logistic variable selection procedure was used to identify demographic, comorbid, and prescriber factors associated with off-label drug use.

Results: 46,976 (75.42%) antidepressant recipients, 38,497 (80.12%) anticonvulsant recipients and 21,252 (63.62%) antipsychotic recipients received at least one of these medications off-label in 2001. For the recipients of these three drug categories, the likelihood of receiving off-label medications increased remarkably with advancing age. Recipients older than 64 were four to six times more likely to receive an off-label prescription relative to those less than 65 years of age (antidepressants recipients: OR: 5.15, 95% CI 4.76 to 5.56; anticonvulsants recipients: OR: 4.54, 95% CI 4.16 to 4.96; antipsychotics recipients: OR: 5.21, 95% CI 4.82 to 5.63). Among anticonvulsant recipients, receiving new agents launched after 1993 was the strongest predictor (OR: 7.63, 95% CI 7.07-8.23) of receiving off-label anticonvulsant medications. However,

exposure to newer agents did not always imply higher risk of receiving off-label medications. Patients exposed to SSRIs (OR: 0.43, 95% CI 0.40-0.45) or atypical antipsychotics, especially clozapine (OR: 0.19, 95% CI 0.16-0.23), were associated with decreased risks of receiving medications off-label as compared with patients exposed to trycyclic antidepressants or conventional antipsychotics respectively. In terms of patient comorbidities, renal failure was the only disease that was associated with a greater likelihood of receiving all three drug categories off-label (antidepressants: OR: 1.43, 95% CI 1.24 to1.64; anticonvulsants: OR: 1.77 95% CI 1.49 to 2.10; antipsychotics: OR: 1.84, 95% CI 1.52 to 2.24). Major depressive disorder was found to be associated with greater likelihoods of receiving both anticonvulsant (OR: 1.40, 95% CI 1.28 to 1.52) and antipsychotic (OR: 2.1, 95% CI 1.94 to 2.27) off-label.

Conclusions: The off-label use of antidepressant, anticonvulsant and antipsychotic medications is highly prevalent. Further research to study the effects of off-label use of these three drug categories in patients with mental and neurological disorders may be an important step toward defining the scope and potential for such use.

Key words: Off-label, Antidepressants, Anticonvulsants, Antipsychotics, Medicaid

INTRODUCTION:

Central nervous system (CNS) drugs are one of the drug categories that have been intensively prescribed off-label. Off-label use of CNS drugs can account for 25% to more than 80% of a drug's annual sales (Decision Resources Inc. 2002). Antidepressants, anticonvulsants and antpsychotics are the three CNS drug categories most commonly prescribed and have ranked among top ten therapeutic classes in both the US and global sales since 1999 (Chawla 2004). The annual sales of these three drug categories increased 40% in the US market from 2000 to 2002 (Chawla 2004). Expanding off-label indications for these three drug categories contribute to their

increased utilization. Recent literature reported that 40% to 70% recipients of the second generation antidepressant, anticonvulsant or antipsychotic prescriptions received these agents for off-label purposes (Barbui 2004; Chen in press; Fountoulakis 2004; Graves 1998; Kaye 2003; Lee 2002; Rosenheck 2001; Stone 2003).

It is generally acknowledged that the off-label use of CNS medications is extensive for the pediatric population (Blumer 1999; Conroy 2000; Nahata 1999). This may stem from a hesitancy to conduct medical experiments on children. However, apart from pediatrics, off-label use evidently plays an important role in adult psychiatry (Lee 2004; Kaye 2003; Shelton 2003; Thase 2002). Although a small proportion of off-label prescriptions are written based on the "gold standard" of proof for a drug's effectiveness and safety such as large scale, carefully controlled clinical trials, many off-label uses may warrant justifications from further studies. For instance, atypical antipsychotics, originally approved for the treatment of schizophrenia and mania, had been used widespread for patients with dementia accompanied behavioral and psychological symptoms, although their safety and clinical efficacy in dementia population was uncertain (Lee 2004; Motsinger 2003). In April, 2005, the Food and Drug Administration issued a warning against this use because clinical studies have shown a higher death rate associated with atypical antipsychotic use compared to dementia patients receiving a placebo (US Food and Drug Administration 2005). Our previous study also showed that only a modest proportion (19% - 57%) of anticonvulsant off-label uses were supported by evidence from randomized controlled trials (Chen in press). Given that off-label drug use is almost unavoidable in clinical psychiatry, post-market surveillance and clinical trials targeting patients who are at high risk of receiving off-label CNS medications is necessary to ensure that the benefits of an off-label treatment outweigh

its risks. However, because very limited research has touched this area, the patient and physician factors associated with off-label prescribing remain to be determined.

The aim of the current study was to determine the prevalence of off-label antidepressants, anticonvulsants and antipsychotics uses in the adult Georgia Medicaid Enrollees, and then to explore patient characteristics (demographic, comorbidities, number of medications filled) and prescriber specialties associated with the off-label uses of these three drug categories.

METHODS:

Data source:

Data for this study was obtained from computerized Georgia Medicaid administrative claims files containing pharmacy, physician, hospital and nursing home claims linked by an encrypted recipient ID.

Research subjects and cohorts:

All Georgia Medicaid enrollees who were 18 years or older as of January 1, 2001 and who had at least one antidepressant, anticonvulsant or antipsychotic prescription filled in 2001 were eligible to be included. 24 months of continuous eligibility for enrollment in Georgia Medicaid from January 1, 2000 to December 31, 2001 was also required.

Three cohorts were constructed for the recipients of antidepressants, anticonvulsants and antipsychotics respectively. Research subjects who received prescriptions from more than one drug category were allowed to enter multiple study cohorts.

Determining off-label prescriptions and off-label recipients:

The primary sources for determining labeled indications were the prescription drug leaflets and the Physician Desk Reference. Since drug labeling is dynamic in nature and the approved indications are continuously evolving, we chose to accept all the indications approved by FDA up to December 2004. Tables 3.1 - 3.3 present the labeled indications of all antidepressant, anticonvulsant and antipsychotic medications. The ICD-9-CM definitions of these indications were identified through a comprehensive literature review and ICD-9-CM databases. Table 3.4 presents the ICD-9-CM codes for each of the labeled indications.

According to the FDA, off-label drug use is characterized as the use of a prescription drug for an indication, in a dosage form or dose regimen for a particular population in a way not stated in the approved labeling (Woodcock 2003). Owing to the limited availability of information from the Georgia Medicaid database, we did not consider the off-label drug use related to dosage, duration of time and route of administration. In addition, prescribing an antidepressant, anticonvulsant or antipsychotic for monotherapy, although it is solely labeled for adjunct therapy, was not considered as off-label in this study because our preliminary study found that less than 4 percent of the off-label anticonvulsant uses could be attributed to this reason and it had a great amount of overlap with off-label uses for non FDA approved clinical conditions (Chen, in press).
An antidepressant, anticonvulsant or antipsychotic prescription filled in 2001 was categorized as off-label if none of the ICD-9-CM codes the patient received within the 24 months observation period (January 2000 – December 2001) could be matched with one of the approved indications of this prescription. Otherwise, it was categorized as on-label.

Determining the prevalence of off-label drug use:

Within each cohort, the unit of analysis for computing the prevalence of off-label antidepressant, anticonvulsant and antipsychotic use was the individual patient who

received at least one prescription of a certain drug category off-label. The denominator used in this study was all recipients exposed to at least one antidepressant, anticonvulsant and antipsychotic respectively during the year 2001.

Determining patient and physician factors associated with off-label drug use:

A comprehensive list of possible factors associated with off-label prescribing was identified by a survey of published literature and expert opinion. In this study, a Medline search using the combination of Mesh terms: off-label and (patient selection, physician practice pattern) was first conducted. However, only a few articles were identified and most of those articles are not actually related to the off-label treatment selection. Therefore, a very liberal inclusion criterion was applied to identify and include all potential covariates available in the Medicaid data after consulting a clinical pharmacist in a psychiatric clinic and a neurologist. This list included patient demographics, diagnosis-related comorbidities, physician specialty, drug classes and the number of antidepressant, anticonvulsant and antipsychotic medications filled in the study period (table 3.5). In terms of diagnosis-related comorbidities, all mental disorders were included because antidepressant, anticonvulsant and antipsychotic medications have been used off-label for various mental disorders. Having a certain mental condition, such as depression with psychotic symptoms, may cause physicians to consider off-label medications. Besides mental disorders, other chronic conditions were also included given the high prevalence of comorbid mental disturbances associated with these diseases. A list of diagnosis-related comorbidities and their ICD9 codes was obtained from the Substance Abuse and Mental Health Services Administration (SAMHSA) which contains detailed classifications of mental and substance related comorbidities and comparatively general classifications for other diseases (MEDSTAT Group 2003).

Statistical analysis:

Three logistic models were estimated for the three cohorts (recipients of antidepressants, anticonvulsants and antipsychotics). A stepwise logistic variable selection procedure was used to identify factors independently associated with the likelihood of patients receiving a certain drug category off-label. The binary treatment indicator (1 = any off-label use, 0 = labeled use) was modeled according to patients' age, race, gender, comorbidities, type of prescriptions (new generation vs. traditional), and physicians' specialty. The c-statistic (area under receiver-operator curve), proportion of variance explained (R^2), and chi-square goodness-of-fit test determined model adequacy. All data manipulations and statistical analyses were performed with SAS (version 8.2, SAS institute, Cary, NC).

RESULTS:

126,685 antidepressant recipients, 87,365 anticonvulsant recipients and 59,404 antipsychotic recipients were identified from the 2001 GA Medicaid data, of which 62,505 antidepressant recipients, 48,261 anticonvulsant recipients and 33,536 antipsychotic recipients met the 24 months continuous Medicaid eligibility criteria. After excluding patients younger than 18 as of January1, 2001 and patients without full Medicaid benefits, the final study sample consisted of 62,289 antidepressant recipients (antidepressant cohort), 48,049 anticonvulsant recipients (anticonvulsant cohort) and 33,406 antipsychotic recipients (antipsychotic cohort). 9,881 subjects received medications from the all three drug categories in 2001. Table 3.6 presents the descriptive statistics for the study populations. The majority of the subjects were female and the average age was between 52 and 54 across the cohorts.

46,976 (75.42%) antidepressant recipients, 38,497 (80.12%) anticonvulsant recipients and 21,252 (63.62%) antipsychotic recipients received at least one of these medications off-label in 2001 (Figure 3.1). Table 3.7 presents the top five prescribed

antidepressant, anticonvulsant and antipsychotic medications in 2001. The second generation agents including SSRI, gabapentin and atypical antipsychotics had replaced the traditional agents as the most popularly prescribed antidepressant, anticonvulsant and antipsychotic medications. Gabapentin was found to be the medication most commonly used off-label. Nearly all gabapentin recipients (98.04%) received the drug for clinical conditions other than partial epilepsy or postherpetic neuralgia in 2001.

Tables 3.8 - 3.10 present the logistic regression results for the recipients of antidepressant, anticonvulsant and antipsychotic medications respectively. Multivariate models revealed that patient demographic factors, especially age, are strong predictors for the likelihood of receiving off-label medications. The recipients older than 64 were four to six times more likely to receive an off-label prescription relative to those less than 64 years of age (antidepressants recipients: OR: 5.15, 95% CI 4.76 to 5.56; anticonvulsants recipients: OR: 4.54, 95% CI 4.16 to 4.96; antipsychotics recipients: OR: 5.21, 95% CI 4.82 to 5.63;). Whites were consistently more likely to receive off-label medications than non-whites (antidepressants recipients: OR: 1.15, 95% CI 1.10 to 1.20; anticonvulsants recipients: OR: 1.71, 95% CI 1.62 to 1.80; antipsychotics recipients: OR: 1.89, 95% CI 1.79 to 1.99).

The results of the logistic regression analyses also demonstrate that exposure to newer generation agents did not always imply higher risk of receiving off-label medications. For anticonvulsant recipients, receiving new agents launched after 1993 was the strongest indicator (OR: 7.63, 95% CI 7.07 to 8.23) of receiving off-label anticonvulsant medications. However, patients exposed to SSRIs (OR: 0.43, 95% CI 0.40 to 0.45) or atypical antipsychotics, especially clozapine (OR: 0.20, 95% CI 0.16 to 0.23), were associated with lower likelihood of receiving medications off-label as compared with patients exposed to tricyclic antidepressants or conventional antipsychotics respectively.

The association between physician specialties and off-label drug use was found to be inconsistent across the cohorts. Antipsychotic recipients who were seeing a psychiatrist during the study period seemed to be more likely to receive antipsychotic medications off-label (OR: 1.44, 95% CI 1.31 to 1.58). Nevertheless, for antidepressant (OR: 0.85, 95% CI 0.80 to 0.91) and anticonvulsant (OR: 0.25, 95% CI 0.24 to 0.27) recipients, seeing a psychiatrist was associated with a lower likelihood of receiving these two drug categories off-label.

Many diagnoses related comorbidities also had factor impacts on the likelihood of receiving off-label medications. Renal failure was the only disease that was associated with a greater likelihood of receiving all three drug categories off-label (antidepressants: OR: 1.43, 95% CI 1.24 to1.64; anticonvulsants: OR: 1.77 95% CI 1.49 to 2.10; antipsychotics: OR: 1.84, 95% CI 1.52 to 2.24). Major depressive disorder was found to be associated with greater likelihoods of receiving both anticonvulsant (OR: 1.40, 95% CI 1.28 to 1.52) and antipsychotic (OR: 2.1, 95% CI 1.94 to 2.27) off-label. Additionally, patients with mental retardation (OR: 2.50, 95% CI 2.31 to 2.71), Alzheimer's disease (OR: 2.10, 95% CI 1.78 to 2.48), neurological disorders such as paralysis (OR: 2.18, 95% CI 1.79 to 2.66) and psychoses due to different reasons were more likely to receive off-label antipsychotics, while patients with schizophrenia (OR: 1.69, 95% CI 1.55 to1.84) and pain problems associated with diabetes or joint diseases were more likely being prescribed anticonvulsants off-label.

DISCUSSION:

This study confirmed the previous finding that off-label use of antidepressant, anticonvulsant and antipsychotic medications is highly prevalent (Barbui 2004; Chen in press; Fountoulakis 2004; Graves 1998; Kaye 2003; Lee 2002; Rosenheck 2001; Stone 2003). Among the three drug categories under investigation, anticonvulsants, especially

gabapentin, was the drug category most frequently prescribed off-label, followed by antidepressants and antipsychotics. Although the off-label use of second generation CNS agents has been frequently mentioned in the recent literature, the results of this study demonstrate that these new generation agents, except for gabapentin, are generally used less often for off-label purposes than traditional agents.

The odds of receiving antidepressant, anticonvulsant or antipsychotic medication off-label were found to increase dramatically with advancing age. This may be explained by some highly prevalent mental disorders among elderly such as dementia. It is very common for senior patients to develop psychosis with delusions or hallucinations, depression, anxiety and/or behavior problems as complications of degenerative dementia. The estimated prevalence of neuropsychiatric disturbance in dementia ranged from 60% to 80% at any one time, and the lifetime risk is almost 100% (Romano 2001). At present, there is not any FDA-approved medication available for the treatment of these problems. Most often, antidepressants were prescribed to control depressive symptoms, while antipsychotic drugs were used for behavior and psychological symptoms in dementia (Brains 2005; Lee2004; Motsinger 2003). Logistic regression analysis also revealed that whites were more likely to receive antidepressant, anticonvulsant and antipsychotic medications off-label than non-whites. Although the Medicaid population generally has low social economic status, this may still be explained by the different health care accessibility between races. While the mental illnesses themselves are prevalent to the same relative degree in minority and white populations, the literature has shown that the impact of the mental disorders is notably more significant for minority populations, chiefly because minorities are less likely to receive mental health care (American Psychiatrist Association 2003).

The comorbidity profile of off-label recipients observed in this study is generally consistent with the literature (Barbui 2004; Lee2002; Rosneheck 2001; Stone 2003; Whitehead 2005; Weiss 2000). For instance, patients with mental retardation were more likely to receive off-label antipsychotics; while patients with schizophrenia were more likely to received off-label anticonvulsants. In general, almost all comorbidities that are positively associated with off-label antipsychotics use are mental disorders or substance abused related conditions, while most comorbidities which were associated with a greater likelihood of receiving off-label anticonvulsants, such as diabetes and joint diseases, imply pain problems. This may partially explain why seeing psychiatrists is associated with a greater likelihood of receiving antipsychotics off-label and a smaller likelihood of receiving anticonvulsants off-label, since only patients with mental disorders or substance abused related diseases would be seeking help from psychiatrists, whereas patients with pain problems or other neurological disorder are usually treated by family physicians or neurologists. Therefore, it is very unlikely for a psychiatrist to write an off-label anticonvulsant prescription for patients with pain problems such as diabetic neuralgia.

The strength of the statistical associations in this study establishes clear service implications. As the likelihood of receiving off-label antidepressants, anticonvulsants and antipsychotic medications were four to six times higher among patients 65 years or older, recognition of the vital role of post-market surveillance and clinical studies targeting the off-label use among senior population is essential. The elderly is a group of patients in whom drug effects are influenced by age-related changes in pharmacokinetics, pharmacodynamics and homeostasis, which render them more susceptible to adverse drug reactions (Hames 2001). Since the risk benefit ratios of most off-label uses are uncertain, using drugs in accordance with evidence to support benefit should be

especially stressed among the senior population. It is also important to note that, besides patients' age, having renal disease is another factor that consistently affects the likelihood of receiving antidepressant, anticonvulsant and antipsychotic medications off-label. Although clinical experience suggests that the majority of psychotropic medications can be safely used with an ESRD patient, remarkably few data are available on the metabolism and efficacy of these agents in patients with renal impairment (Cohen 2004). Given the enormous prevalence of comorbid renal and psychiatric disorders, more outcomes research is imperative to help psychiatric consultants and nephrologists to manage this substantial patient population.

The main limitation of this study is the potential different understanding regarding off-label use between clinicians and researchers. For instance, none of the antipsychotic medications has been approved for relieving the psychotic symptoms in mental disorders other than schizophrenia and bipolar disorders. Thus, using an antipsychotic for depression patients with psychotic symptoms is usually regarded as labeled treatment in clinical practice, but was categorized as off-label in this study. The operational definition of labeled indications adopted in the study strictly followed the drug information from PDR and drug leaflets. This definition is generally narrower than clinicians' common sense, therefore, the estimates derived form this study, though generally consistent with other literature, may slightly inflate the prevalence of off-label use for some medications. Also, the data source employed is an administrative database and as such, it is associated with the limitations that affect all administrative databases including coding errors, missing codes and lack of direct links between diagnosis codes and prescriptions. To mitigate the presence of missing codes, we expanded the study window to a two-year period to identify ICD-9-CM codes for labeled indications in the year prior to the claim for an antidepressant, anticonvulsant or antipsychotic prescription. Finally, the ICD9-CM

definitions of mental disorders used in the study were collected from other published claims studies and may not agree exactly with those adopted in physician offices. The misclassification of off-label and on-label uses was another potential issue in the study.

CONCLUSIONS:

The off-label use of antidepressant, anticonvulsant and antipsychotic medications is highly prevalent. Further research to study the effects of off-label use of these three drug categories in patients with mental and neurological disorders may be an important step toward defining the scope and potential for such use.

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Table 3.1: Labeled indications of antidepressants

Antidepressants	FDA approved indications for adults
Bupropion	depression, smoking cessation
maprotiline	depression
mirtazapine*	depression
nefazodone*	depression
Trazodone	depression
venlafaxine*	depression, generalized anxiety disorder, social anxiety disorder (social phobia)
citalopram*	depression
fluoxetine*	depression, obsessive compulsive disorder, bulimia nervosa, panic disorder
fluvoxamine*	obsessive compulsive disorder
paroxetine*	depression, obsessive compulsive disorder, social anxiety disorder (social phobia), panic disorder, generalized anxiety disorder, posttraumatic stress disorder
sertraline*	depression, obsessive compulsive disorder, social anxiety disorder (social phobia), panic disorder, generalized anxiety disorder, posttraumatic stress disorder
amitriptyline	depression, depression accompanied by anxiety
amoxapine	depression
clomipramine	obsessive compulsive disorder
desipramine	depression
doxepin	psychoneurotic patients with depression and/or anxiety, depression and/or anxiety associated with alcoholism (not to be taken concomitantly with alcohol), depression and/or anxiety associated with organic disease, psychotic depressive disorders with associated anxiety including involutional depression and manic-depressive disorders
imipramine	depression
nortriptyline	depression
protriptyline	depression
trimipramine	depression

*: New generation medications

Table 3.2. Labeled indications of anticonvulsants

Anticonvulsants	FDA approved indications for adults
acetazolamide	edema due to congestive heart failure, drug induced edema, epilepsies (petit mal, unlocalized seizures), chronic simple angle glaucoma, secondary glaucoma, acute angle -closure glaucoma, acute mountain sickness
carbamazepine	partial seizures (psychomotor or temporal lobe), generalized Tonic-clonic (grand mal) seizure, mild, partial or generalized seizure
clonazepam	seizure disorders, panic disorder
clorazepate	anxiety disorder, partial seizures, symptomatic relief of acute alcohol withdrawal
Diazepam	anxiety disorder, alcohol withdraw, skeletal muscle spasm, seizure
Divalproex sodium	mania in bipolar disorder, partial epilepsy, migraine
ethosuximide	Absence (petit mal) epilepsy
felbamate*	generalized epilepsy
fosphentoin*	short-term parental administration, generalized convulsive epilepticus, seizure in surgery
gabapentin*	partial seizure with epilepsy for patient, postherpetic neuralgia
lamotrigine*	partial seizure and generalized seizures of Lennox-Gastaut syndrome, bipolar disorder
levetiracetam*	partial onset seizures with epilepsy
lorazepam	anxiety disorder
mephobarbital	sedative for relief of anxiety, tension and apprehension, anticonvulsant in treatment of grand mal and petit mal epilepsy
methsuximide	Absence (petit mal) seizure
oxcarbazepine*	partial seizure with epilepsy
paraldehyde	alcohol or drug withdraw, poisoning by convulsive drug, convulsive episode arising from tetanus, status epilepticus, insomnia
phenobarbital	sedative, hypnotic for short term treatment of insomnia, preanesthetics, long term anticonvulsants for generalized tonic clonic seizures and cortical local seizures, emergency control of acute convulsive of status epilepticus
phenytoin	tonic-clonic (grand mal) and psychomotor (temporal lobe) seizures
primidone	tonic-clonic (grand -mal) seizure, psychomotor (temporal lobe seizures)
Tiagabine*	partial seizure
topiramate*	partial seizure, primary generalized tonic-clonic seizures, seizure associate with LGS
valproic acid	mania in bipolar disorder, epilepsy, migraine
zonisamide*	partial seizure in epilepsy

*: New generation medications

Table 3.3. Labeled indications of antipsychotics

Antipsychotics	FDA approved indications for adults
clozapine*	severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia, reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorders
haloperidol	schizophrenic patients who require prolonged parenteral antipsychotic therapy
loxapine*	schizophrenia
molindone	schizophrenia
olanzapine*	schizophrenia, bipolar mania
quetiapine*	schizophrenia, acute bipolar mania
risperidone	schizophrenia, bipolar mania
thiothixene	schizophrenia, psychotic disorder (injection use)
ziprasidone	schizophrenia
chlorpromazine	schizophrenia, mania, acute intermittent porphyria, intractable hiccups, nausea and vomiting, presurgical apprehension, tetanus
fluphenazine	schizophrenia
mesoridazine	schizophrenic patients who fail to respond adequately to treatment with other antipsychotic drugs
perphenazine	schizophrenia, nausea and vomiting
prochlorperazine	schizophrenia, severe nausea and vomiting, non-psychotic anxiety **
promazine	schizophrenia
thioridazine	patients who fail to respond adequately to treatment with other antipsychotic drugs
trifluoperazine	schizophrenia, non-psychotic anxiety
trifluprom azine	schizophrenia (acute treatment), nausea and vomiting

*: New generation medications

Table 3.4: ICD9-CM assigned to the labeled indications of antidepressants, anticonvulsants and antipsychotics.

Labeled indications	**ICD9- CM**
Absence (petit mal) seizure	345.0x, 345.2x
acute intermittent porphyria	277.1x
alcohol or drug withdrawal	291.0x, 291.3x, 291.8x, 292.0x
bulimia nervosa	307.51
convulsive episode arising from tetanus	037.xx, 771.3x, 978.4x, E9484
Depression	296.2x-296.3x
depression accompanied by anxiety	300.4x
depression and/or anxiety associated with alcoholism (not to be taken concomitantly with alcohol)	291.xx
depression and/or anxiety associated with organic disease	310.8x, 294.8x
drug induced edema	782.3x
edema due to congestive heart failure	428.xx
Epilepsy	345.xx, 780.39
generalized anxiety disorder	300.02
generalized epilepsy	345.0x. 345.1x, 345.2x, 345.3x, 780.39
intractable hiccups	786.8x, 306.1x
mania and mania episode in bipolar disorders	296.0x, 296.1x, 296.4x-296.8x
Migraine	346.xx
nausea and vomiting	787.0x
non-psychotic anxiety	300.0x
obsessive compulsive disorder	300.3x
panic disorder	300.01, 300.21
partial seizure	345.4x, 345.5x
poisoning by convulsive drug	E858, 780.39
postherpetic neuralgia	53.19
posttraumatic stress disorder	309.81
premenstrual dysphonic disorder	625.4x
primary generalized tonic-clonic seizures	345.1x, 780.9x
psychoneurotic patients with depression and/or anxiety	300.0x, 300.4x
psychotic depressive disorders with associated anxiety including involutional depression and manic-depressive disorders	296.xx
psychomotor (temporal lobe seizures)	345.4x, 345.7x
Schizophrenia	295.xx
Sedative for relief of anxiety, tension and apprehension	293.xx, 300.xx, 309.xx, 625.4x
seizure associate with LGS	345.01
skeletal muscle spasm	728.85
social anxiety disorder (social phobia)	300.23
status epilepticus	345.3x

Table 3.5: Initial list of candidate factors associated with the off-label use of antidepressant, anticonvulsant and antipsychotic medications.

Demographics	**ICD9 definitions of diagnosis-related comorbidities**
Age, Gender, Race	
Physician specialties	
Psychiatrist vs. non psychiatrist	
Diagnosis-related comorbidities	
Mental and substance abuse related comorbidities	
Acute reaction to stress	308.xx
Adjustment reaction	309.xx
Alcoholic psychoses	291.xx
Alzheimer's disease	290.xx, 331.0x
Bipolar affective disorders	296.4x–296.7x
Cyclothymic disorders	301.13
Depressive disorder, not elsewhere specified	311.xx
Drug psychoses	292.xx
Major depressive disorder	296.2x, 296.3x
Manic disorders	296.0x, 296.1x
Mental retardation	315.xx, 317.xx–319.xx
Neurotic disorders	300.xx
Other mental disorders*	302.xx, 306.xx, 307.xx, 310.xx, 316.xx, 648.4x
Other non-organic psychoses	298.xx
Other organic psychotic conditions, chronic	294.xx
Paranoid / Delusion disorders	297.xx
Personality disorders	301.xx, excluding 301.13
Psychoses with origin specified to childhood	299.xx
Schizophrenic disorders	295.xx
Transient organic psychotic conditions	293.xx
Unspecified affective psychoses	296.8x, 296.9x
Other comorbidities	
Anemia	280.0x, 280.1x-281.9x, 285.9x
Asthma	493.xx
Cancer	140.0x-172.9x, 174.0x-175.9x, 179.xx-195.8x, V10.00-V10.69, V10.8-V10.9, 196.0x-199.1x, 200.00-202.38, 202.50-203.01, 203.8x-203.81, 238.6x, 273.3x, V10.71, V10.72, V10.79
Cardiovascular disease	426.10, 426.11, 426.13,426.2x-426.53, 426.6x-426.89, 427.0x, 427.2x, 427.31, 427.60, 427.9x, 785.0x, V45.0, V53.3, 398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 428.0x-428.9x, 401.1x, 401.9x, 402.10, 402.90, 404.10, 404.90, 405.11, 405.19, 405.91, 405.99, 440.0x-440.9x, 441.2x, 441.4x, 441.7x, 441.9x, 443.1x-443.9x, 447.1x, 557.1x, 557.9x, V43.4, 416.0x-416.9x, 417.9x, 093.20-093.24, 394.0x-397.1x, 424.0x-424.91, 746.3x-746.6x, V42.2, V43.3
Chronic pulmonary diseases	490.xx-492.8x, 494.xx, 495.0x-505.xx, 506.4x

Coagulation	286.0x-286.9x, 287.1x, 287.3x-287.5x
Connective tissue disorders*	701.0x, 710.0x-710.9x, 714.0x-714.9x, 720.0x-720.9x, 725.xx
Diabetes	250.xx, 357.2x, 362.01, 362.02, 366.41, 648.0x and NOT 648.8x
Epilepsy	345.0x-345.9x
HIV or AIDS	042.xx–044.xx
Hypothyroidism	243.xx-244.2x, 244.8x, 244.9x
Liver diseases	070.32, 070.33, 070.54, 456.0x-456.1x, 456.20, 456.21, 572.3x, 572.8x, V42.7
Other neurological disorders	331.9x, 332.0x, 333.4x, 333.5x, 334.0x-334.3x, 334.5x-335.9x, 340.xx, 341.1x-341.9x, 348.1x, 348.3x, 784.3x
Nutritional disorders	276.0x-276.9x, 278.0x, 260.xx-263.9x
Paralysis	342.0x-342.12, 342.9x-344.9x
Peptic ulcer disease	531.70, 531.90, 532.70, 532.90, 533.70, 533.90, 534.70, 534.90, V12.71
Renal failure	403.11, 403.91, 404.12, 404.92, 585.xx, 586.xx, V42.0, V45.1, V56.0, V56.8

Remarks:

1. Other mental disorders:

Sexual deviations and disorders

Physiological malfunction arising from mental factors

Special symptoms or syndromes, not elsewhere specified

Specific non-psychotic mental disorders due to organic brain damage

Psychotic factors associated with diseases specified elsewhere

Mental disorders in pregnancy, antepartum and postpartum

2. Connective tissue disorders: Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, etc.

Table 3.6: Demographic characteristics of antidepressants, anticonvulsants and antipsychotic recipients (cohorts).

	Total	Age (Yrs)	Female (% Total)	Race (% Total)		
				White	Black	Others
Antidepressant cohort (recipients)	62,289	53.97	47,831 (76.79%)	32,964 (52.92%)	21,713 (34.86%)	7,612 (12.22%)
Anticonvulsant cohort (recipients)	33,406	52.14	21,876 (65.49%)	15,663 (46.89%)	14,512 (43.44%)	3,231 (9.67%)
Antipsychotic cohort (recipients)	48,049	52.46	32,691 (68.04%)	25,533 (53.14%)	17,068 (35.52%)	5,448 (11.34%)

Table 3.7: Prevalence of off-label uses of top five prescribed antidepressants, anticonvulsants and antipsychotics in 2001.

Drug categories	Drug Names	N	On-label	Off-label	% off-label
Antidepressants	sertraline*	14,077	4,700	9,377	66.61
	Amitriptyline	11,724	2,191	9,533	81.31
	paroxetine*	11,000	3,647	7,353	66.85
	fluoxetine*	10,588	3,518	7,070	66.77
	Trazodone	9,748	3,358	6,390	65.55
Anticonvulsants	gabapentin*	11,540	226	11,314	98.04
	Lorazepam	10,233	1,171	9,062	88.56
	Phenytoin	9,898	4,933	4,965	50.16
	divalproex sodium	8,495	3,606	4,889	57.55
	Diazepam	6,160	1,278	4,882	79.25
Antipsychotics	risperidone*	12,970	4,307	8,663	66.79
	olanzapine*	11,161	5,392	5,769	51.69
	Haloperidol	5,371	2,556	2,815	52.41
	quetiapine*	4,521	1,840	2,681	59.30
	Prochlorperazine	1,925	685	1,240	64.42

*: New generation agents

Table 3.8: Independent factors associated with the off-label use of antidepressants identified from the stepwise logistic variable selection procedure.

Factors	Off-label (N = 45,909) n (% prev) or mean (std)	On-label (N = 15,282) n (% prev) or mean (std)	Odds ratio	95% CI	p-value
Age (>=65 vs. <65)	17,088 (37.2%)	867 (5.7%)	5.149	(4.764, 5.564)	<.0001
Race (White vs. Non White)	24,350 (53.0%)	7,687 (50.3%)	1.15	(1.099, 1.204)	<.0001
Gender (Male vs. female)	11,336 (24.7%)	2,909 (19.0%)	1.549	(1.465, 1.638)	<.0001
Prescription class (SSRI vs. tricyclic)	25,939 (56.5%)	11,163 (73.0%)	0.428	(0.404, 0.453)	<.0001
Prescription class (Other second generation AD vs. tricyclic)	16,008 (34.9%)	7,485 (49.0%)	0.55	(0.518, 0.584)	<.0001
Physician specialty (psychiatrist vs. non psychiatrist)	3,955 (8.6%)	2,615 (17.1%)	0.853	(0.797, 0.914)	<.0001
Drug numbers	1.333 (0.651)	1.719 (0.94)	0.9	(0.869, 0.932)	<.0001
Manic disorders	95 (0.2%)	179 (1.2%)	0.432	(0.321, 0.581)	<.0001
Transient organic psychotic conditions	384 (0.8%)	397 (2.6%)	0.775	(0.649, 0.926)	0.0049
Other organic psychotic conditions, chronic	1,134 (2.5%)	306 (2.0%)	0.826	(0.698, 0.977)	0.0259
Paranoid/Delusion disorders	138 (0.3%)	139 (0.9%)	0.714	(0.529, 0.964)	0.0279
Other non-organic psychoses	1,364 (3.0%)	1,091 (7.1%)	0.868	(0.782, 0.963)	0.0076
Adjustment reaction	494 (1.1%)	1,396 (9.1%)	0.212	(0.189, 0.239)	<.0001

Personality disorders	181 (0.4%)	543 (3.6%)	0.465	(0.378, 0.571)	<.0001
Neurotic disorders	2,951 (6.4%)	6,535 (42.8%)	0.173	(0.164, 0.183)	<.0001
Other mental disorders	1,213 (2.6%)	1,278 (8.4%)	0.698	(0.632, 0.771)	<.0001
Alcoholic psychoses	1,169 (2.5%)	1,437 (9.4%)	0.634	(0.572, 0.703)	<.0001
Drug psychoses	1,135 (2.5%)	1,853 (12.1%)	0.617	(0.56, 0.681)	<.0001
Alzheimer's disease	1,426 (3.1%)	252 (1.6%)	0.792	(0.667, 0.941)	0.0079
HIV or AIDS	483 (1.1%)	365 (2.4%)	0.746	(0.631, 0.882)	0.0006
Epilepsy	856 (1.9%)	715 (4.7%)	0.838	(0.737, 0.953)	0.0071
Asthma	2,883 (6.3%)	2,605 (17.0%)	0.811	(0.756, 0.871)	<.0001
Cardiovascular disease	15,874 (34.6%)	7,719 (50.5%)	0.762	(0.726, 0.8)	<.0001
Connective tissue disorders	1,368 (3.0%)	928 (6.1%)	0.891	(0.803, 0.989)	0.0302
Hypothyroidism	1,713 (3.7%)	1,435 (9.4%)	0.814	(0.745, 0.89)	<.0001
Nutritional disorders	4,894 (10.7%)	4,189 (27.4%)	0.73	(0.687, 0.776)	<.0001
Peptic ulcer disease	886 (1.9%)	781 (5.1%)	0.882	(0.78, 0.997)	0.045
Renal failure	1,200 (2.6%)	398 (2.6%)	1.425	(1.239, 1.64)	<.0001

Table 3.9: Independent factors associated with the off-label use of anticonvulsants identified from the stepwise logistic variable selection procedure.

Factors	Off-label (N = 37,156) n (% prev) or mean (std)	On-label (N = 10,030) n (% prev) or mean (std)	Odds ratio	95% CI	p-value
Age (>=65 vs. <65)	12,310 (33.1%)	687 (6.8%)	4.544	(4.159, 4.964)	<.0001
Race (White vs. Non White)	20,277 (54.6%)	4,571 (45.6%)	1.708	(1.62, 1.8)	<.0001
Gender (Male vs. female)	11,150 (30.0%)	3,943 (39.3%)	0.742	(0.701, 0.784)	<.0001
Physician specialty (psychiatrist vs. non psychiatrist)	4,430 (11.9%)	3,166 (31.6%)	0.253	(0.237, 0.27)	<.0001
Prescription class (New generation vs. conventional)	14,295 (38.5%)	1,625 (16.2%)	7.628	(7.071, 8.23)	<.0001
Drug numbers	1.42 (0.757)	1.53 (0.811)	0.745	(0.718, 0.772)	<.0001
Acute reaction to stress	158 (0.4%)	133 (1.3%)	0.68	(0.518, 0.894)	0.0058
Alcoholic psychoses	1,212 (3.3%)	931 (9.3%)	0.561	(0.502, 0.626)	<.0001
Alzheimer's disease	1,121 (3.0%)	235 (2.3%)	0.811	(0.678, 0.971)	0.0227
Bipolar affective disorders	1,361 (3.7%)	999 (10.0%)	0.364	(0.326, 0.405)	<.0001
Drug psychoses	1,401 (3.8%)	759 (7.6%)	1.216	(1.081, 1.368)	0.0011
Major depressive disorder	3,366 (9.1%)	1,331 (13.3%)	1.397	(1.282, 1.524)	<.0001
Mental retardation	3,083 (8.3%)	1,662 (16.6%)	0.663	(0.614, 0.716)	<.0001
Neurotic disorders	3,286 (8.8%)	2,886 (28.8%)	0.253	(0.235, 0.272)	<.0001
Other non-organic psychoses	1,482 (4.0%)	694 (6.9%)	1.145	(1.019, 1.287)	0.023
Other organic psychotic conditions, chronic	959 (2.6%)	311 (3.1%)	0.775	(0.655, 0.917)	0.003
Schizophrenic disorders	3,995 (10.8%)	1,230 (12.3%)	1.689	(1.551, 1.839)	<.0001
Unspecified affective psychoses	564 (1.5%)	402 (4.0%)	0.727	(0.617, 0.856)	0.0001
Cardiovascular disease	11,951 (32.2%)	4,272 (42.6%)	0.781	(0.736, 0.828)	<.0001

Coagulation disorders	489 (1.3%)	306 (3.1%)	0.742	(0.621, 0.886)	0.001
Connective tissue disorders	1,138 (3.1%)	332 (3.3%)	1.455	(1.254, 1.689)	<.0001
Diabetes	6,123 (16.5%)	1,598 (15.9%)	1.232	(1.142, 1.329)	<.0001
Hypothyroidism	1,448 (3.9%)	721 (7.2%)	0.814	(0.728, 0.909)	0.0003
Liver diseases	302 (0.8%)	131 (1.3%)	1.367	(1.07, 1.747)	0.0124
Neurological disorders other than paralysis	639 (1.7%)	473 (4.7%)	0.71	(0.611, 0.824)	<.0001
Nutritional disorders	4,411 (11.9%)	2,312 (23.1%)	0.734	(0.682, 0.791)	<.0001
Paralysis	1,314 (3.5%)	847 (8.4%)	0.575	(0.518, 0.639)	<.0001
Renal failure	1,044 (2.8%)	225 (2.2%)	1.768	(1.49, 2.097)	<.0001

Table 3.10: Independent factors associated with the off-label use of antipsychotics identified from the stepwise logistic variable selection procedure.

Factors	Off-label (N = 20,482) n (% prev) or mean (std)	On-label (N = 12,126) n (% prev) or mean (std)	Odds ratio	95% CI	p-value
Age (>=65 vs. <65)	7,948 (38.8%)	1,027 (8.5%)	5.209	(4.82, 5.629)	<.0001
Race (White vs. Non White)	10,683 (52.2%)	4,340 (35.8%)	1.889	(1.791, 1.992)	<.0001
Gender (Male vs. female)	6,548 (32.0%)	4,781 (39.4%)	0.834	(0.788, 0.881)	<.0001
Prescription class (atypical except for clozapine vs. conventional)	8,262 (40.3%)	6,170 (50.9%)	0.757	(0.716, 0.8)	<.0001
Prescription class (clozapine vs. conventional)	136 (0.7%)	537 (4.4%)	0.191	(0.156, 0.234)	<.0001
Physician specialty (psychiatrist vs. non psychiatrist)	1,808 (8.8%)	931 (7.7%)	1.441	(1.312, 1.583)	<.0001
Drug numbers	1.313 (0.641)	1.551 (0.814)	0.828	(0.797, 0.86)	<.0001
Major depressive disorder	3,046 (14.9%)	1,825 (15.1%)	2.1	(1.944, 2.268)	<.0001
Manic disorders	88 (0.4%)	230 (1.9%)	0.497	(0.377, 0.656)	<.0001
Bipolar affective disorders	942 (4.6%)	1,671 (13.8%)	0.491	(0.446, 0.541)	<.0001
Unspecified affective psychoses	402 (2.0%)	684 (5.6%)	0.661	(0.572, 0.764)	<.0001
Other organic psychotic conditions, chronic	1,252 (6.1%)	279 (2.3%)	1.723	(1.478, 2.01)	<.0001
Paranoid/Delusion disorders	141 (0.7%)	277 (2.3%)	0.469	(0.37, 0.593)	<.0001
Other non-organic psychoses	1,548 (7.6%)	2,101 (17.3%)	0.57	(0.526, 0.618)	<.0001
Psychoses with origin specified to childhood	223 (1.1%)	48 (0.4%)	2.715	(1.945, 3.79)	<.0001

Adjustment reaction	555 (2.7%)	385 (3.2%)	1.452	(1.25, 1.685)	<.0001
Personality disorders	259 (1.3%)	400 (3.3%)	0.671	(0.557, 0.807)	<.0001
Neurotic disorders	2,177 (10.6%)	2,305 (19.0%)	0.852	(0.787, 0.921)	<.0001
Cyclothymic disorders	15 (0.1%)	5 (0.0%)	3.913	(1.341, 11.421)	0.0125
Depressive disorder, not elsewhere specified	1,688 (8.2%)	1,699 (14.0%)	0.878	(0.803, 0.959)	0.004
Other mental disorders	776 (3.8%)	596 (4.9%)	1.138	(1.003, 1.29)	0.044
Drug psychoses	730 (3.6%)	1,214 (10.0%)	0.696	(0.623, 0.777)	<.0001
Other alcohol & drug related psychoses	915 (4.5%)	1,384 (11.4%)	0.674	(0.608, 0.748)	<.0001
Alzheimer's disease	1,541 (7.5%)	211 (1.7%)	2.1	(1.779, 2.479)	<.0001
HIV and AIDS	197 (1.0%)	183 (1.5%)	1.42	(1.137, 1.773)	0.002
Mental retardation	2,945 (14.4%)	1,162 (9.6%)	2.5	(2.305, 2.711)	<.0001
Cancer	784 (3.8%)	391 (3.2%)	1.236	(1.073, 1.423)	0.0033
Cardiovascular disease	5,870 (28.7%)	4,298 (35.4%)	0.865	(0.814, 0.92)	<.0001
Connective tissue disorders	391 (1.9%)	236 (1.9%)	1.427	(1.19, 1.712)	0.0001
Diabetes	2,735 (13.4%)	2,127 (17.5%)	0.894	(0.83, 0.964)	0.0036
Hypothyroidism	677 (3.3%)	756 (6.2%)	0.79	(0.699, 0.893)	0.0002
Nutritional disorders	2,049 (10.0%)	2,158 (17.8%)	0.702	(0.646, 0.762)	<.0001
Renal failure	398 (1.9%)	199 (1.6%)	1.844	(1.521, 2.235)	<.0001
Paralysis	524 (2.6%)	150 (1.2%)	2.179	(1.785, 2.66)	<.0001

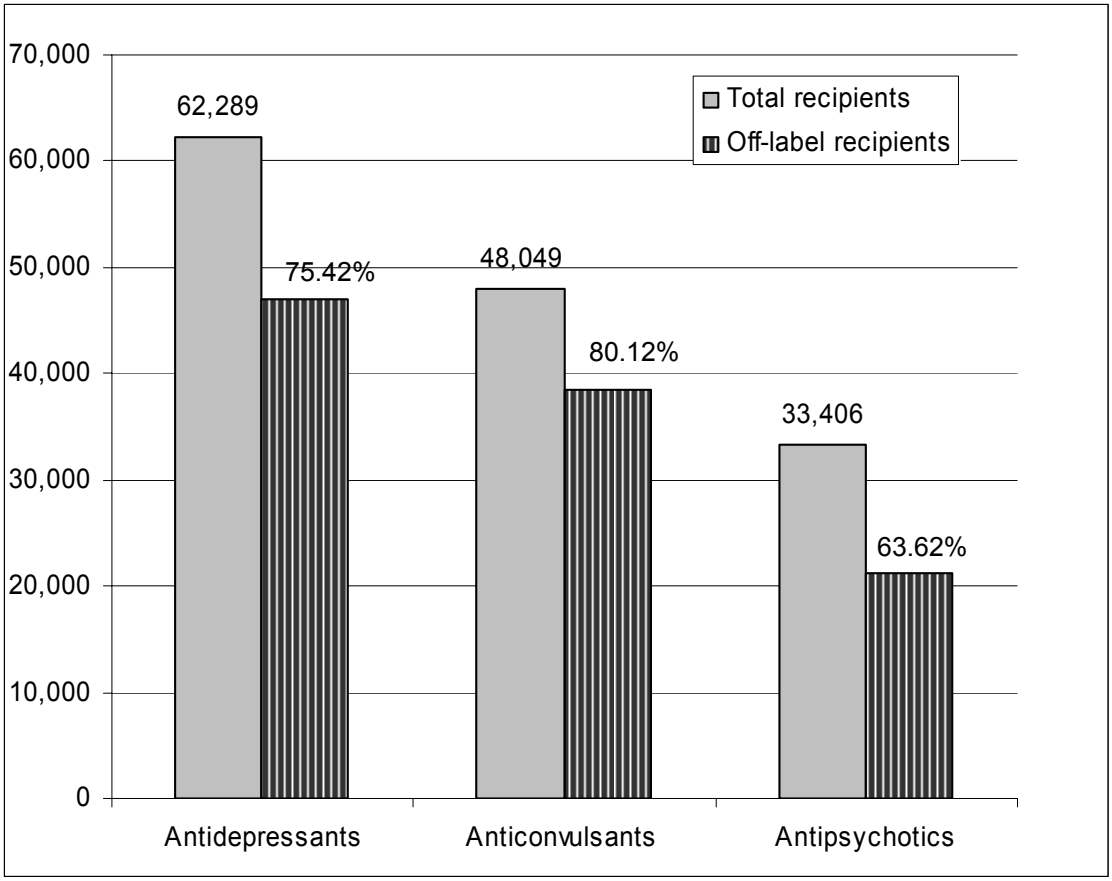

Figure 3.1: The prevalence of antidepressants, anticonvulsants and antipsychotics off-label use.

CHAPTER 4

THE ECONOMIC AND CLINICAL IMPACTS OF PRESCRIBING ANTIDEPRESSANT, ANTCONVULSANT AND ANTIPSYCHOTIC MEDICATIONS OFF-LABEL FOR PATIENTS WITH SCHIZOPHRENIA, BIPOLAR DISORDERS, DEPRESSION AND ANXIETY[1]

[1] H. Chen, J. Reeves, J.E. Fincham, K. Kennedy, J.H. Dorfman, B.C. Martin. To be submitted to *Value in Health*

ABSTRACT:

Background: Prescribing antidepressants, anticonvulsants and antipsychotics for off-label purposes is widespread in the treatment of mental disorders despite the fact that benefits of most of these off-label uses remain uncertain. The resultant influences of using off-label antidepressants, anticonvulsants and antipsychotics on health resource utilizations are not well understood.

Objective: This study examined the effects of using off-label antidepressant, anticonvulsant and antipsychotic medications on total health expenditures, inpatient hospitalizations and emergency room (ER) visits in Medicaid enrollees with schizophrenia, bipolar disorders, depression, or anxiety.

Methods: A retrospective cohort study was conducted using 1999 through 2001 Georgia Medicaid data. Four disease-specific cohorts were constructed for subjects with schizophrenia, bipolar disorders, depression and anxiety disorders. Within each cohort, the treatment group was formed of subjects who received off-label antidepressant, anticonvulsant or antipsychotic medications at the beginning of a 12 months observation period, while the comparison group consisted of subjects who did not have any exposure to these off-label medications in the entire observation period. Differences in annual outcomes were estimated between propensity score matched off-label (experimental subjects) and on-label users (comparison subjects). Rosenbaum bounds sensitivity analysis was performed to test the robustness of the outcome estimates against hidden bias.

Results: Relative to the on-label users, the off-label users experienced significantly higher per capita annual prescription expenditures across the cohorts (net difference: schizophrenia cohort $892.88; bipolar cohort $555.51; depression cohort: $783.87; anxiety cohort: $640.72). Besides prescription costs, the off-label users in the

depression cohort also had higher outpatient, inpatient, long-term care and mental health related expenditures compared to the on-label users, which in total, results in a $2,209.36 average cost difference between the off-label and the on-label groups. Relative to the on-label users, the off-label users in the schizophrenia cohort had significantly lower hospital utilizations and expenditures. No statistically significant differences were found in ER use rates between the on-label and the off-label users across the cohorts.

Conclusions: Using off-label antidepressant, anticonvulsant and antipsychotic medications is associated with significantly increased prescription expenditures across the cohorts. For other outcome measures including medical expenditures, ER and hospital utilizations, the influences of off-label drug use are heterogeneous in different mental disorders. Future studies will be required to confirm and extend these findings.

Key words: Off-label, Antidepressants, Anticonvulsants, Antipsychotics, Schizophrenia, bipolar disorders, depression, Anxiety, Medicaid, Costs, Hospitalizations, Emergency Room visits

INTRODUCTION:

Antidepressant, anticonvulsant and antipsychotic medications have been the top three prescribed central nervous system (CNS) drug classes in both the US and global market since 1999 (Chawla 2004). Although approved by the US Food and Drug Administration (FDA) mainly for treating depressive disorders, epilepsy and schizophrenia respectively, these drugs are widely prescribed in almost all mental disorders. The New York State Office of Mental Health reported that 34.9 percent of state hospital patients with a diagnosis of schizophrenia were receiving valproate in 2001, and almost half of all patients were receiving an anticonvulsant (Citrome 2002). In the

outpatient setting, a retrospective analysis based on the prescription files from the VA Drug Benefit Management System found that the average per patient annual VA costs for atypical antipsychotic medications for patients with major depressive disorder was $858 (Rosenheck 2001). This average cost would be 40% higher without the substantial VA drug discount.

Despite a few recent clinical trials conducted to examine benefits of these off-label uses, the value of using off-label antidepressants, anticonvulsants and antipsychotics in most mental disorders still remains uncertain. The Cochrane Collaboration recently reviewed all the studies of valproate for schizophrenia and emphasized the fact that divalproex had no sustained effect after an initial accelerated response in the four-week study (Basan 2004). The review stated that there was "very little evidence to support the use of valproate in schizophrenia." Although combinations of new antipsychotics and antidepressants showed some benefits in treatment resistant depression (Shelton 2003), Mortimer and colleagues reported that discontinuation of off-label conventional antipsychotic treatment for patients with unipolar, non-psychotic depression was associated with significant improvements in symptoms and reductions in side effects (Mortimer 2003).

Besides the uncertainty of drug benefits, some off-label uses of antidepressant, anticonvulsant and antipsychotic medications can be potentially dangerous. The risks of these off-label uses usually can not be discovered until large scale, randomized, well controlled clinical trials are conducted. For dementia patients with behavior disorders, recent clinical studies found a higher death rate associated with atypical antipsychotic use compared to patients receiving a placebo (US Food and Drug Administration 2005). Also, the pooled results of three unpublished trials involving pediatric patients with major depressive disorder showed that suicidal thoughts, suicide attempts and episodes of

self-harm were more frequent among the paroxetine users than among those in the placebo group (GlaxoSmithKline Inc, 2003).

Most mental disorders are chronic. Without appropriate treatments, they could become progressively worse. For episodic conditions such as depression and bipolar disorder, inadequate or inefficient treatments might prolong disease episodes and increase recurrence rates. Off-label use with uncertain efficacy and side effects might have the potential to increase health resource utilizations and therefore increase health care costs. Beyond efficacy and safety issues, concern over excessive use and irrational prescribing of expensive new generation agents such as atypical antipsychotics has been voiced for many years. Government and commercial insurance plans including Medicaid have tried to restrict the off-label uses of expensive CNS agents in various ways including instituting prescribing guidelines, formulary restrictions, increased patient co-payments, and drug utilization reviews. With the ever increasing off-label drug use in clinical psychiatry, there is considerable interest in the clinical and economic outcomes associated with off-label drug use within governments, health insurance plans and pharmaceutical industries. However, very little information is currently available.

The objective of this study was to estimate the effects of using off-label antidepressants, anticonvulsants and antipsychotics alone or as an adjunct to labeled pharmacotherapy vs. using only labeled pharmacotherapy for treating anxiety, depression, bipolar disorder or schizophrenia on three main outcome measures: total health expenditures, hospitalizations and emergency room (ER) visits.

METHODS:

Data sources

Medicaid claims data from 1999 through 2001 were obtained from the Georgia Department of Community Health. The Georgia Medicaid files contain eligibility details,

demographics and claims history for various health care services, including Medicaid paid amount, outpatient prescription drugs, inpatient stays, and disease diagnoses.

Research subjects

Patients were selected for inclusion in the primary cohort based on the following inclusion and exclusion criteria

- Filled at least one antidepressant, anticonvulsant, antipsychotic or anxiolytic medication during the period April 1999 through December 2000.
- 15 months continuous eligibility were applied 3 months prior and 1 year post the index prescription
- Primary diagnosis of schizophrenia (ICD9 codes: 295), bipolar disorders (ICD9 codes: 296.4- 296.8), depression (296.2, 296.3, 300.4, 311) or anxiety (ICD9 codes: 300.0 –300.2 and 313.0) recorded on at least one paid claim during the 15 months study period.
- At least 16 years of age as of January 1st, 1999.

Index prescription, pre-treatment period and observation period

An index prescription was defined as the first pharmacy claim for antidepressant anticonvulsant or antipsychotic medications after a 90-day period free of prescriptions from these three drug categories. This 90-day pre-treatment period was established to identify persons who had a new episode of treatment with one of the studied drugs. Because this analysis focused on patients who initiate their therapy of a new treatment episode, it is necessary to exclude those continuing on therapy from an earlier period. The length of this pre-treatment period was carefully selected based on published claims data analysis (Lyu 2001; Kerr 2000) and our preliminary analyses. A 90-day pre-treatment is regarded as long enough to separate two treatment episodes by most literature and short enough to keep adequate research subjects (30,050 based on preliminary analyses) for the study.

The observation period was defined as the 1-year period after the index prescription. The 3-month pre-treatment period was used to collect the comorbidities and health care utilization information to adjust for selection bias while the one-year period post the index prescription was used to compare health and economic outcomes.

Building disease-specific cohorts

The impact of prescribing antidepressants, anticonvulsants and antipsychotics off-label was evaluated in patients with one of the follow four psychiatric conditions: schizophrenia, bipolar disorders, depression and anxiety. Research subjects were hierarchically categorized into these four disease-specific cohorts based on their primary diagnoses received during the 15 months study period. The hierarchy was arranged according to the degree of increased severity and expenditure with diagnoses. Schizophrenia is the most expensive and severe diagnosis category, followed by bipolar disorders, depression and anxiety (Figure 4.1). For research subjects with multiple diagnoses, they were categorized to the disease cohort according to their most severe and expensive diagnosis. For example, a subject with both schizophrenia and depression was assigned to schizophrenia rather than depression cohort. This categorization was based on the finding from diagnoses based risk adjustment models. When a severe and expensive condition exists, an additional diagnosis of a less severe condition is probably not of much significance for cost (Kronick 2000). Furthermore, when less severe conditions such as depression and anxiety were investigated, this classification excluded subjects with comorbid schizophrenia and bipolar disorders from the cohorts. It therefore prevented these more severe and expensive conditions from affecting the outcome measures (costs, hospitalization and emergency room visits) associated with depression and anxiety.

Defining off-label vs. on-label prescriptions

The primary sources for determining labeled indications were the prescription drug leaflets and the Physician Desk Reference. Since drug labeling is dynamic in nature and the approved indications are continuously evolving, we chose to accept all the indications approved by FDA up to December 2004. Tables 4.1 - 4.3 present the labeled indications of all antidepressant, anticonvulsant and antipsychotic medications. The ICD-9-CM definitions of these indications were identified through a comprehensive literature review and ICD-9-CM databases. Table 4.4 presents the ICD-9-CM codes for each of the labeled indications.

According to the FDA, off-label drug use is characterized as the use of a prescription drug for an indication, in a dosage form or dose regimen for a particular population in a way not stated in the approved labeling (Woodcock 2003). Owing to the limited availability of information from the Georgia Medicaid database, we did not consider the off-label drug use related to dosage, duration of time and route of administration. In addition, prescribing an antidepressant, anticonvulsant or antipsychotic for monotherapy, although it is solely labeled for adjunct therapy, was not considered as off-label in this study because our preliminary study found that less than 4 percent of the off-label anticonvulsant uses could be attributed to this reason and it had a great amount of overlap with off-label uses for non FDA approved clinical conditions (Chen, in press).
An antidepressant, anticonvulsant or antipsychotic prescription was defined as off-label if none of the ICD-9-CM codes a patient received within the 15 months study period could be matched with the labeled indications of this prescription. Otherwise, it was being regarded as on-label.

Treatment (off-label) group & comparison (on-label) group

The treatment group was formed of subjects who received off-label antidepressant, anticonvulsant or antipsychotic medications at the beginning of a 12

month observation period, while the comparison group consisted of subjects who did not have any exposure to these off-label medications in the entire observation period.

Measurement of outcomes

Three outcome measures, costs using the Georgia Medicaid perspective, inpatient hospitalization and emergency room visits, were estimated for both off-label and on-label groups. The inpatient hospitalizations were measured using the percentage of subjects who had been hospitalized (hospitalization rate) and the emergency room visits were estimated using the percentage of subjects with one or more emergency room visits (ER use rate). The total health care expenditure was calculated by summing the Medicaid paid amount over the observation period. The effects of using antidepressant, anticonvulsant and antipsychotic off-label on different cost categories – inpatient, outpatient, long-term care and prescription were also estimated.

Matching off-label and on-label users based on propensity score

Ultimately, a causal inference about the effectiveness of off-label drug use on health resource utilizations for people with mental disorders was sought, however, without randomization, the off-label and the on-label users were very likely to be different at the baseline. Any differences directly observed between the off-label and the on-label groups during the 12 months follow up period might be due to off-label drug use, differences in characteristics between groups or due to both. To minimize the influences of different characteristics between the off-label and the on-label groups on outcome measures, propensity score matching was employed.

In this study, a propensity score is a model based predicted probability of receiving antidepressants, anticonvulsants or antipsychotics off-label. This predicted probability was estimated according to a group of covariates that are related to both off-label prescribing (treatment assignment) and health resource utilizations (outcomes) using the following logit model:

$$P(Y=\text{off-label} \mid X) = \frac{e^{(\beta 0+\beta 1x1+\beta 2x2+\ldots+\beta nxn)}}{1+e^{(\beta 0+\beta 1x1+\beta 2x2+\ldots+\beta nxn)}}$$

Instead of matching the on-label and off-label groups on each of these covariates, the basic idea of propensity score matching is to match cases and controls with similar propensity scores and then test the effect of off-label uses between homogenous Off-label and on-label groups.

Covariates for propensity score estimation were identified by a survey of published literature and expert opinion. Since the marginal effects of each covariate (β hat) on the predicted probability of receiving off-label medications (Y hat) is not a concern in propensity score matching, a very liberal inclusion criterion was applied to identify and include as many relevant covariates as possible.

The relevant covariates include:

- All patient demographic variables (age, gender, and race) that was available in the Georgia Medicaid data.
- Factors that could predict the extent of future health resource utilization including prior health resource utilizations, diagnoses and prescriptions. Since direct measures of health status are usually not available, patient diagnoses and pharmacy data are increasingly being used as proxies of health status (Meenan 2003). Diagnoses or prescriptions based risk adjustment model can account for more than 10% (up to 25%) variation in cost (Kronick 2000). In addition to the detailed diagnoses and prescriptions patients received during the pretreatment period, the Chronic Illness and Disability Payment System (CDPS) was also used in this study to derive a diagnoses based risk adjustment measures.

  Prior health care expense is another important predictor of future health utilization. A recent study reported that, among Medicaid patients, 1-year

expense prior to the observation period (1-year) was able to capture 45% of high cost dollars and 43% of high cost enrollees, given a 1% prevalence target (Rosen 2003). Although the association between the health expenditure during the pre-treatment period and the period following treatment selection has not been investigated, based on expert opinions, patients' previous health status is one of the key factors that influence physicians' decision of prescribing a drug off-label. Considering the strong relationship between current health status and future health resource utilization, it may be reasonable to postulate that the proxies of health status (diagnoses, prescriptions and previous health expenditure) may also affect physicians' decision to use a particular therapy.

- Expert opinions regarding treatment selections (on-label vs. off-label) were also adopted.

  A clinical pharmacist specializing in psychiatry and a neurologist were interviewed for the following two questions: 1) Based on your experience, which patient factors can affect physicians' decision to prescribe an antidepressant, antipsychotic or anticonvulsant off-label? 2) Besides patient characteristics, what other factors do you believe to have some impact on treatment selections, especially on-label vs. off-label?

  Their opinions were summarized into the following five factors. Since direct measures of those factors are generally not available in claims data, a Medline search was conducted to find the possible proxies.

  - Treatment failure or treatment resistance

    Because this study focused on treatment patterns among patients initiating therapy for a new treatment episode, patients continuing on therapy from an early period were excluded. Therefore, most treatment resistant patients were not included in the study.

- Presence of a disease state where off-label use is recommended by the treatment guideline or supported by recent publications.

  The off-label indications of antidepressants, anticonvulsants and antipsychotics that are supported by at least one randomized clinical trial or recommended to be at least second line therapy by peer-reviewed articles were used as the proxies for this factor. (Evins 2003; Fountoulakis 2004; Hirschfeld 2003; Lee 2002; Stone 2003; Thomson Healthcare Inc 2004).

- Prescriber preferences

  Our previous study of anticonvulsant off-label use found that the patients seeing specialists tended to received off-label anticonvulsant more often than patients seeing primary care physicians only. Seeing a psychiatrist was considered a potential factor that affected patients' propensity of receiving off-label medications in this study.

- Comorbidity where one might get synergy or dual-utility from using a medication off-label.

  In this study, this factor did not actually affect the assignment of a subject to the on-label or the off-label groups because if a drug was prescribed for both an on-label indication and an off-label indication, it would be categorized to be an on-label prescription.

- Identical mechanism of action between drugs that were and were not approved by FDA for a certain condition.

  Because this factor was not associated with research subjects, it should be independent from the treatment selections in terms of on-label vs. off-label among research subjects. Therefore, this factor was not considered in this study.

Table 4.5 presents the candidate covariates available in Medicaid data that could influence treatment assignment, cost and health resource utilization. A stepwise logistic variable selection procedure using a 0.50 significant level (Rosenbaum 1984; D'agostino 1998) was applied to select the final list of covariates, and then the propensity score for each research subject was estimated using a logit model.

After propensity scores had been estimated, subjects in the off-label and in the on-label groups were matched by nearest available Mahalanobis metric matching within calipers defined by the propensity score (D'agostino 1998). It combines two other matching algorithms, the nearest available matching and Mahalanobis metric matching, into a single method. As compared to the other two matching methods, the nearest available Mahalanobis metric matching within calipers defined by the propensity score produced the best balance between covariates in the treated and control groups (D'agostino 1998). The nearest available Mahalanobis metric matching within calipers defined by the propensity score was performed as follows. First, as suggested by Rosenbaum and Rubin (Rosenbaum 1985), the caliper size in this study was defined as a quarter of the standard deviation of the propensity score. And then the control subjects were randomly ordered. All treated subjects within a preset amount of the control subject's estimated propensity score were selected, and Mahalanobis distance was calculated between these subjects and the control subject.

$$d(i,j) = (u - v)^T C^{-1} (u - v)$$

d(i,j) = distance

u = value of covariates for the control (on-label) subject

v = value of covariates for the treated (off-label) subject

C = variance covariance matrix for covariates

The closest control and the treated subjects were then removed from the pool, and the process was repeated. All remaining treated subjects would be available for the next

matching with a control subject. A subject that could not find a correspondent match would be discarded.

Two-sample t-statistic and standardized percentage differences were calculated to explore the differences in distribution of covariates between the off-label users and the on-label users before and after the matching (D'agostino 1998). The standardized difference in % is the mean difference as a percentage of the average standard deviation: 100 $(\overline{X}o-\overline{X}l)/\sqrt{\{(So^2+ Sl^2)\}}$, where for each covariate $\overline{X}o$ and $\overline{X}l$ are the sample means in the off-label and on-label groups, respectively, and So^2 and Sl^2 are the corresponding sample variances.

Analysis

All statistical analyses were carried out using SAS 8.2 (SAS 2002). Differences for total medical costs; hospitalization rates and ER use rates were calculated between the off-label drug users (treated subjects) and matched on-label drug users (comparison subjects). Considering the uncertain distributions of the cost differences, both parametric (paired t test) and nonparametric (Wilcoxon signed rank test) statistics were calculated to explore the cost differences between the off-label and the on-label groups. Different ER and hospital utilizations between the groups were tested using the Chi-square statistic.

Sensitivity analyses

Sensitivity analyses were performed to estimate the extent to which the results were influenced by unobserved confounding factors and the changes in operational definitions.

Mental health and substance abuse related outcomes

Mental health and substance abuse related outcomes were calculated from services associated with a mental illness. The definition of mental illness was chosen to

capture comorbidity in the broadest terms while maintaining a focus on mental health issues—an approach similar to that of several other investigators (Nardini 1998; Sabin 1996). The diagnoses included ICD-9 codes 190.0 through 198.9 and 300.0 through 312.9.

Using 180 days instead of 90 days drug free period

To ensure that the pre-treatment drug free period was long enough to 1) eliminate the influence of the previous treatment and 2) catch prior resource utilization information, all outcomes were re-estimated by imposing a 180 days pre-treatment period that was free of antidepressant, anticonvulsant and antipsychotic medications.

Rosenbaum bounds method of sensitivity analysis for the estimation of treatment effects using data on matched pairs

Propensity score matching provides an estimate of the effect of a "treatment" variable on an outcome variable that is largely free of bias arising from an association between treatment status and observable variables. However, matching methods are not robust against "hidden bias" arising from unobserved variables that simultaneously affect assignment to the treatment and the outcome variable. One strategy for addressing this problem is the Rosenbaum bounds approach, which allows the analyst to determine how strongly an unmeasured confounding variable must affect selection into treatment in order to undermine the conclusions about causal effects from a matching analysis (Diprete 2004; Hujer 2003).

The test statistic of Wilcoxon signed rank statistic has the form:

$$T = t(Z, r) = \sum_{s=1}^{S} d_s \sum_{i=1}^{2} c_{si} Z_{si}$$

Where Z is the variable that registers which of each of the s pairs was treated, and r measures the outcome for each case. Z_{si} equals 1 if a case is treated and 0 otherwise. “c” is defined as follows:

$$c_{s1} = 1,\ c_{s2} = 0 \quad \text{if } r_{s1} > r_{s2}$$
$$c_{s1} = 0,\ c_{s2} = 1 \quad \text{if } r_{s1} < r_{s2}$$
$$c_{s1} = 0,\ c_{s2} = 0 \quad \text{if } r_{s1} = r_{s2}$$

Finally, d_s is the rank of $| r_{s,1} - r_{s,2} |$ with average ranks used for ties. Essentially, the product of the c and Z variables causes pairs to be selected where the outcome for the treatment was greater than the outcome for the control. The rank of these cases is summed and compared to the distribution of the test statistic under the null hypothesis that the treatment has no effect.

Rosenbaum proposed that one assumes that there is an unmeasured variable U that affects the probability of receiving the treatment (off-label Rx). If we let π_i be the probability that the ith subject receives the treatment, X are the observed covariates, then the following treatment assignment equation applies

$$\text{Log}\,[\pi_i / (1-\pi_i)] = k\,(X_i) + r\,U_i$$

Clearly, if the study is free of hidden bias, *r* will be zero and the participation probability will solely be determined by X_i. However, if there is hidden bias, two individuals with the same observed covariates *x* have different chances of receiving treatment.

This relationship implies the following bounds on the ratio of the odds that either of two subjects which are matched on propensity score P(X) will received the treatment

$$[1/\exp(r)] \le [\pi_{s,1}(1-\pi_{s,2})] / [\pi_{s,2}(1-\pi_{s,1})] \le \exp(r)$$

If exp(r) = 1 the bounds are equal to the 'base' scenario of no hidden bias. With increasing exp(r) the bounds move apart reflecting uncertainty about the test-statistics in the presence of unobserved selection bias. Under the assumption that a confounding variable U exists (exp(r) > 1), P_s is defined as the probability that the rank (d_s) remains the same.

$$P_s^+ = 0 \quad \text{if } c_{s1} = c_{s2} = 0;\ P_s(+) = \exp(r) / [1+\exp(r)] \quad \text{if } c_{s1} \neq c_{s2};$$

$$P_s^- = 0 \quad \text{if } c_{s1} = c_{s2} = 0;\ P_s(-) = 1 / [1+\exp(r)] \quad \text{if } c_{s1} \neq c_{s2};$$

Therefore, the null distribution of the test statistic of Wilcoxon signed rank test t(Z,r) is bounded by two known distributions for T^+ (the sum of the positive rank) and T^- (the sum of the negative rank) where:

$$E(T^+) = \sum_{s=1}^{S} d_s P_s^+ \qquad Var(T^+) = \sum_{s=1}^{S} d_s^2 P_s^+ (1- P_s^+)$$

$$E(T^-) = \sum_{s=1}^{S} d_s P_s^- \qquad Var(T^-) = \sum_{s=1}^{S} d_s^2 P_s^- (1- P_s^-)$$

For this sensitivity analysis, exp(r) was increased by a 0.05 scale between 1 and 2. For each specific exp(r), the bounds of the significance level of the one sided test for no effect of the treatment were calculated:

$$(T- E(T^+)) / \text{sqrt}(Var(T^+)) \quad \text{and} \quad (T- E(T^+)) / \text{sqrt}(Var(T^+))$$

The critical value was defined as the value exp(r) at which the outcome estimates become insignificant. The larger the critical value, the less sensitive estimated outcomes are to unobserved selection bias. This critical level can be interpreted as when an unobserved variable caused the odds ratio of treatment assignment to differ between

treatment and control groups by this level, this covariate rather than the treatment factor (off-label) can almost perfectly determine the differences in the outcome measures between treatment and control groups.

RESULTS:

Description of the study population

216,714 adults had at least one antidepressant, anticonvulsant or antipsychotic prescription filled between 1999 and 2000, out of which 62,030 (28.62 %) had a 90 days window free of prescriptions from these three drug categories and met the continuous Medicaid eligibility criteria 3 months prior and 12 months post the index prescription. According to their primary diagnoses received during this 15 months study period, research subjects were hierarchically categorized into the following four disease-specific cohorts: schizophrenia (N= 4,210), bipolar disorders (N= 1,085), depression (N= 8,063) and anxiety (N=2,686). Within each cohort, the treatment group was formed of subjects who received off-label antidepressant, anticonvulsant or antipsychotic medications at the beginning of the 12 months observation period, while the comparison group consisted of subjects who did not have any exposure to these off-label medications in the entire observation period. Subjects who started from labeled prescriptions and then switched to or augmented their original treatment with off-label prescriptions were excluded. Therefore, the final study cohorts consisted of 3,414 subjects (on-label group: 1,982; off-label group: 1,432) in the schizophrenia cohort, 772 (on-label group: 333; off-label group: 439) in the bipolar cohort, 6,922 (on-label group: 4,522; off-label group: 2,400) in the depression cohort and 2,517 (on-label group: 1,252; off-label group: 1,265) in the anxiety cohort.

Table 4.6 presents the demographic characteristics for the subjects of each cohort. The average age of the subjects was around 40 years across the cohorts. Female was dominant in bipolar, depression and anxiety cohorts. More than 75% of the research subjects in these three cohorts were female, with the highest found among patients with depression (82.20%). Less than a quarter (23.87%) of the subjects in the schizophrenia cohort were white.

Patient characteristics

Tables 4.7 - 4.10 compare the characteristics of on-label and off-label users for each cohort before and after propensity score matching. Before propensity score matching, the off-label users and the on-label users were very similar in the anxiety cohort. Only three covariates were significantly different between the off-label and on-label groups and none of these covariates had standardized difference greater than 20%. While statistically significant differences were found in more than fifteen covariates between the on-label and the off-label groups for schizophrenia, bipolar and depression cohorts. However, the differences in these covariates were generally small. Only one covariate in the depression cohort, four in the schizophrenia cohort and six in the bipolar cohort had standardized percent difference of more than 20%.

In schizophrenia and bipolar cohorts, the on-label users received significantly more mental health and substance abuse related diagnoses than the off-label users during the pre-treatment period. The prior health resource utilizations in terms of total and mental health expenditure, inpatient days and emergency room visits were also higher for the on-label users. While in the depression cohort, in contrast, off-label users received more diagnoses of psychoses and personality disorders and incurred significantly higher mental health costs, more psychiatrist visits and psychotherapies. The CDPs predicted values, which predict the future health expenditure based on the diagnoses patient received during the pre-treatment period, reflect a similar pattern as the prior health resource utilizations across the cohorts.

Drug utilization patterns

Table 4.11 - 4.14 compared the utilization patterns of antidepressant, anticonvulsant and antipsychotic medications between the off-label and the on-label groups. The FDA approved treatments were found to be prevalent in both the off-label and the on-label groups across the cohorts. For instance, similar numbers of the off-label and the on-label

users in the schizophrenia cohort received antipsychotic medications and most patients in the bipolar cohort received divalproex and antidepressants during the observation period. This implied that most off-label prescriptions were written as adjuncts to the labeled pharmacotherapies.

As compared to the on-label users, the off-label users seemed to be on more intensive pharmacotherapies across the cohorts with an especially obvious trend found among subjects with depression. A majority of the on-label users in the depression cohort were treated by antidepressants exclusively, while almost all off-label users received an antipsychotic or anticonvulsant in addition to the antidepressant medications. The most popularly used antipsychotic and anticonvulsant medications among the off-label users in the depression cohort included atypical antipsychotics, gabapentin and benzodiazepine anticonvulsants.

Propensity score adjustment for selection bias

1,265 pairs off-label and on-label users in the schizophrenia cohort, 274 pairs in the bipolar cohort, 1,996 pairs in the depression cohort and 856 pairs in the anxiety cohort were successfully matched for all the covariates using the propensity matching technique (Tables 4.7 - 4.10). Before matching, patients in the on-label groups had significantly lower mean propensity score (probability of receiving off-label antidepressant, anticonvulsant or antipsychotic medication) than patients in the off-label groups. After matching, none of the covariate was significantly different between the on-label and the off-label groups. Post match standardized difference was below 5% for all the covariates. The mean propensity score was comparable after matching for the on-label and the off-label groups in all the cohorts.

Analysis after propensity score matching

Parametric cost estimations:

After propensity score matching, the highest per capita annual expenditure was observed in patients with depression (off-label group: $7,955.86; on-label group: $6,851.18), followed by patients with schizophrenia (off-label group: $7,765.03; on-label group: $7,204.95), bipolar disorders (off-label group: $6,789.15; on-label group: $6,350.24) and anxiety (off-label group: $6,815.45; on-label group: $5,258.13) (table 4.15).

The per capital total expenditure was higher for the off-label users as compared with the on-label users in all disease-specific cohorts although the increases were not always statistically significant (table 4.15). Statistically significant differences were found in depression and anxiety cohorts (mean of the net differences: depression cohort: $2,209.36; anxiety cohort: $1,557.32). The increased total health expenditure could be explained mainly by a higher average prescription cost that was consistently associated with the off-label users (net difference: schizophrenia cohort $892.88; bipolar cohort $555.51; depression cohort: $783.87; anxiety cohort: $640.72). Besides prescription costs, the off-label users in the depression cohort and the anxiety cohort also had higher average inpatient (depression cohort: $627.94; anxiety cohort: $ 482.51), outpatient (depression cohort: $508.78; anxiety cohort: $354.61) and long-term care (depression cohort: $288.78; anxiety cohort: $79.46) costs compared to the on-label users. While in the bipolar and schizophrenia cohorts, the comparatively low average inpatient costs associated with the off-label users (schizophrenia cohort: -510.95; bipolar cohort: -575.79) partially offset the impact of their high prescription costs on total health expenditures.

Nonparametric cost estimations:

The median estimates of all cost categories were consistently lower than their correspondent mean estimates (table 4.16). This suggested that the cost distributions were positively skewed in both the off-label and the on-label groups across all cost categories and disease specific cohorts. The median estimates of the annual total health expenditures followed a similar pattern as the mean estimates. The highest median annual total health expenditures were found in depression cohort (off-label group: $5,020.82; on-label group: $3,674.18) and followed by schizophrenia (off-label group: $4,825.87; on-label group: $3,892.43), bipolar (off-label group: $4,275.71; on-label group: $4,174.39) and anxiety (off-label group: $4,105.35; on-label group: $2,709.37) cohorts.

Although the median estimates of cost differences between the off-label and the on-label groups were generally lower than their correspondent mean estimates, the statistically significant differences derived from the parametric estimations (paired t test) were also found to be statistically significant in the nonparametric analysis (Wilcoxon signed rank test.

Estimations of the ER and hospital utilizations:

The percentage of all cause hospitalizations was around 20% among all disease-specific cohorts, with the highest found in patients with bipolar disorders (23.54%) and the lowest in patients with anxiety disorders (15.77%). The difference between on-label and off-label groups in terms of hospitalization rate was consistent with the findings in the inpatient costs (table 4.17). Relative to the on-label users, less off-label users had been hospitalized during the observation period in the schizophrenia and bipolar cohorts. In contrast, the hospitalization rates associated with the off-label users were higher than the on-label users in the depression and anxiety cohorts. Statistically significant difference in terms of hospital utilizations was only observed in the schizophrenia cohort (off-label group: 17.08%; on-label group: 22.13%). No statistically significant differences

were found in ER use rates between the on-label and the off-label groups across the cohorts.

To explore whether the different hospitalization rates between the off-label and the on-label groups were due to the mental disorders under investigation, the most prevalent primary diagnoses in inpatient claims were identified for the subjects in each cohort (table 4.18). Similar to the findings in hospital utilizations and expenditures, the off-label users in the schizophrenia and bipolar cohorts had much less diagnosis codes associated with schizophrenia or affective disorders compared to the on–label users, while it was in reverse in the depression cohort.

Sub-analysis by off-label drug categories within the depression cohort

Parametric cost estimations:

Because the off-label users in the depression cohort experienced significantly higher expenditures in all cost subcategories and the per capita annual total health expenditure was $ 2,209.36 higher than the on-label users, a post-hoc sub-analysis was performed to estimate the independent effects of using off-label antipsychotics and anticonvulsants for treating depression patients on the three main outcome measures. Table 4.19 shows that the depression patients who were treated by off-label anticonvulsants experienced much higher per capital annual health expenditures (off-label group: $11,099.53; on-label group: $8102.65) as compared with patients who were treated by off-label antipsychotics (off-label group: $7787.98; on-label group: $6012.98). This mainly results from the unusually high average inpatient costs ($ 3661.49) and long term care costs ($1002.36) associated with the off-label anticonvulsant users.

Relative to the on-label users, both the off-label anticonvulsant users and the off-label antipsychotic users had significantly higher per capital total health expenditure (net difference: anticonvulsant: $2,996.90; antipsychotic: $1,775.00). The increased total health expenditure associated with the off-label antipsychotic users can be mainly

explained by their high prescription costs compared to the on-label users (net difference: off-label vs. on-label: $855.85). Whereas the off-label anticonvulsant users had significantly higher prescription (net difference: off-label vs. on-label: $855.85), inpatient (net difference: off-label vs. on-label: $855.85), outpatient (net difference: off-label vs. on-label: $855.85) and long term care (net difference: off-label vs. on-label: $855.85) costs compared to the on-label users.

Nonparametric cost estimations:

Similar to the results observed in the general analysis, the cost distributions were positively skewed (table 4.20). The median estimates of the annual total health expenditures are lower than their correspondent mean estimates. The results derived from both the nonparametric (Wilcoxon signed rank test) and the parametric (paired t test) cost analyses are consistent with each other.

Estimations of the ER and hospital utilizations:

In this subanalysis, the hospitalization rates and the ER use rates were generally comparable between the off-label and the on-label groups except that the anticonvulsant off-label users had significantly higher hospital utilizations compared to the on-label users (off-label vs. on-label: 26.32% vs. 21.74%) (Table 4.21). Among the subjects who had been hospitalized during the observation period, much more anticonvulsant off-label users received primary diagnoses related to depression (ICD9: 296.xx, 311.xx) than the correspondent on-label users in the inpatient setting (Table 4.22).

Sensitivity analyses

Mental health related outcomes

The difference in per capita one-year mental health and substance abuse related expenditures between off-label and on-label groups followed a trend similar to the total medical expenditure (Table 4.23). The mental heath related costs were found to be higher for the off-label users relative to the on-label users in depression (net difference:

$ 453.10) and anxiety (net difference: $ 40.98) cohorts, and lower in schizophrenia (net difference: $ -311.02) and bipolar (net difference: $ -411.36) cohorts.

The proportion of mental health and substance abuse related hospitalizations in all cause hospitalizations was highly correlated with the severity of mental disorders (Table 4.24). 90% of the hospitalizations for patients with schizophrenia were mental health and substance abuse related, followed by bipolar disorders (65.89%), depression (53.74%) and anxiety (28.15%). This trend was also found in mental health and substance abused related emergency room visits. Consistent with the results observed in all-cause hospitalizations and emergency room visits, mental health and substance abused related hospitalization rates and ER use rates were higher for the off-label users relative to the on-label users in depression and anxiety cohort and lower in schizophrenia and bipolar cohorts. However, the increases observed in depression and anxiety cohorts were not statistically significant.

Imposing a 180 days period free of antidepressant, anticonvulsant and antipsychotic medications

The sample sizes of study cohorts decreased around 30% to 50% after imposing a 180 days drug free period (Table 4.23). After propensity score matching, only 659 pairs off-label and on-label users in the schizophrenia cohort, 193 pairs in the bipolar cohort, 1,178 pairs in the depression cohort and 568 pairs in the anxiety cohort were successfully matched. Though the sample size was drastically affected by the length of the drug free period, the estimated differences between the off-label and the on-label groups in terms of total health expenditure, hospitalization rates and ER use rates were very similar no matter a 180 days or a 90 days drug free period was used (Tables 4.23 - 4.24).

Rosenbaum bounds sensitivity analysis

In terms of per capita total health expenditures, statistically significant differences were found between the off-label and the on-label groups in depression and anxiety cohorts. Rosenbaum bounds sensitivity analysis was performed to test the robustness of these estimates against unmeasured selection bias. Table 4.25 demonstrates that the critical level of hidden bias at which we would have to question our conclusion of a positive effect of off-label drug use on total health expenditures in the depression cohort was between 1.35 and 1.40. This was attained if an unobserved covariate caused the odds ratio of treatment assignment to differ between off-label and on-label cases by a factor of about 1.40. For the anxiety cohort it would require a hidden bias of between 1.40 and 1.45 to render spurious the conclusion of a positive effect of off-label drug use on total health expenditures.

DISCUSSIONS AND CONCLUSIONS:

This study examined the effect of using off-label antidepressants, anticonvulsants and antipsychotics on health resource utilizations in terms of health expenditures, inpatient hospitalizations and emergency room visits among patients with mental disorders. Findings indicate that the off-label users experienced significantly higher prescription expenditures relative to the on-label users across the cohorts. The impacts of using off-label medications on the other outcome measures were heterogeneous in different mental disorders with the most striking results found in patients with depression.

After propensity score matching, the highest per capita annual expenditure was observed in patients with depression ($7,955.86). Nevertheless, this does not suggest that the depression patients identified for this study had more severe mental disabilities than patients with schizophrenia and bipolar disorders. The sensitivity analysis revealed that the proportion of mental health related health resource utilizations in total health resource utilizations is positively correlated with the severity of mental disorders. Nearly

60% of the total medical expenditures for schizophrenia patients were mental health related, 35% for bipolar patients, 20% for depression patients and only 11% for anxiety patients. Consistent with our common sense, patients in the schizophrenia cohort had the highest average mental health and substance abuse related costs ($2,994.86), followed by patients in bipolar ($1,632.85), depression ($1,299.64) and anxiety ($482.59) cohorts. The chronic conditions other than mental disorders were found to be especially prevalent among patients with depression. For instance, 16% of the subjects in the depression cohort received diagnoses of cardiovascular diseases and 20% of the subjects received diagnoses of chronic pulmonary diseases during the 90 days pre-treatment period. These expensive comorbidities may explain away the high non-mental health expenditure for the depression patients.

Both general and independent effects of using off-label anticonvulsant and antipsychotic medications on depression patients were examined. Besides the significantly higher prescription costs, off-label users in the depression cohort also had much higher outpatient, inpatient, long-term care and mental health related costs compared to the on-label users, resulting, in total, in a $2,209 average cost difference between the off-label group and the on-label group. More than one third of this increased net cost can be explained by the higher prescription costs (net difference: $783.87) for the off-label users relative to the on-label users; another 21% can be attributed to the mental health and substance abuse related medical services (net difference: $453.10); leaving about 44% caused by other reasons. Given that almost all off-label users in the depression cohort received an antidepressant in addition to the off-label medications and more than half of them received at least one off-label atypical antipsychotic medication during the observation period, the high prescription expenditures for the off-label users can be well explained by a high prevalence of polypharmacy and atypical antipsychotic utilization. The subanalysis demonstrates that 50% ($855.85) of the total cost difference

between the antipsychotic off-label users and the on-label users in the depression cohort can be explained by prescription expenditure, while only 17% ($528.43) of the cost difference found between the anticonvulsant off-label users and the on-label users is due to this reason.

In terms of the medical benefits, there have been a growing number of reports on the benefits of using atypical antipsychotics as an augmenting agent in non psychotic treatment resistant depression (Shelton 2003) during the past several years. However, no published study has ever touched patients with non-treatment resistant depression. In this study, there was no evidence that using off-label antipsychotic medications in non-treatment resistant depression can lead to any negative clinical outcomes such as increased ER or hospital utilization. However, when using anticonvulsants off-label, nearly $3,000 average difference was observed between the off-label and the on-label groups. This net cost was primarily resulted from the much higher hospitalization rate and expenditures associated with the off-label users. The descriptive analysis also revealed that the anticonvulsant off-label users had more depression associated hosiptializations as compared to the on-label users. Although a clinical trial of combining lamotrigine and paroxetine for the depression patients partially supports the antidepressive properties of lamotrigine (Normann 2002), the general pharmacological mechanisms of anticonvulsant medications suggest that this group of drugs should have strong antimanic rather than antidepressive properties. Considering the widespread utilization of anticonvulsants in unipolar depression and the potential negative outcomes associated with this use, more studies, especially clinical trials, should be conducted to further clarify these findings.

For patients with schizophrenia, the possible benefits associated with using off-label antidepressants and anticonvulsants were observed in the inpatient setting. Relative to the on-label users, the off-label users had significantly less all cause and

mental health related hospitalizations and experience lower inpatient expenditures. This is consistent with the findings of a recent clinical trial which suggests that the combination therapy with divalproex (an anticonvulsant) can decrease the mental pain and suffering from many patients with schizophrenia and shorten the length of their inpatient stays (Casey 2003). Antidepressants and antipsychotics have been recommended by treatment guidelines to relieve depression, agitation and aggression accompanied with schizophrenia (National Institute for Clinical Excellence 2002). The results of the current study provides some evidence that off-label antidepressant and anticonvulsant use may offer some benefits in the schizophrenia population offsetting the higher prescription costs. However, overall, the experimental evidence is still too limited to support or refute the value of using off-label antidepressants and anticonvulsants in schizophrenia. It will require future studies to confirm and extend this finding.

Similar to the results observed in the schizophrenia cohort, off-label drug use was found to have some benefits in terms of mental health related hospitalizations and emergency room visits for patients with bipolar disorders. Bipolar disorder, like epilepsy and migraine, is episodic in nature. Based on twenty-eight reports of the efficacy of novel antiepileptic medications in bipolar disorder, almost all new generation anticonvulsants showed some positive effects except for gabapentin (Evins, 2003). Upon the finding that gabapentin was the most popularly used anticonvulsant among the off-label users with bipolar disorders, the outcomes associated with off-label gabapentin use may worth further exploration. For the on-label and the off-label users in the anxiety cohort, they were generally comparable even before propensity matching. After propensity matching, the annual average total health expenditure of the off-label users was $1557.32 higher relative to the on-label users. However, the difference is mainly due to the higher prescription costs associated with the off-label users. The two groups are very similar in

terms of mental health related expenditure and the primary diagnoses associated with hospitalizations.

Several potential limitations should be noted. First, as with most non-experimental research, we cannot rule out the possibility that our results simply reflect the effects of unmeasured selection bias (e.g., differences in disease severity between off-label and on-label users) rather than those of off-label medication use *per se*. We especially have a concern regarding patients with both Medicaid and Medicare dual eligibility. Dually eligible beneficiaries are estimated to represent 19 percent of total enrollment and 35 percent of Medicaid expenditures (Murray 1998). Without matching this variable, we can exclude the possibility that the off-label and on-label groups may be different in terms of disease severity. However, in the depression cohort, the pre-treatment health resource utilizations in terms of total and medical expenditures, emergency room visits and inpatient stays were not significantly different between the off-label and the on-label groups even before the propensity score matching. It is unlikely that the differences in disease severity can cause a $2,200 post-treatment cost difference between the off-label and the on-label users in the depression cohort without affecting their pre-treatment total and medical expenditures. The Rosenbaum bounds sensitivity analysis shows that the endogenous selection caused by the unmeasured founders, if it does exist, would have to attain a value of 1.4 to render spurious the conclusion of a positive effect of the off-label drug use on total health expenditures among depression patients, which would be possible for some unmeasured covariate. .

Limitations inherent to the use of claims databases must also be recognized. The classification of the off-label and the on-label uses in this study relies upon the accuracy and completeness of diagnostic code data. Diagnostic test or error, miss coding or missing code associated with the Medicaid claims data may cause misclassifications of off-label and on-label users and therefore affect the outcome measures.

Finally, since the findings of this study were based on a Medicaid population which contains people with comparatively low social economic status, the results might not be generalizable to any given setting (e.g., a large employer group); Also, to examine whether there is a causal relationship between off-label drug use and negative clinical and economic outcomes, a 90 days drug free period was imposed, which excluded most patients with treatment resistant mental disorders.

Despite these limitations, we believe that our study has important implications. To the best of our knowledge, it is the first to comprehensively examine the economic and clinical impacts of using off-label antidepressant, anticonvulsant and antipsychotic medications in patients with mental disorders. The findings of this study suggest that in a "real world" clinical setting, using off-label medications, especially off-label anticonvulsants, alone or as adjunct to antidepressant therapy for depression patients is associated with significantly higher total health expenditures and hospital utilizations. While for patients with schizophrenia, the use of off-label antidepressants and anticonvulsants offers meaningful reductions in the hospitalization rate and inpatient costs compared to the FDA approved treatments. The results derived from this study support the research hypotheses that patients who are prescribed antidepressant, anticonvulsant and antipsychotic medications off-label alone or as adjunct to labeled pharmacotherapy vs. patients who are prescribed only labeled pharmacotherapy for schizophrenia, bipolar disorder, depression or anxiety differ significantly in total health care cost, inpatient hospitalizations, and number of emergency room visits. As off-label drug use continues to grow, more examinations of this type should be conducted to provide evidence for policy making and clinical management.

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Table 4.1: Labeled indications of antidepressants.

Antidepressants	FDA approved indications for adults
Bupropion	depression, smoking cessation
maprotiline	depression
mirtazapine*	depression
nefazodone*	depression
Trazodone	depression
venlafaxine*	depression, generalized anxiety disorder, social anxiety disorder (social phobia)
citalopram*	depression
fluoxetine*	depression, obsessive compulsive disorder, bulimia nervosa, panic disorder
fluvoxamine*	obsessive compulsive disorder
paroxetine*	depression, obsessive compulsive disorder, social anxiety disorder (social phobia), panic disorder, generalized anxiety disorder, posttraumatic stress disorder
sertraline*	depression, obsessive compulsive disorder, social anxiety disorder (social phobia), panic disorder, generalized anxiety disorder, posttraumatic stress disorder
Amitriptyline	depression, depression accompanied by anxiety
Amoxapine	depression
Clomipramine	obsessive compulsive disorder
Desipramine	depression
Doxepin	psychoneurotic patients with depression and/or anxiety, depression and/or anxiety associated with alcoholism (not to be taken concomitantly with alcohol), depression and/or anxiety associated with organic disease, psychotic depressive disorders with associated anxiety including involutional depression and manic-depressive disorders
Imipramine	depression
Nortriptyline	depression
Protriptyline	depression
Trimipramine	depression

*: New generation medications

Table 4.2: Labeled indications of anticonvulsants.

Anticonvulsants	FDA approved indications for adults
Acetazolamide	edema due to congestive heart failure, drug induced edema, epilepsies (petit mal, unlocalized seizures), chronic simple angle glaucoma, secondary glaucoma, acute angle -closure glaucoma, acute mountain sickness
Carbamazepine	partial seizures (psychomotor or temporal lobe), generalized Tonic-clonic (grand mal) seizure, mild, partial or generalized seizure
Clonazepam	seizure disorders, panic disorder
Clorazepate	anxiety disorder, partial seizures, symptomatic relief of acute alcohol withdrawal
Diazepam	anxiety disorder, alcohol withdraw, skeletal muscle spasm, seizure
divalproex sodium	mania in bipolar disorder, partial epilepsy, migraine
Ethosuximide	absence (petit mal) epilepsy
felbamate*	generalized epilepsy
fosphentoin*	short-term parental administration, generalized convulsive epilepticus, seizure in surgery
gabapentin*	partial seizure with epilepsy for patient, postherpetic neuralgia
lamotrigine*	partial seizure and generalized seizures of Lennox-Gastaut syndrome, bipolar disorder
levetiracetam*	partial onset seizures with epilepsy
Lorazepam	anxiety disorder
Mephobarbital	sedative for relief of anxiety, tension and apprehension, anticonvulsant in treatment of grand mal and petit mal epilepsy
Methsuximide	absence (petit mal) seizure
oxcarbazepine*	partial seizure with epilepsy
Paraldehyde	alcohol or drug withdraw, poisoning by convulsive drug, convulsive episode arising from tetanus, status epilepticus, insomnia
Phenobarbital	sedative, hypnotic for short term treatment of insomnia, preanesthetics, long term anticonvulsants for generalized tonic clonic seizures and cortical local seizures, emergency control of acute convulsive of status epilepticus
Phenytoin	tonic-clonic (grand mal) and psychomotor (temporal lobe) seizures
Primidone	tonic-clonic (grand -mal) seizure, psychomotor (temporal lobe seizures)
tiagabine*	partial seizure
topiramate*	partial seizure, primary generalized tonic-clonic seizures, seizure associate with LGS
valproic acid	mania in bipolar disorder, epilepsy, migraine
zonisamide*	partial seizure in epilepsy

*: New generation medications

Table 4.3: Labeled indications of antipsychotics.

Antipsychotics	FDA approved indications for adults
clozapine*	severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia, reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorders
Haloperidol	schizophrenic patients who require prolonged parenteral antipsychotic therapy
loxapine*	schizophrenia
Molindone	schizophrenia
olanzapine*	schizophrenia, bipolar mania
quetiapine*	schizophrenia, acute bipolar mania
Risperidone	schizophrenia, bipolar mania
Thiothixene	schizophrenia, psychotic disorder (injection use)
Ziprasidone	schizophrenia
chlorpromazine	schizophrenia, mania, acute intermittent porphyria, intractable hiccups, nausea and vomiting, presurgical apprehension, tetanus
Fluphenazine	schizophrenia
Mesoridazine	schizophrenic patients who fail to respond adequately to treatment with other antipsychotic drugs
Perphenazine	schizophrenia, nausea and vomiting
prochlorperazine	schizophrenia, severe nausea and vomiting, non-psychotic anxiety **
Promazine	schizophrenia
Thioridazine	patients who fail to respond adequately to treatment with other antipsychotic drugs
trifluoperazine	schizophrenia, non-psychotic anxiety
trifluprom azine	schizophrenia (acute treatment), nausea and vomiting

*: New generation medications

Table 4.4: ICD9-CM assigned to the labeled indications of antidepressants, anticonvulsants and antipsychotics.

Labeled indications	ICD9- CM
absence (petit mal) seizure	345.0x, 345.2x
acute intermittent porphyria	277.1x
alcohol or drug withdrawal	291.0x, 291.3x, 291.8x, 292.0x
bulimia nervosa	307.51
convulsive episode arising from tetanus	037.xx, 771.3x, 978.4x, E9484
Depression	296.2x-296.3x
depression accompanied by anxiety	300.4x
depression and/or anxiety associated with alcoholism (not to be taken concomitantly with alcohol)	291.xx
depression and/or anxiety associated with organic disease	310.8x, 294.8x
drug induced edema	782.3x
edema due to congestive heart failure	428.xx
Epilepsy	345.xx, 780.39
generalized anxiety disorder	300.02
generalized epilepsy	345.0x. 345.1x, 345.2x, 345.3x, 780.39
intractable hiccups	786.8x, 306.1x
mania and mania episode in bipolar disorders	296.0x, 296.1x, 296.4x-296.8x
Migraine	346.xx
nausea and vomiting	787.0x
non-psychotic anxiety	300.0x
obsessive compulsive disorder	300.3x
panic disorder	300.01, 300.21
partial seizure	345.4x, 345.5x
poisoning by convulsive drug	E858, 780.39
postherpetic neuralgia	53.19
posttraumatic stress disorder	309.81
premenstrual dysphonic disorder	625.4x
primary generalized tonic-clonic seizures	345.1x, 780.9x
psychoneurotic patients with depression and/or anxiety	300.0x, 300.4x
psychotic depressive disorders with associated anxiety including involutional depression and manic-depressive disorders	296.xx
psychomotor (temporal lobe seizures)	345.4x, 345.7x
Schizophrenia	295.xx
sedative for relief of anxiety, tension and apprehension	293.xx, 300.xx, 309.xx, 625.4x
seizure associate with LGS	345.01
skeletal muscle spasm	728.85
social anxiety disorder (social phobia)	300.23
status epilepticus	345.3x

Table 4.5: Initial list of candidate factors associated with the off-label use of antidepressant, anticonvulsant and antipsychotic medications.

Demographics

Age, Gender, Race

Prescriptions filled during the three months pre-treatment period

Cardiac agents
Anti-Parkinson agents
Coagulation modifiers
Antihypertensives
Respiratory agents
Drugs for NID diabetes
Insulins
Antineoplastics (cancer)
Antiepileptics/anticonvulsants
Acid peptic disease agents
Anti-glaucoma agents
Antigout agents
Anti-hyperlipidemia, hypercholesterolemia
Antiretrovirals (aids)
Thyroid agents
Narcotic analgesics
Antidepressants
Neuroleptics
Dementia agents
Antituberculosis agents
Drug for rheumatologic conditions
Systemic steroids
Drugs for irritable bowel disease
End stage renal disease
Immunosuppressive agents
Antimigraine agents
Drugs for bone diseases (Padget's disease, osteoporosis)

Chronic Illness and Disability Payment System (CDPS)

CDPS predicted value
Number of CDPS categories
Number of CDPS diagnoses

Resource Utilization during the three months prior period

Total costs
Total hospitalization costs
Total mental health costs

Diagnosis-related comorbidities

Mental and substance abuse related comorbidities

Acute reaction to stress
Adjustment reaction
Alcoholic psychoses
Alzheimer's disease
Bipolar affective disorders
Cyclothymic disorders
Depressive disorder, not elsewhere specified
Drug psychoses
Major depressive disorder
Manic disorders
Mental retardation
Neurotic disorders
Other alcohol & drug related psychoses
Other mental disorders
Other non-organic psychoses
Other organic psychotic conditions, chronic
Paranoid/Delusion disorders
Personality disorders
Psychoses with origin specified to childhood
Schizophrenic disorders
Transient organic psychotic conditions
Unspecified affective psychoses

Other comorbidities

Anemia
Asthma
Cancer
Cardiovascular disease
Chronic pulmonary diseases
Coagulation
Connective tissue
Diabetes
Epilepsy
HIV or AIDS
Hypothyroidism
Liver diseases
Neurological disorders

Total Medical costs
Total drug costs
Specialist visits (day episodes)
Psychotherapies
Emergency room visits (day episodes)
Hospitalization (total inpatient days)
Nutritional disorders
Paralysis
Peptic ulcer disease
Renal failure

Table 4.6: Patient demographic characteristics of each disease-specific cohort.

Classification	Total	Average age (Years)	Male (%Total)	White (%Total)
Schizophrenia cohort	3,414	40.31	1,560 (45.69%)	808 (23.87%)
Bipolar cohort	772	36.40	184 (23.83%)	449 (58.16%)
Depression cohort	6,922	39.35	1,232 (17.80%)	3,282 (47.41%)
Anxiety cohort	2,517	42.36	494 (19.63%)	1,329 (52.8%)

Table 4.7: Group comparisons before and after propensity score matching in the schizophrenia cohort.

	BEFORE PROPENSITY MATCHING				AFTER PROPENSITY MATCHING			
	On-label	Off-label			On-label	Off-label		
	N = 1,982	N = 1,432		Standardized	N = 1,265	N = 1,265		Standardized
	% prevalence	% prevalence	2-sample	difference	% prevalence	% prevalence	2-sample	difference
Demographics	or mean	or mean	t-statistic	in %**	or mean	or mean	t-statistic	in %**
Age	40.46	40.09	0.81	2.80	40.09	39.94	0.30	1.19
White	0.19	0.30	-7.15**	-25.09	0.24	0.24	-0.09	-0.37
Male	0.47	0.44	2.11*	7.33	0.43	0.44	-0.52	-2.07
Chronic Illness and Disability Payment System (CDPS)								
CDPS predicted value	1.04	0.96	2.98**	10.23	0.97	0.97	0.00	0.01
Number of CDPS categories	0.29	0.36	-4.33**	-15.08	0.35	0.35	0.38	1.49
Number of CDPS diagnoses	1.14	0.94	5.44**	18.69	0.96	0.94	0.37	1.46
Resource Utilization during the three months prior period								
Total costs	1593.26	1272.56	2.95**	9.92	1235.04	1216.54	0.19	0.74
Total hospitalization costs	756.41	433.27	3.52**	11.72	464.37	460.95	0.04	0.17
Total mental health costs	983.90	630.83	4.49**	14.86	645.91	653.19	-0.11	-0.44
Total Medical costs	1527.71	1190.38	3.13**	10.53	1172.73	1147.91	0.25	1.00
Total drug costs	65.56	82.18	-2.15*	-7.69	62.31	68.63	-0.84	-3.33
Specialist visits (day episodes)	0.03	0.02	0.26	0.85	0.02	0.02	-0.78	-3.11
Psychotherapies	0.21	0.15	2.66**	9.00	0.14	0.16	-0.81	-3.23
Emergency room visits (day episodes)	0.41	0.26	4.92**	16.60	0.28	0.27	0.42	1.68

Hospitalization (total inpatient days)	1.13	0.70	2.94**	10.11	0.75	0.76	-0.07	-0.28
Comorbidities during the three months prior period								
Bipolar affective disorders	0.04	0.01	4.36**	14.57	0.01	0.02	-0.69	-2.75
Schizophrenia disorders	0.57	0.55	0.85	2.95	0.54	0.56	-1.04	-4.13
Acute reaction to stress	0.00	0.00	-1.82	-6.69	0.00	0.00	1.00	3.98
Adjustment reaction	0.02	0.01	2.57*	8.60	0.01	0.01	0.86	3.40
Alzheimer's disease	0.00	0.00	0.48	1.66	0.00	0.00	0.30	1.20
Other organic psychotic conditions, chronic	0.00	0.00	0.48	1.66	0.00	0.00	0.00	0.00
Transient organic psychotic conditions	0.01	0.00	1.79	6.03	0.01	0.00	0.58	2.30
Alcoholic psychoses	0.06	0.03	4.09**	13.84	0.03	0.03	0.22	0.89
Manic disorders	0.00	0.00	1.88	6.17	0.00	0.00	-1.00	-3.98
Major depressive disorder	0.08	0.03	6.95**	23.17	0.04	0.03	1.21	4.83
Mental retardation	0.02	0.02	0.32	1.10	0.02	0.02	-0.40	-1.57
Other non-organic psychoses	0.08	0.06	2.4*	8.24	0.07	0.07	0.24	0.95
Other alcohol & drug related psychoses	0.03	0.02	2.46*	8.34	0.02	0.02	-0.15	-0.60
Other mental disorders	0.01	0.00	2.08*	6.98	0.00	0.00	-0.63	-2.52
Depressive disorder, not elsewhere specified	0.06	0.01	7.55**	24.81	0.01	0.01	-0.17	-0.68
Paranoid/Delusion disorders	0.01	0.00	1.94	6.53	0.01	0.00	0.91	3.60
Personality disorders	0.02	0.01	4.02**	13.33	0.01	0.01	0.22	0.87
Drug psychoses	0.06	0.04	3.15**	10.75	0.04	0.04	-0.10	-0.39
Epilepsy	0.01	0.01	0.36	1.25	0.00	0.01	-0.54	-2.13
Neurological disorders	0.00	0.00	1.04	3.51	0.00	0.00	-1.00	-3.98
Neurotic disorders	0.06	0.03	3.96**	13.40	0.03	0.04	-0.32	-1.29
Paralysis	0.00	0.00	0.12	0.43	0.00	0.00	-0.45	-1.78

Unspecified affective psychoses	0.01	0.00	2.78**	9.24	0.00	0.00	0.00	0.00
Chronic pulmonary diseases	0.05	0.05	-0.25	-0.87	0.05	0.05	-0.19	-0.75
Cardiovascular disease	0.12	0.09	2.61**	8.96	0.09	0.09	0.69	2.76
Coagulation	0.00	0.00	-0.05	-0.17	0.00	0.00	-1.00	-3.98
HIV or AIDS	0.01	0.01	-0.77	-2.69	0.01	0.01	-0.71	-2.83
Hypothyroidism	0.01	0.01	1.22	4.15	0.01	0.01	0.58	2.31
Nutritional disorders	0.04	0.03	1.72	5.88	0.03	0.03	-0.24	-0.96
Peptic ulcer disease	0.01	0.00	0.90	3.07	0.00	0.00	-0.71	-2.82
Renal failure	0.00	0.00	0.13	0.43	0.00	0.00	0.71	2.82
Asthma	0.03	0.02	0.42	1.46	0.02	0.02	0.00	0.00
Cancer	0.01	0.01	0.88	3.02	0.01	0.01	0.50	1.99
Connective tissue	0.01	0.00	0.70	2.38	0.00	0.00	0.00	0.00
Diabetes	0.06	0.04	1.60	5.51	0.05	0.05	0.65	2.59
Liver diseases	0.00	0.00	-0.45	-1.58	0.00	0.00	0.58	2.30
Prescriptions filled during the three months prior period								
Number of drug categories	0.50	0.48	0.64	2.22	0.41	0.43	-0.69	-2.75
Antiretrovirals	0.00	0.01	-1.56	-5.56	0.00	0.00	0.00	0.00
Anti-Parkinson agents	0.07	0.02	7.15**	23.76	0.02	0.03	-0.78	-3.12
Antigout agents	0.00	0.00	1.41	4.49	0.00	0.00	.	
Drugs for bone diseases	0.00	0.00	0.09	0.31	0.00	0.00	1.00	3.98
Antineoplastics	0.01	0.01	-1.55	-5.52	0.01	0.01	-0.50	-1.99
Cardiac agents	0.06	0.06	0.36	1.25	0.05	0.06	-0.61	-2.43
Coagulation modifiers	0.03	0.04	-1.72	-6.05	0.03	0.03	0.24	0.94
Dementia agents	0.00	0.00	0.31	1.06	0.00	0.00	1.41	5.63
Drugs for NID diabetes	0.04	0.03	1.14	3.91	0.03	0.03	-0.11	-0.45
Anti-glaucoma agents	0.00	0.00	-0.07	-0.24	0.00	0.00	-0.33	-1.33
Antihyperlipidemia	0.02	0.02	0.53	1.82	0.01	0.02	-0.17	-0.66

Antihypertensives	0.06	0.04	1.95	6.68	0.04	0.05	-0.47	-1.88
Insulin	0.02	0.02	1.96*	6.68	0.02	0.02	0.31	1.24
Antimigraine agents	0.00	0.00	-0.05	-0.17	0.00	0.00	0.00	0.00
Narcotic analgesics	0.10	0.12	-1.89	-6.58	0.10	0.11	-0.33	-1.30
Respiratory agents	0.04	0.06	-2.36*	-8.31	0.05	0.05	-0.37	-1.49
Drug for rheumatologic conditions	0.00	0.00	-1.21	-4.41	0.00	0.00	0.00	0.00
Systemic steroids	0.02	0.03	-0.33	-1.15	0.02	0.02	-1.12	-4.46
Thyroid agents	0.01	0.02	-1.56	-5.52	0.02	0.02	0.16	0.64
Propensity & Logit								
Estimated probability of receiving an off-label prescription	0.38	0.47	-18.28**	-62.66	0.45	0.45	-0.03	-0.12
Logit	-0.56	-0.13	-18.28**	-61.73	-0.23	-0.23	-0.03	-0.11

*: $0.01<P<0.05$

**: $P<0.01$

Table 4.8: Group comparisons before and after propensity score matching in the bipolar cohort.

	BEFORE PROPENSITY MATCHING				AFTER PROPENSITY MATCHING			
	On-label	Off-label			On-label	Off-label		
	N = 333	N = 439		Standardized	N = 274	N = 274		Standardized
	% prevalence	% prevalence	2-sample	difference	% prevalence	% prevalence	2-sample	difference
Demographics	or mean	or mean	t-statistic	in %**	or mean	or mean	t-statistic	in %**
Age	35.23	37.29	-2.14*	-15.66	35.71	36.03	-0.30	-2.60
White	0.59	0.57	0.64	4.63	0.60	0.58	0.35	2.96
Male	0.24	0.23	0.28	2.02	0.25	0.21	1.12	9.56
Chronic Illness and Disability Payment System (CDPS)								
CDPS predicted value	0.82	0.78	0.86	6.23	0.76	0.74	0.44	3.79
Number of CDPS categories	0.35	0.42	-2.04*	-14.87	0.41	0.43	-0.43	-3.69
Number of CDPS diagnoses	1.08	0.91	2.11*	15.43	0.90	0.91	-0.04	-0.35
Resource Utilization during the 3 months prior period								
Total costs	1577.70	1098.08	2.61**	19.38	1039.70	1132.11	-0.55	-4.70
Total hospitalization costs	820.83	433.51	2.68**	20.00	395.70	475.33	-0.64	-5.44
Total mental health costs	663.40	426.37	2.37*	17.58	430.83	406.26	0.25	2.15
Total Medical costs	1424.00	998.34	2.42*	17.92	934.96	1016.91	-0.50	-4.30
Total drug costs	153.70	99.74	1.58	12.02	104.74	115.20	-0.46	-3.92
Specialist visits (day episodes)	0.04	0.01	1.69	12.70	0.01	0.02	-0.54	-4.59
Psychotherapies	0.18	0.17	0.27	1.92	0.18	0.16	0.31	2.69
Emergency room visits (day episodes)	0.49	0.29	3.42**	25.37	0.37	0.35	0.22	1.86
Hospitalization (total inpatient days)	1.02	0.53	1.58	12.06	0.36	0.55	-1.33	-11.35

Comorbidities during the three months prior period								
Adjustment reaction	0.02	0.02	0.33	2.38	0.03	0.02	0.28	2.39
Alcoholic psychoses	0.05	0.03	0.76	5.57	0.04	0.04	0.43	3.71
Asthma	0.03	0.02	1.05	7.76	0.03	0.02	0.28	2.39
Bipolar disorders	0.27	0.34	-2.1*	-15.33	0.30	0.27	0.76	6.49
Cardiovascular disease	0.08	0.10	-0.97	-7.01	0.06	0.07	-0.52	-4.47
Chronic pulmonary diseases	0.06	0.04	1.35	9.93	0.05	0.05	0.19	1.63
Connective tissue	0.01	0.00	0.27	2.00	0.00	0.01	-0.58	-4.94
Depressive disorder, not elsewhere specified	0.09	0.04	3.1**	23.14	0.04	0.04	0.00	0.00
Diabetes	0.03	0.05	-0.90	-6.44	0.04	0.04	-0.22	-1.90
Drug psychoses	0.08	0.03	2.43*	18.05	0.05	0.04	0.83	7.13
HIV or AIDS	0.03	0.02	1.27	9.40	0.03	0.02	0.84	7.19
Hypothyroidism	0.02	0.02	-0.10	-0.75	0.01	0.01	0.00	0.00
Liver diseases	0.00	0.01	-0.77	-5.47	0.00	0.01	-0.58	-4.94
Major depressive disorder	0.13	0.07	2.76**	20.46	0.10	0.08	0.73	6.27
Manic disorders	0.02	0.01	1.04	7.69	0.01	0.01	-0.38	-3.24
Mental retardation	0.01	0.02	-1.35	-9.53	0.01	0.00	1.00	8.57
Neurological disorders	0.00	0.00	-0.35	-2.53	0.00	0.00	-1.00	-8.54
Neurotic disorders	0.10	0.06	1.62	11.92	0.07	0.07	-0.17	-1.45
Nutritional disorders	0.04	0.03	0.71	5.17	0.02	0.03	-0.78	-6.70
Other alcohol & drug related psychoses	0.06	0.02	2.92**	22.02	0.02	0.03	-0.28	-2.39
Other mental disorders	0.03	0.03	0.03	0.24	0.02	0.03	-0.28	-2.39
Other non-organic psychoses	0.02	0.03	-1.75	-12.38	0.01	0.01	0.38	3.24
Peptic ulcer disease	0.01	0.00	0.77	5.80	0.00	0.00	0.00	0.00
Personality disorders	0.02	0.00	1.69	12.75	0.01	0.01	0.82	7.01
Transient organic psychotic conditions	0.00	0.00	-0.35	-2.53	0.00	0.00	0.00	0.00

Unspecific affective psychoses	0.13	0.07	2.76**	20.46	0.09	0.09	-0.15	-1.25
Prescriptions filled during the 3 months prior period								
Number of drug categories	0.73	0.57	2.02*	14.87	0.68	0.64	0.48	4.13
Antiretrovirals	0.01	0.01	0.08	0.58	0.01	0.01	0.00	0.00
Anti-glaucoma agents	0.00	0.00	0.19	1.41	0.00	0.00	0.00	0.00
Antihyperlipidemia	0.02	0.02	0.55	4.03	0.03	0.02	0.58	4.98
Antihypertensives	0.05	0.04	0.59	4.34	0.04	0.04	0.00	0.00
Antimigraine agents	0.01	0.00	1.10	8.22	0.01	0.01	0.00	0.00
Antineoplastics	0.02	0.02	0.28	2.01	0.03	0.02	0.58	4.98
Anti-Parkinson agents	0.00	0.01	-1.12	-7.87	0.00	0.01	-0.58	-4.94
Cardiac agents	0.05	0.06	-0.56	-4.13	0.05	0.06	-0.75	-6.41
Coagulation modifiers	0.07	0.04	1.51	11.14	0.06	0.04	0.95	8.14
Drugs for NID diabetes	0.02	0.02	0.28	2.01	0.02	0.02	0.30	2.60
Insulin	0.03	0.02	0.58	4.28	0.03	0.03	0.00	0.00
Narcotic analgesics	0.26	0.18	2.5*	18.30	0.24	0.22	0.41	3.46
Respiratory agents	0.10	0.06	1.89	13.91	0.09	0.08	0.46	3.90
Systemic steroids	0.05	0.04	0.68	5.00	0.05	0.04	0.42	3.56
Thyroid agents	0.03	0.03	0.09	0.64	0.03	0.03	0.00	0.00
Propensity & Logit								
Estimated probability of receiving an off-label prescription	0.51	0.61	-8.69**	-64.22	0.56	0.56	0.00	-0.03
Logit	0.03	0.48	-8.67**	-64.13	0.26	0.26	0.00	0.00

*: $0.01<P<0.05$

**: $P<0.01$

Table 4.9: Group comparisons before and after propensity score matching in the depression cohort.

	BEFORE PROPENSITY MATCHING				AFTER PROPENSITY MATCHING			
	On-label	Off-label			On-label	Off-label		
	N = 4,522	N = 2,400		Standardized	N = 1,996	N = 1,996		Standardized
	% prevalence	% prevalence	2-sample	difference	% prevalence	% prevalence	2-sample	difference
Demographics	or mean	or mean	t-statistic	in %	or mean	or mean	t-statistic	in %
Age	38.52	40.91	-6.48**	-16.41	41.04	40.80	0.55	1.61
White	0.49	0.45	3.24**	8.18	0.45	0.45	-0.09	-0.26
Male	0.15	0.23	-7.48**	-18.46	0.22	0.22	-0.18	-0.52
Chronic Illness and Disability Payment System (CDPS)								
CDPS predicted value	0.80	0.83	-1.38	-3.54	0.83	0.82	0.48	1.40
Number of CDPS categories	0.33	0.33	-0.34	-0.85	0.34	0.34	0.12	0.36
Number of CDPS diagnoses	1.22	1.24	-0.62	-1.58	1.23	1.22	0.22	0.65
Resource Utilization during the three months prior period								
Total costs	1894.64	2076.05	-1.32	-3.29	1995.14	2021.18	-0.17	-0.50
Total hospitalization costs	920.57	930.48	-0.08	-0.19	899.22	918.32	-0.14	-0.40
Total mental health costs	365.69	491.53	-2.61**	-6.78	451.73	457.55	-0.10	-0.30
Total Medical costs	1682.92	1854.82	-1.26	-3.15	1774.02	1800.09	-0.17	-0.51
Total drug costs	211.72	221.23	-0.85	-2.16	221.12	221.08	0.00	0.01
Specialist visits (day episodes)	0.05	0.08	-2.56*	-6.71	0.07	0.07	-0.12	-0.34
Psychotherapies	0.10	0.15	-3.36**	-8.86	0.14	0.14	0.13	0.38
Emergency room visits (day episodes)	0.46	0.44	0.75	1.89	0.44	0.43	0.18	0.53
Hospitalization (total inpatient days)	0.85	0.99	-1.03	-2.65	0.89	0.94	-0.36	-1.05

Comorbidities during the three months prior period								
Acute reaction to stress	0.00	0.00	-0.54	-1.39	0.00	0.00	-0.33	-0.98
Adjustment reaction	0.02	0.02	0.20	0.52	0.02	0.02	0.19	0.56
Alcoholic psychoses	0.03	0.03	-0.62	-1.57	0.04	0.03	0.65	1.91
Alzheimer's disease	0.00	0.00	-1.02	-2.68	0.00	0.00	0.33	0.98
Asthma	0.04	0.03	1.94	4.81	0.03	0.03	0.66	1.93
Cancer	0.01	0.02	-1.84	-4.78	0.02	0.01	0.48	1.40
Cardiovascular disease	0.16	0.15	1.37	3.47	0.16	0.15	0.69	2.03
Chronic pulmonary diseases	0.09	0.08	1.62	4.05	0.08	0.08	0.38	1.13
Coagulation	0.01	0.01	-0.18	-0.46	0.01	0.01	0.00	0.00
Connective tissue	0.02	0.01	1.83	4.48	0.01	0.01	-0.29	-0.85
Depressive disorder, not elsewhere specified	0.15	0.11	5.09**	12.58	0.10	0.11	-0.19	-0.56
Diabetes	0.08	0.08	-0.52	-1.32	0.08	0.08	0.70	2.05
Drug psychoses	0.03	0.04	-2.13*	-5.49	0.03	0.04	-0.71	-2.07
Epilepsy	0.01	0.00	2.13*	5.03	0.00	0.00	0.00	0.00
HIV or AIDS	0.02	0.02	-0.72	-1.83	0.02	0.02	0.60	1.76
Hypothyroidism	0.02	0.02	0.58	1.46	0.02	0.02	-0.11	-0.33
Liver diseases	0.00	0.01	-1.00	-2.61	0.00	0.01	-0.66	-1.93
Major depressive disorder	0.20	0.30	-8.71**	-22.44	0.29	0.29	0.06	0.19
Mental retardation	0.01	0.01	-1.46	-3.77	0.01	0.01	0.26	0.76
Neurological disorders	0.00	0.01	-0.59	-1.52	0.01	0.00	0.90	2.63
Neurotic disorders	0.14	0.09	6.36**	15.59	0.08	0.09	-1.10	-3.24
Nutritional disorders	0.05	0.05	-0.67	-1.70	0.05	0.05	-0.20	-0.58
Other alcohol & drug related psychoses	0.03	0.03	0.57	1.43	0.03	0.03	0.59	1.73
Other mental disorders	0.02	0.02	0.71	1.77	0.02	0.02	0.65	1.90
Other non-organic psychoses	0.00	0.02	-6.43**	-18.11	0.00	0.00	0.00	0.00
Other organic psychotic	0.00	0.01	-2.27*	-6.16	0.00	0.01	-0.66	-1.93

conditions, chronic								
Paralysis	0.01	0.01	-1.12	-2.89	0.01	0.01	-0.14	-0.42
Paranoid/Delusion disorders	0.00	0.00	-1.95	-5.49	0.00	0.00	0.00	0.00
Peptic ulcer disease	0.01	0.00	2.75**	6.53	0.01	0.00	0.96	2.83
Personality disorders	0.00	0.01	-2.4*	-6.42	0.01	0.01	-0.35	-1.04
Psychosis with origin specific to childhood	0.00	0.00	-0.41	-1.09	0.00	0.00	0.00	0.00
Renal failure	0.01	0.01	-1.11	-2.86	0.01	0.01	-0.32	-0.93
Transient organic psychotic conditions	0.00	0.01	-1.83	-4.89	0.01	0.00	0.43	1.25
Prescriptions filled during the three months prior period								
Number of drug categories	1.02	1.07	-1.30	-3.31	1.06	1.06	-0.04	-0.13
Antiretrovirals	0.01	0.02	-1.67	-4.33	0.02	0.02	0.47	1.38
Anti-glaucoma agents	0.01	0.01	-1.21	-3.13	0.01	0.01	0.30	0.87
Antigout agents	0.01	0.01	-0.25	-0.65	0.01	0.01	-0.39	-1.15
Antihyperlipidemia	0.04	0.04	0.32	0.81	0.04	0.04	0.46	1.36
Antihypertensives	0.09	0.10	-1.74	-4.43	0.10	0.10	-0.25	-0.72
Antimigraine agents	0.01	0.01	1.21	2.99	0.01	0.01	0.00	0.00
Antineoplastics	0.03	0.02	2.52*	6.17	0.02	0.02	-1.01	-2.96
Anti-Parkinson agents	0.01	0.01	-2.67**	-7.10	0.01	0.01	-0.58	-1.70
Cardiac agents	0.12	0.12	-0.62	-1.58	0.12	0.12	0.14	0.40
Coagulation modifiers	0.09	0.11	-2.2*	-5.48	0.11	0.11	-0.33	-0.98
Dementia agents	0.00	0.00	-0.61	-1.58	0.00	0.00	0.30	0.89
Drug for rheumatologic conditions	0.00	0.00	0.43	1.07	0.00	0.00	-0.26	-0.76
Drugs for bone diseases	0.01	0.01	-0.69	-1.76	0.01	0.01	0.00	0.00
Drugs for NID diabetes	0.05	0.06	-1.48	-3.77	0.05	0.05	-0.39	-1.15
Insulin	0.04	0.04	-1.34	-3.44	0.05	0.04	0.50	1.47
Immunosuppressive agents	0.00	0.00	2.06*	4.75	0.00	0.00	0.00	0.00

Narcotic analgesics	0.31	0.32	-0.54	-1.36	0.32	0.32	0.03	0.09
Respiratory agents	0.11	0.10	1.01	2.56	0.11	0.10	0.19	0.56
Systemic steroids	0.07	0.06	0.72	1.83	0.06	0.06	-0.31	-0.90
Thyroid agents	0.03	0.03	0.22	0.57	0.03	0.03	0.50	1.46
Propensity & Logit								
Estimated probability of receiving an off-label prescription	0.33	0.38	-20.39**	-49.77	0.37	0.37	0.00	0.01
Logit	-0.76	-0.49	-20.4**	-49.95	-0.55	-0.55	0.00	0.01

*: $0.01<P<0.05$

**: $P<0.01$

Table 4.10: Group comparisons before and after propensity score matching in the anxiety cohort.

	BEFORE PROPENSITY MATCHING				AFTER PROPENSITY MATCHING			
	On-label	Off-label			On-label	Off-label		
	N = 1,265	N = 1,252		Standardized	N = 856	N = 856		Standardized
	% prevalence	% prevalence	2-sample	difference	% prevalence	% prevalence	2-sample	difference
Demographics	or mean	or mean	t-statistic	in %**	or mean	or mean	t-statistic	in %**
Age	43.34	41.37	2.93**	12.80	42.81	42.70	0.16	0.75
White	0.52	0.55	-1.47	-6.46	0.52	0.52	0	0.00
Male	0.20	0.20	-0.02	-0.07	0.20	0.19	0.37	1.78
Chronic Illness and Disability Payment System (CDPS)								
CDPS predicted value	0.70	0.66	1.23	5.47	0.62	0.64	-0.64	-3.09
Number of CDPS categories	0.48	0.48	-0.43	-1.90	0.49	0.48	0.29	1.40
Number of CDPS diagnoses	0.93	0.89	0.67	2.96	0.85	0.89	-0.72	-3.50
Resource Utilization during the 3 months prior period								
Total costs	1842.14	1786.54	0.2	0.86	1545.32	1619.44	-0.28	-1.37
Total hospitalization costs	886.95	850.43	0.14	0.60	661.51	703.97	-0.17	-0.84
Total mental health costs	159.30	163.72	-0.12	-0.53	147.12	134.71	0.33	1.61
Total Medical costs	1604.93	1539.89	0.23	1.01	1321.77	1389.72	-0.26	-1.27
Total drug costs	237.21	246.65	-0.61	-2.67	223.55	229.72	-0.4	-1.94
Specialist visits (day episodes)	0.04	0.06	-1.56	-6.58	0.04	0.03	0.98	4.74
Psychotherapies	0.03	0.04	-0.35	-1.52	0.03	0.04	-0.3	-1.43
Emergency room visits (day episodes)	0.54	0.48	1.29	5.74	0.48	0.47	0.07	0.34
Hospitalization (total inpatient days)	0.62	0.54	0.48	2.12	0.40	0.49	-0.65	-3.16

Comorbidities during the three months prior period								
Acute reaction to stress	0.01	0.00	0.52	2.33	0.01	0.00	0.33	1.61
Adjustment reaction	0.02	0.01	0.91	4.06	0.02	0.01	0.2	0.97
Alzheimer's disease	0.00	0.00	0.79	3.55	0.00	0.00	0	0.00
Transient organic psychotic conditions	0.00	0.00	-0.42	-1.83	0.00	0.00	-0.82	-3.95
Alcoholic psychoses	0.02	0.02	0.35	1.51	0.02	0.02	-0.18	-0.85
Mental retardation	0.01	0.01	-1.1	-4.73	0.01	0.01	-0.54	-2.59
Other organic psychotic conditions, chronic	0.01	0.01	-1.07	-4.58	0.01	0.01	-0.58	-2.80
Other alcohol & drug related psychoses	0.03	0.03	0.53	2.36	0.03	0.02	0.47	2.29
Other mental disorders	0.02	0.01	1.13	5.02	0.02	0.02	0.37	1.78
Drug psychoses	0.01	0.02	-1.24	-5.34	0.01	0.01	0	0.00
Epilepsy	0.01	0.00	1.37	6.20	0.00	0.00	0	0.00
Neurological disorders	0.01	0.01	0.62	2.76	0.01	0.00	0.63	3.06
Other non-organic psychoses	0.28	0.29	-0.5	-2.20	0.28	0.29	-0.37	-1.81
Paralysis	0.01	0.01	-0.43	-1.87	0.01	0.01	0	0.00
Chronic pulmonary diseases	0.11	0.10	1	4.34	0.10	0.09	0.41	1.99
Cardiovascular disease	0.22	0.18	2.1*	9.27	0.20	0.20	0.36	1.75
Coagulation	0.00	0.01	-1.02	-4.34	0.00	0.00	0	0.00
HIV or AIDS	0.00	0.01	-1.27	-5.36	0.00	0.00	0.58	2.79
Hypothyroidism	0.02	0.02	-1.09	-4.72	0.02	0.02	-0.83	-4.02
Nutritional disorders	0.06	0.05	0.96	4.25	0.05	0.04	0.47	2.27
Peptic ulcer disease	0.01	0.01	-1.1	-4.73	0.01	0.01	0.3	1.46
Renal failure	0.01	0.01	0.17	0.76	0.01	0.01	-0.3	-1.46
Asthma	0.04	0.04	-0.19	-0.82	0.04	0.03	0.9	4.34
Cancer	0.01	0.02	-0.11	-0.50	0.01	0.01	-0.22	-1.06
Connective tissue	0.01	0.01	-0.8	-3.43	0.01	0.01	-0.26	-1.25

Diabetes	0.08	0.08	-0.74	-3.23	0.07	0.08	-1.02	-4.94
Liver diseases	0.00	0.00	1.22	5.63	0.00	0.00	1	4.83
Prescriptions filled during the 3 months prior period								
Drug categories	1.23	1.24	-0.25	-1.08	1.18	1.19	-0.22	-1.04
Anti-Parkinson agents	0.00	0.00	-0.24	-1.04	0.00	0.00	-0.38	-1.83
Antigout agents	0.01	0.01	-0.13	-0.56	0.01	0.00	0.63	3.06
Drugs for bone diseases	0.02	0.01	1.95	8.85	0.01	0.01	-1.07	-5.19
Antineoplastics	0.02	0.02	-0.27	-1.18	0.02	0.02	-0.36	-1.72
Cardiac agents	0.18	0.16	1.37	5.96	0.17	0.18	-0.38	-1.86
Coagulation modifiers	0.09	0.11	-1.61	-7.01	0.09	0.08	0.79	3.82
Dementia agents	0.00	0.00	-0.3	-1.29	0.00	0.00	-0.58	-2.79
Drugs for NID diabetes	0.05	0.06	-1.03	-4.47	0.05	0.06	-0.75	-3.64
Anti-glaucoma agents	0.01	0.01	0.36	1.60	0.01	0.01	0.23	1.11
Antihyperlipidemia	0.06	0.06	-0.37	-1.65	0.06	0.06	0	0.00
Antihypertensives	0.11	0.11	0.09	0.40	0.10	0.11	-0.54	-2.63
Insulin	0.03	0.05	-2.17*	-9.30	0.03	0.04	-0.96	-4.64
Antimigraine agents	0.01	0.01	-0.51	-2.22	0.01	0.01	0.26	1.25
Narcotic analgesics	0.38	0.37	0.35	1.52	0.37	0.36	0.45	2.18
Respiratory agents	0.14	0.14	0.33	1.44	0.13	0.14	-0.07	-0.34
Drug for rheumatologic conditions	0.00	0.00	-0.42	-1.83	0.00	0.00	-0.45	-2.16
Systemic steroids	0.08	0.08	0.39	1.69	0.08	0.07	0.65	3.14
Thyroid agents	0.04	0.04	-0.17	-0.76	0.04	0.05	-0.6	-2.89
Propensity & Logit								
Estimated probability of receiving an off-label prescription	0.57	0.60	-7.84**	-34.24	0.58	0.58	0.01	0.03
Logit	0.28	0.40	-7.81**	-34.44	0.32	0.32	0	0.01

*: 0.01<*P*<0.05; **: *P*<0.01

Table 4.11: Antidepressants, anticonvulsants and antipsychotics use pattern for the off-label and the on-label users in the schizophrenia cohort during the observation period.

	Antidepressants			Anticonvulsants			Antipsychotics	
	Drug name	Num of recipients		Drug name	Num of recipients		Drug name	Num of recipients
Off-label group	Trazodone	253		divalproex sodium	343		olanzapine	513
	Sertraline	241		lorazepam	153		risperidone	473
	Fluoxetine	189		gabapentin	99		haloperidol	297
	Paroxetine	182		Valproic acid	84		quetiapine	173
	Bupropion	89		clonazepam	68		lithium	124
	Mirtazapine	84		carbamazepine	59		fluphenazine	118
	Amitriptyline	83		phenytoin	51		perphenazine	40
	Venlafaxine	68		diazepam	49		thiothixene	38
	Citalopram	62		topiramate	27		trifluoperazine	36
	Nefazodone	55		phenobarbital	16		thioridazine	30
On-label group	Sertraline	110		divalproex sodium	68		olanzapine	450
	Trazodone	86		phenytoin	40		risperidone	431
	Paroxetine	74		lorazepam	29		haloperidol	354
	Fluoxetine	73		Valproic acid	21		fluphenazine	179
	Venlafaxine	41		diazepam	12		quetiapine	117
	Bupropion	39		phenobarbital	12		thioridazine	53
	Mirtazapine	37		carbamazepine	9		trifluoperazine	36
	Citalopram	29		clonazepam	6		chlorpromazine	32
	Amitriptyline	24		gabapentin	4		thiothixene	32
	Nefazodone	22		topiramate	3		lithium	22

Table 4.12: Antidepressants, anticonvulsants and antipsychotics use pattern for the off-label and the on-label users in the bipolar cohort during the observation period.

	Antidepressants			Anticonvulsants			Antipsychotics	
	Drug name	Num of recipients		Drug name	Num of recipients		Drug name	Num of recipients
Off-label group	Trazodone	60		divalproex sodium	90		risperidone	108
	Sertraline	53		gabapentin	53		olanzapine	72
	Paroxetine	41		clonazepam	34		lithium	67
	Fluoxetine	40		lorazepam	34		quetiapine	30
	Bupropion	29		carbamazepine	26		haloperidol	21
	Mirtazapine	28		diazepam	22		thioridazine	14
	Venlafaxine	24		topiramate	22		fluphenazine	10
	Citalopram	22		valproic acid	12		perphenazine	8
	Nefazodone	20		lamotrigine	9		ziprasidone	8
	Amitriptyline	18		oxcarbazepine	4		thiothixene	7
On-label group	Sertraline	66		divalproex sodium	115		olanzapine	75
	Trazodone	61		lorazepam	10		lithium	66
	Fluoxetine	54		diazepam	8		chlorpromazine	3
	Paroxetine	49		valproic acid	8		prochlorperazine	3
	Bupropion	42		clonazepam	3			
	Venlafaxine	30		lamotrigine	1			
	Citalopram	23		phenobarbital	1			
	Mirtazapine	21						
	Nefazodone	16						
	Amitriptyline	14						

Table 4.13: Antidepressants, anticonvulsants and antipsychotics use pattern for the off-label and the on-label users in the depression cohort during the observation period.

	Antidepressants			Anticonvulsants			Antipsychotics	
	Drug name	Num of recipients		Drug name	Num of recipients		Drug name	Num of recipients
Off-label group	Sertraline	433		gabapentin	374		risperidone	543
	Fluoxetine	372		lorazepam	324		olanzapine	405
	Paroxetine	361		diazepam	229		quetiapine	145
	Trazodone	356		divalproex sodium	195		haloperidol	110
	Venlafaxine	234		clonazepam	155		prochlorperazine	91
	Amitriptyline	232		carbamazepine	64		thioridazine	67
	Mirtazapine	222		phenytoin	59		lithium	47
	Citalopram	218		topiramate	47		perphenazine	37
	Bupropion	203		clorazepate	43		chlorpromazine	34
	Nefazodone	137		valproic acid	31		trifluoperazine	28
On-label group	Sertraline	595		diazepam	62		prochlorperazine	26
	Paroxetine	467		lorazepam	61		chlorpromazine	2
	Fluoxetine	454		phenytoin	46		perphenazine	1
	Trazodone	368		divalproex sodium	40		trifluoperazine	1
	Amitriptyline	283		carbamazepine	24			
	Venlafaxine	224		phenobarbital	13			
	Bupropion	218		clonazepam	11			
	Mirtazapine	195		clorazepate	10			
	Citalopram	190		gabapentin	6			
	Nefazodone	159		acetazolamide	4			

Table 4.14: Antidepressants, anticonvulsants and antipsychotics use pattern for the off-label and the on-label users in the anxiety cohort during the observation period.

	Antidepressants			Anticonvulsants			Antipsychotics	
	Drugname	Num of recipients		Drugname	Num of recipients		Drugname	Num of recipients
Off-label group	paroxetine	223		gabapentin	115		risperidone	47
	sertraline	183		lorazepam	93		olanzapine	28
	amitriptyline	181		diazepam	77		quetiapine	15
	trazodone	125		clonazepam	42		prochlorperazine	11
	fluoxetine	107		divalproex sodium	28		thioridazine	8
	bupropion	103		phenytoin	23		haloperidol	7
	citalopram	80		topiramate	12		lithium	6
	venlafaxine	77		carbamazepine	10		chlorpromazine	4
	nefazodone	74		clorazepate	10		perphenazine	3
	mirtazapine	61		phenobarbital	8		trifluoperazine	3
On-label group	paroxetine	96		lorazepam	180		prochlorperazine	28
	sertraline	54		diazepam	113			
	doxepin	26		phenytoin	34			
	fluoxetine	18		clorazepate	25			
	amitriptyline	10		phenobarbital	17			
	trazodone	8		clonazepam	14			
	venlafaxine	8		divalproex sodium	9			
	bupropion	7		carbamazepine	8			
	nefazodone	6		gabapentin	2			
	mirtazapine	2		valproic acid	1			

Table 4.15: Comparing average one year health expenditures between the off-label and the on-label groups after propensity score matching using paired t test.

	Mean expenditure ($)	Mean expenditure ($)	Net expenditure ($)	Paired t-statistic	P value
	off-label	on-label	(off-label vs. on-label)	(off-label vs. on-label)	
Schizophrenia cohort (n=1,265)					
Total medical & prescription costs	7,765.03	7,204.95	560.08	1.42	0.1569
Total prescription costs	2,650.64	1,757.76	892.88	10.16	<.0001**
Total inpatient costs	1,325.81	1,836.76	-510.95	-2.14	0.0323*
Total outpatient costs	2,727.03	2,814.52	-87.49	-0.54	0.5907
Total long-term care costs	1,061.55	795.92	265.63	1.32	0.1887
Bipolar cohort (n=274)					
Total medical & prescription costs	6,789.15	6,350.24	438.91	0.61	0.5424
Total prescription costs	2,392.31	1,837.16	555.15	3.05	0.0025**
Total inpatient costs	1,235.49	1,811.28	-575.79	-1.38	0.1673
Total outpatient costs	2,698.84	2,452.15	246.69	0.64	0.5236
Total long-term care costs	462.51	249.65	212.86	0.83	0.4057
Depression cohort (n=1,996)					
Total medical & prescription costs	9,060.54	6,851.18	2,209.36	6.27	<.0001**
Total prescription costs	2,546.58	1,762.71	783.87	9.45	<.0001**
Total inpatient costs	2,447.02	1,819.08	627.94	2.72	0.0065**
Total outpatient costs	3,262.09	2,753.31	508.78	3.68	0.0002**
Total long-term care costs	804.86	516.07	288.78	2.37	0.0181*
Anxiety cohort (n=856)					
Total medical & prescription costs	6,815.45	5,258.13	1,557.32	3.99	<.0001**
Total prescription costs	2,051.23	1,410.51	640.72	7.36	<.0001**
Total inpatient costs	1,696.57	1,214.06	482.51	1.93	0.0544
Total outpatient costs	2,836.21	2,481.60	354.61	1.72	0.0857
Total long-term care costs	231.43	151.97	79.46	0.78	0.4358

*: 0.01<*P*<0.05; **: *P*<0.01

Table 4.16: Comparing the median one year health expenditures between the off-label and the on-label groups after propensity score matching using Wilcoxon signed rank test.

	Median expenditure ($)	Median expenditure ($)	Median net expenditure ($)	Wilcoxon signed rank test statistic	P value
	off-label	on-label	(off-label minus on-label)	(off-label minus on-label)	
Schizophrenia cohort (n=1,265)					
Total medical & prescription costs	4825.87	3892.43	629.36	47032.5	0.0003**
Total prescription costs	1912.30	1166.26	567.14	134718.5	<.0001**
Total inpatient costs	0.00	0.00	0.00	-8802.5	0.0014**
Total outpatient costs	1522.00	1449.00	32.00	5714	0.66
Total long term care costs	0.00	0.00	0.00	407	0.1882
Bipolar cohort (n=274)					
Total medical & prescription costs	4275.71	4174.39	-273.34	59.5	0.964
Total prescription costs	1648.71	1170.29	274.33	3872.5	0.003**
Total inpatient costs	0.00	0.00	0.00	-885	0.0141*
Total outpatient costs	1521.50	1555.00	-42.00	-349	0.7909
Total long term care costs	0.00	0.00	0.00	8.5	0.3594
Depression cohort (n=1,996)					
Total medical & prescription costs	5020.82	3674.18	1002.50	203469	<.0001**
Total prescription costs	1804.86	1131.31	435.75	291017	<.0001**
Total inpatient costs	0.00	0.00	0.00	12937	0.0206**
Total outpatient costs	1797.50	1131.31	194.50	121127	<.0001**
Total long term care costs	0.00	0.00	0.00	849.5	0.0219**
Anxiety cohort (n=856)					
Total medical & prescription costs	4105.35	2709.39	878.60	42373	<.0001**
Total prescription costs	1467.23	863.67	351.18	53095	<.0001**
Total inpatient costs	0.00	0.00	0.00	2526.5	0.0209*
Total outpatient costs	1672.00	1151.00	298.00	32284	<.0001**
Total long term care costs	0.00	0.00	0.00	24	0.3884

*: 0.01<*P*<0.05; **: *P*<0.01

Table 4.17: Comparing the one year hospitalizations and ER visits between the off-label and the on-label groups after propensity score matching.

	Num of patients (% n)	Num of patients (% n)	Chi square statistic	P value
	Off-label	On-label		
Schizophrenia cohort (n=1,265)				
ER visits (yes/no)	451 (35.65%)	490 (38.74%)	2.57	0.1087
Hospitalizations (yes/no)	216 (17.08%)	280 (22.13%)	10.27	0.0014**
Bipolar cohort (n=274)				
ER visits (yes/no)	117 (42.70%)	128 (46.72%)	0.89	0.3446
Hospitalizations (yes/no)	55 (20.07%)	74 (27.01%)	3.66	0.0557
Depression cohort (n=1,996)				
ER visits (yes/no)	944 (47.29%)	999 (50.05%)	3.03	0.0816
Hospitalizations (yes/no)	417 (20.89%)	385 (19.29%)	1.60	0.2062
Anxiety cohort (n=856)				
ER visits (yes/no)	465 (54.32%)	442 (51.64%)	1.24	0.2654
Hospitalizations (yes/no)	150 (17.52%)	120 (14.02%)	3.96	0.0467*

*: $0.01<P<0.05$

**: $P<0.01$

Table 4.18: The top ten primary ICD9 diagnosis codes in the inpatient claims for the off-label and the on-label users within each disease specific cohort.

	OFF-LABEL GROUP			ON-LABEL GROUP		
	ICD9 Diagnosis	**Description**	**Num of recipients**	**ICD9 Diagnosis**	**Description**	**Num of recipients**
Schizophrenia cohort	295.xx	Schizophrenia	126	295.xx	Schizophrenia	158
	786.xx	Respiratory symptoms	34	296.xx	Affective psychoses	52
	250.xx	Diabetes	24	786.xx	Respiratory symptoms	50
	296.xx	Affective psychoses	24	780.xx	General symptoms	38
	305.xx	Alcohol or drug abuse	24	250.xx	Diabetes	34
	276.xx	Disorders of fluid, electrolyte, and acid-base balance	20	298.xx	Other nonorganic psychoses	32
	401.xx	Essential hypertension	19	305.xx	Alcohol or drug abuse	29
	298.xx	Other nonorganic psychoses	16	276.xx	Disorders of fluid, electrolyte, and acid-base balance	28
	780.xx	General symptoms	16	311.xx	Depressive disorder not elsewhere classified	26
	518.xx	Other diseases of lung	14	401.xx	Essential hypertension	26

Bipolar disorder cohort	296.xx	Affective psychoses	25	296.xx	Affective psychoses	44
	V27.xx	Outcome of delivery	14	786.xx	Respiratory symptoms	13
	786.xx	Respiratory symptoms	9	300.xx	Non psychotic disorders (including anxiety)	10
	650.xx	Delivery in a completely normal case	8	648.xx	Other current conditions in the mother classifiable elsewhere, but complicating pregnancy, childbirth, or the puerperium Requires fifth digit	9
	789.xx	Abdomen/pelvis symptoms	7	789.xx	Abdomen/pelvis symptoms	9
	276.xx	Disorders of fluid, electrolyte, and acid-base balance	6	V27.xx	Outcome of delivery	9
	V22.xx	Normal pregnancy	6	311.xx	Depressive disorder not elsewhere classified	7
	305.xx	Alcohol or drug abuse	5	650.xx	Delivery in a completely normal case	7
	401.xx	Essential hypertension	4	276.xx	Disorders of fluid, electrolyte, and acid-base balance	6
	278.xx	0besity and other hyperalimentation	4	305.xx	Alcohol or drug abuse	6
Depression cohort	296.xx	Affective psychoses	90	786.xx	Respiratory symtoms	86
	786.xx	Respiratory symtoms	84	296.xx	Affective psychoses	73

	789.xx	Abdomen/pelvis symptoms	70	789.xx	Abdomen/pelvis symptoms	55
	276.xx	Disorders of fluid, electrolyte, and acid-base balance	55	250.xx	Diabetes	51
	311.xx	Depressive disorder not elsewhere classified	51	276.xx	Disorders of fluid, electrolyte, and acid-base balance	44
	250.xx	Diabetes	50	780.xx	General symptoms	38
	780.xx	General symptoms	42	311.xx	Depressive disorder not elsewhere classified	34
	401.xx	Essential hypertension	35	305.xx	Alcohol or drug abuse	33
	486.xx	Pneumonia, organism unspecified	33	401.xx	Essential hypertension	33
	518.xx	Other diseases of lung	33	300.xx	Non psychotic disorders (including anxiety)	32
Anxiety cohort	786.xx	Respiratory symptoms	35	786.xx	Respiratory symptoms	34
	780.xx	General symptoms	22	300.xx	Non psychotic disorders (including anxiety)	23
	300.xx	Non psychotic disorders (including anxiety)	20	401.xx	Essential hypertension	17
	276.xx	Disorders of fluid, electrolyte, and acid-base balance	18	V27.xx	Outcome of delivery	17
	401.xx	Essential hypertension	18	276.xx	Disorders of fluid, electrolyte, and acid-base balance	15

	650.xx	Delivery in a completely normal case	18	250.xx	Diabetes	13
	428.xx	Heart failure	17	650.xx	Delivery in a completely normal case	13
	V27.xx	Outcome of delivery	17	780.xx	General symptoms	12
	250.xx	Diabetes	16	789.xx	Abdomen/pelvis symptoms	11
	305.xx	Alcohol or drug abuse	15	427.xx	Cardiac dysrhythmias	10

Table 4.19: Independent effects of using anticonvulsants and antipsychotics on average one year health expenditure for depression patients using paired t test.

	Mean expenditure ($)	Mean expenditure ($)	Net expenditure ($)	Paired t-statistic	P value
	off-label	on-label	(off-label vs. on-label)	(off-label vs. on-label)	
Using off-label Anticonvulsant (n=874)					
Total medical & prescription costs	11,099.53	8,102.65	2,996.90	4.82	<.0001**
Total prescription costs	2,703.97	2,175.54	528.43	4.13	<.0001**
Total inpatient costs	3,661.49	2,504.45	1,157.00	2.56	0.0108*
Total outpatient costs	3,731.71	3,035.40	696.31	3.59	0.0003**
Total long term care costs	1,002.36	387.26	615.11	3.07	0.0022**
Using off-label antipsychotic (n=954)					
Total medical & prescription costs	7,787.98	6,012.98	1,775.00	3.85	0.0004**
Total prescription costs	2,392.41	1,536.56	855.85	7.09	<.0001**
Total inpatient costs	1,648.33	1,571.13	77.20	0.27	0.7872
Total outpatient costs	2,979.49	2,448.17	531.33	2.62	0.0088**
Total long term care costs	767.74	457.12	310.62	1.65	0.0983

*: 0.01<*P*<0.05

**: *P*<0.01

Table 4.20: Independent effects of using anticonvulsants and antipsychotics on the median of one year health expenditure for depression patients using Wilcoxon signed rank test.

	Median expenditure ($)	Median expenditure ($)	Median net expenditure ($)	Wilcoxon signed rank test statistic	P value
	off-label	on-label	(off-label vs. on-label)	(off-label vs. on-label)	
Using off-label Anticonvulsant (n=874)					
Total medical & prescription costs	5,848.30	4,429.00	1,497.25	44230.5	<.0001**
Total prescription costs	1,918.54	1,343.60	322.61	41430	<.0001**
Total inpatient costs	0.00	0.00	0.00	5480	0.0062**
Total outpatient costs	2,251.50	1,740.50	323.00	26874.5	0.0003**
Total long term care costs	0.00	0.00	0.00	331	0.0058**
Using off-label antipsychotic (n=954)					
Total medical & prescription costs	4,524.73	3,144.53	939.20	49274.5	<0.0001**
Total prescription costs	1,640.47	919.25	547.86	81869	<0.0001**
Total inpatient costs	0.00	0.00	0.00	152	0.9209
Total outpatient costs	1,486.00	1,364.50	137.50	21080.5	0.0132 *
Total long term care costs	0.00	0.00	0.00	178.50	0.1149

*: 0.01<*P*<0.05

**: *P*<0.01

Table 4.21: Independent effects of using anticonvulsants and antipsychotics on one year hospitalizations and ER visits for depression patients.

	Num of patients (% n)	Num of patients (% n)	Chi square statistic	P value
	Off-label	On-label		
Using off-label anticonvulsant (n=874)				
ER visits (yes/no)	463 (52.97%)	473 (54.12%)	0.89	0.3446
Hospitalizations (yes/no)	230 (26.32%)	190 (21.74%)	3.66	0.0557
Using off-label antipsychotic (n=954)				
ER visits (yes/no)	410 (42.98%)	448 (46.96%)	2.57	0.1087
Hospitalizations (yes/no)	168 (17.61%)	159 (16.67%)	10.27	0.0014**

*: $0.01<P<0.05$

**: $P<0.01$

Table 4.22: The top ten primary ICD9 diagnosis codes in the inpatient claims for the off-label anticonvulsant users and the on-label users within the depression cohort.

	OFF-LABEL GROUP			OFF-LABEL GROUP		
	ICD9 Diagnosis	**Description**	**Num of recipients**	**ICD9 Diagnosis**	**Description**	**Num of recipients**
Depression cohort (using off-label anticonvulsants)	786.xx	Respiratory symptoms	51	786.xx	Respiratory symptoms	46
	296.xx	Affective psychoses	47	296.xx	Affective psychoses	36
	789.xx	Abdomen/pelvis symptoms	39	250.xx	Diabetes	34
	276.xx	Disorders of fluid, electrolyte, and acid-base balance	34	789.xx	Abdomen/pelvis symptoms	31
	305.xx	Alcohol or drug abuse	26	276.xx	Disorders of fluid, electrolyte, and acid-base balance	26
	311.xx	Depressive disorder not elsewhere classified	26	780.xx	General symptoms	23
	780.xx	General symptoms	25	300.xx	Non psychotic disorders (including anxiety)	20
	250.xx	Diabetes	23	518.xx	Other diseases of lung	20
	486.xx	Pneumonia, organism unspecified	23	486.xx	Pneumonia, organism unspecified	19
	518.xx	Other diseases of lung	22	787.xx	Symptoms involving digestive system	18

Table 4.23: Sensitivity analysis on per capita one year health expenditures.

	Matched pairs	Mean expenditure ($)	Mean expenditure ($)	Net expenditure ($)	Paired t-statistic	P value
		off-label	on-label	(off-label vs. on-label)	(off-label vs. on-label)	
Schizophrenia cohort						
Total costs	1,265	7,765.03	7,204.95	560.08	1.42	0.1569
Mental health related costs	1,265	2,839.35	3,150.37	-311.02	-1.41	0.1576
Total costs using 180 days drug free period	659	7,495.82	6,922.74	573.08	0.98	0.3275
Bipolar cohort						
Total costs	274	6,789.15	6,350.24	438.91	0.61	0.5424
Mental health related costs	274	1,427.17	1,838.53	-411.36	-1.66	0.0974
Total costs using 180 days drug free period	193	5,392.33	4,391.53	1,000.80	1.52	0.1313
Depression cohort						
Total costs	1,996	9,060.54	6,851.18	2,209.36	6.27	<.0001**
Mental health related costs	1,996	1,526.19	1,073.09	453.10	4.72	<.0001**
Total costs using 180 days drug free period	1,178	8,812.92	6,561.22	2,251.7	4.77	<.0001**
Anxiety cohort						
Total costs	856	6,815.45	5,258.13	1,557.32	3.99	<.0001**
Mental health related costs	856	503.08	462.10	40.98	0.52	0.6025
Total costs using 180 days drug free period	568	6,442.30	5,146.20	1,296	2.43	0.0155*

*: 0.01<*P*<0.05, **: *P*<0.01

Table 4.24: Sensitivity analysis on one year hospitalizations and ER visits.

	Matched pairs (n)	Num of patients (% n)	Num of patients (% n)	Chi-square statistic	P value
		Off-label	On-label		
Schizophrenia cohort					
ER visits (yes/no)	1,265	451 (35.65%)	490 (38.74%)	2.57	0.1087
Mental health related ER visits (yes/no)	1,265	138 (10.91%)	199 (15.73%)	12.74	0.0004**
ER visits using 180 days drug free period	659	235 (35.66%)	239 (36.27%)	0.12	0.7315
Hospitalizations (yes/no)	1,265	216 (17.08%)	280 (22.13%)	10.27	0.0014**
Mental health related hospitalizations (yes/no)	1,265	192 (15.18%)	253 (20.00%)	10.15	0.0014**
Hospitalization using 180 days drug free period	659	108 (16.39%)	139 (21.09%)	4.79	0.0287*
Bipolar cohort					
ER visits (yes/no)	274	117 (42.70%)	128 (46.72%)	0.89	0.3446
Mental health related ER visits (yes/no)	274	20 (7.30%)	34 (12.41%)	4.03	0.0448*
ER visits using 180 days drug free period	193	57 (29.53%)	69 (35.75%)	1.70	0.1927
Hospitalizations (yes/no)	274	55 (20.07%)	74 (27.01%)	3.66	0.0557
Mental health related hospitalizations (yes/no)	274	32 (11.68%)	53 (19.34%)	6.14	0.0132*
Hospitalizations using 180 days drug free period	193	27 (13.99%)	37 (19.17%)	1.87	0.1711
Depression cohort					
ER visits (yes/no)	1,996	944 (47.29%)	999 (50.05%)	3.03	0.0816
Mental health related ER visits (yes/no)	1,996	142 (7.11%)	118 (5.91%)	2.37	0.1237
ER visits using 180 days drug free period	1,178	571 (48.47%)	555 (47.11%)	0.44	0.5093
Hospitalizations (yes/no)	1,996	417 (20.89%)	385 (19.29%)	1.60	0.2062
Mental health related hospitalizations (yes/no)	1,996	228 (11.42%)	203 (10.17%)	1.63	0.2023
Hospitalization using 180 days drug free period	1,178	262 (22.24%)	216 (18.34%)	5.55	0.0184*

Anxiety cohort					
ER visits (yes/no)	856	465 (54.32%)	442 (51.64%)	1.24	0.2654
Mental health related ER visits (yes/no)	856	62 (7.24%)	68 (7.94%)	0.30	0.5841
ER visits using 180 days drug free period	568	307 (54.05%)	297 (52.29%)	0.35	0.5521
Hospitalizations (yes/no)	856	150 (7.52%)	120 (14.02%)	3.96	0.0467*
Mental health related hospitalizations (yes/no)	856	39 (4.56%)	37 (4.32%)	0.06	0.8145
Hospitalization using 180 days drug free period	568	93 (16.37%)	77 (13.56%)	1.77	0.1833

*: $0.01<P<0.05$

**: $P<0.01$

Table 4.25: Rosenbaum bounds sensitivity analysis on per capita one year total expenditures for depression and anxiety cohort.

Depression cohort		Anxiety cohort	
Gamma*	upper bound significance level	Gamma*	upper bound significance level
1.00	-	1.00	-
1.05	0.00	1.05	0.00
1.10	0.00	1.10	0.00
1.15	0.00	1.15	0.00
1.20	0.00	1.20	0.00
1.25	0.00	1.25	0.00
1.30	0.00	1.30	0.01
1.35	0.01	1.35	0.02
1.40	0.06	1.40	0.04
1.45	0.20	1.45	0.11
1.50	0.45	1.50	0.21
1.55	0.70	1.55	0.35
1.60	0.88	1.60	0.50
1.65	0.96	1.65	0.65
1.70	0.99	1.70	0.77
1.75	1.00	1.75	0.86
1.80	1.00	1.80	0.93
1.85	1.00	1.85	0.96
1.90	1.00	1.90	0.98
1.95	1.00	1.95	0.99
2.00	1.00	2.00	1.00

*gamma - log odds of differential assignment due to unobserved factors

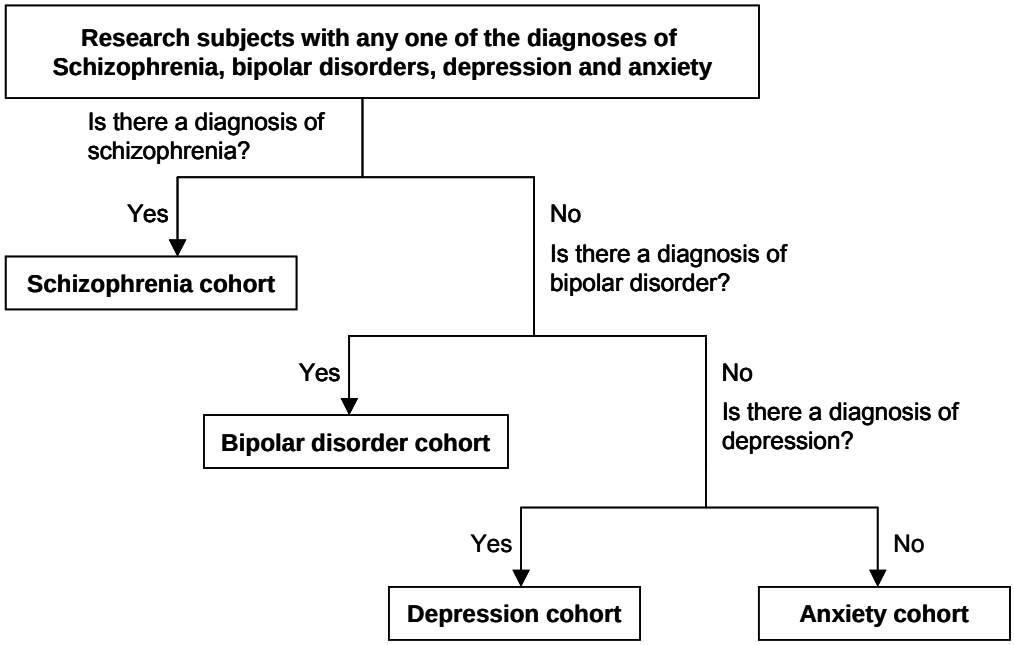

Figure 4.1: Disease-specific cohorts

CHAPTER 5

CONCLUSION

The off-label use of antidepressant (75.42%), anticonvulsant (80.12%) and antipsychotic (63.62%) medications are highly prevalent in Georgia Medicaid. Almost all gabapentin recipients received this drug for off-label purposes. Elderly, whites and people with renal failure were consistently associated with greater likelihoods of receiving AD, AC and AP off-label.

Among patients with schizophrenia, bipolar disorders, depression and anxiety, the off-label users experienced significantly higher prescription expenditures relative to the on-label users. The impacts of using off-label medications on the other outcome measures were heterogeneous in different mental disorders with the most striking results found in patients with depression. Using off-label medications, especially off-label anticonvulsants, alone or as adjunct to antidepressant therapy for depression patients is associated with significantly higher total health expenditures and hospital utilizations. While for patients with schizophrenia and bipolar disorders, the use of off-label antidepressants and anticonvulsants offers meaningful reductions in the hospitalization rate and inpatient costs.

The results derived from this study support the research hypotheses that patients who are prescribed antidepressant, anticonvulsant and antipsychotic medications off-label alone or as adjunct to labeled pharmacotherapy vs. patients who are prescribed only labeled pharmacotherapy for schizophrenia, bipolar disorder, depression or anxiety differ significantly in total health care cost, inpatient hospitalizations, and number of

emergency room visits. As off-label drug use continues to grow, more examinations of this type should be conducted to provide evidence for policy making and clinical management.