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Medication misadventures: the case of benzodiazepines

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MEDICATION MISADVENTURES:
THE CASE OF BENZODIAZEPINES

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Pharmacy
at the University of Kentucky

By
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Lexington, Kentucky
2015

ABSTRACT OF DISSERTATION

MEDICATION MISADVENTRUES:
THE CASE OF BENZODIAZEPINES

For patients afflicted with symptoms of anxiety and insomnia, benzodiazepines are generally a safe and effective short-term pharmacological treatment option. Although considered safer than other sedative-hypnotic medications, substantial concern exists regarding the addictive nature and abuse potential of benzodiazepines along with potentially inappropriate prescribing and utilization in clinically vulnerable populations. These medication misadventures can have a significant impact on public health. Examples of medication misadventures as they pertain to benzodiazepines include the prescribing and use in clinically vulnerable populations for whom they are contraindicated or their efficacy has not been evaluated, the development of tolerance or addiction, abuse of the medication, and the manifestation of negative health outcomes including cognitive impairment, withdrawal symptoms upon discontinuation, or the reoccurrence of a preexisting substance use disorder.

In order to better understand medication misadventures associated with benzodiazepines retrospective analyses using populations extracted from large health claims databases are employed. To understand how benzodiazepine use may lead to adverse events causing patient harm, the risk of exacerbations in benzodiazepine users diagnosed with chronic obstructive pulmonary disease was estimated. The inherent risk of benzodiazepine addiction and abuse was estimated in an HIV-infected population, a population with a high prevalence of substance use disorders. This risk was estimated by first determining whether HIV-infected individuals are more likely to have any benzodiazepine use compared to their uninfected counterparts, and secondly, by examining the association between HIV-infection and potentially problematic benzodiazepine use. Finally, in an effort to mitigate unexpected and undesirable consequences to public health associated with the prescription drug abuse epidemic in the US, states have implemented prescription drug monitoring programs (PDMPs) to track the prescribing and dispensing of controlled substance medications. The effect of these programs on benzodiazepine dispensing is evaluated on a state and national level.

Findings will provide healthcare professionals a better understanding regarding the risk of medication misadventures involving benzodiazepines when evaluating their appropriateness in patients with anxiety, depression, and insomnia. Additionally, policymakers will understand the implications of PDMPs on the dispensing of benzodiazepines as they become a more widely used tool to combat prescription drug abuse and diversion.

Keywords: benzodiazepines, Prescription drug abuse, Medication misadventures, substance abuse, prescription drug monitoring programs

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July 13, 2015

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THE CASE OF BENZODIAZEPINES

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To Scott, Mom, Dad, and Gan

I could not have accomplished this without your love, support, and encouragement

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BACKGROUND

In 1955, chemist Leo Sternbach, while working for the Hoffmann La Roche company, created the drug chlordiazepoxide, the first drug in the chemical class of benzodiazepines (informally "benzo"; abbreviated "BZD").[1] Benzodiazepines are indicated for use as anxiolytics, sedatives, hypnotics, anticonvulsants, and/or skeletal muscle relaxants.[2] At the time of their discovery, benzodiazepines were comparatively efficacious and appeared to be safer than similar drugs on the market including barbiturates and meprobamate.[3] Compared to these drugs, benzodiazepines had a lower abuse potential,[2,3] produced less toxicity in acute overdoses,[2] and reduced the risk of respiratory depression.[4] Additionally, barbiturates and meprobamate often produced unwanted effects including sedation at anxiolytic dosages, headaches, paradoxical excitement, confusion, and cognitive and psychomotor impairment.[3] Hoffmann La Roche patented Sternbach's discovery in 1959, and in 1960 the first benzodiazepine was marketed as Librium® (chlordiazepoxide).[1] Following the success of chlordiazepoxide Roche launched the popular drug Valium® (diazepam). Between 1969 and 1982, diazepam was the most prescribed drug in the United States with greater than 2.8 billion tablets sold in 1978[3] and was celebrated as "mother's little helper" after being referenced as such in a 1966 song by the Rolling Stones of the same name.[5]

The effects benzodiazepines produce result from action at the limbic, thalamic, and hypothalamic levels of the central nervous system (CNS). Benzodiazepines bind to receptors for the main inhibitory neurotransmitter in the CNS, the γ-aminobutyric acid (GABA), specifically the $GABA_A$ receptor located in the synapses of neurons.[6] Benzodiazepines bind to the $GABA_A$ receptor they do not activate it directly, instead they serve to potentiate the inhibitory effects of

GABA.[6] Effects are produced after the first dose and, following oral administration, occur within 15 to 45 minutes with a duration of action of approximately seven to eight hours.[2] In general, most benzodiazepines can be used interchangeably[6] and diazepam milligram equivalents (DMEs) are used to adjust for variations in the potency between individual drugs.[7] Differences in use between benzodiazepines reflect the manner in which the drugs have been studied and marketed by the manufacturer.[2] While there is no evidence to suggest that one benzodiazepine is more effective than any other at equivalent dosages, pharmacokinetic differences, such as the metabolic half-life, are important to consider when prescribing these drugs.[2] For example, benzodiazepines with a shorter half-life are often preferred in the management of insomnia in order to minimize daytime drowsiness[8] while longer half-life benzodiazepines are recommended for managing symptoms of anxiety to allow the drug to accumulate in the body.[9] Drug marketing information, therapeutic uses, and DME ratios of benzodiazepines currently marketed in the United States are summarized in Table 1.1.

To date, more than 1,000 benzodiazepines have been synthesized,[10] and remain the most frequently dispensed psychotropic drug class.[11] In 2012 benzodiazepines were the 10th most prescribed drug class in the United States with approximately 94 million prescriptions dispensed.[12] Alprazolam was the most commonly dispensed benzodiazepine with 49 million prescriptions dispensed in 2012 and ranked as the 13th most commonly dispensed medication in the United States.[13] Although considered safer than other sedative-hypnotics drugs, such as barbiturates and meprobamate,[2,3,6] the potential exists for benzodiazepines to be abused because of their addictive nature. Due to their abuse potential benzodiazepines are classified as a Schedule IV controlled substance (CS) in the classification system implemented by the Controlled Substance Act of 1970.

The abuse of benzodiazepines typically refers to recreational, non-medical use of the drug in order to achieve a "high" or euphoric effect[14] and frequently begins with a legitimate prescription that is intentionally misused.[15] Rarely are benzodiazepines the preferred or the sole drug of abuse; instead abuse commonly occurs in conjunction with other substances, mainly opioids and alcohol.[16] Clinical evidence shows that benzodiazepines and opioids, when used concurrently exert synergistic effects.[17-23] Further evidence explaining the reasons for the concomitant use of these drugs suggest benzodiazepines increase the rewarding and reinforcing effects of opioids.[24-27] Benzodiazepines with a rapid onset of action tend to be abused more frequently.[15,28,29] The exception is diazepam, while considered a long-acting benzodiazepine, it is highly lipophilic and crosses the blood-brain barrier rapidly making it very susceptible for abuse.[15,28]

Medication misadventures

Despite guidelines and recommendations regarding the appropriate prescribing of benzodiazepines, they are often misused in the clinical setting. This inappropriate use can result in medication misadventures, defined by the American Society of Health-System Pharmacists as an iatrogenic hazard or incident associated with medication therapy.[30] Medication misadventures are comprised of medication errors (any preventable event that may cause or lead to inappropriate medication use or patient harm), adverse drug events (an injury from a medicine or lack of intended medicine), and adverse drug reactions (any unexpected, unintended, undesired, or excessive response to a medicine).[30] The literature provides several examples of medication misadventures as they pertain to benzodiazepines.

For example, benzodiazepines are only recommended for short-term use, as their long-term anxiolytic efficacy (less than or equal to 4 months) has not been evaluated;[2] however, a

sizable proportion of the population are considered to be chronic users. Studies from several countries have estimated that between 0.5% and 5.8% of the adult population engages in long-term benzodiazepine use of one year or more.[31-33] Concerns have risen that long-term benzodiazepine use may lead to cognitive impairment. A significant effect on cognitive functions including sensory processing, psychomotor speed, attention/concentration, and motor control/performance has been observed following long-term benzodiazepine use.[34] Long-term use of benzodiazepines also carries the risk of increasing tolerance to the drug's effects and the development of dependence. Tolerance to the effects of benzodiazepines often leads to dosage escalation in order to maintain the same level of desired effects.[28,35] This tolerance and subsequent increase in dosage can lead to dependency although it is possible for benzodiazepine dependency to develop within normal therapeutic ranges.[34,35] Benzodiazepine dependency can manifest physiologically or psychologically and it is has been estimated that approximated 35% of all patients who have taken a benzodiazepine for at least four weeks develop some type of dependency upon the drug.[36]

Physiologic dependence on benzodiazepines leads to the risk of withdrawal symptoms if the drug is suddenly discontinued or the dosage drastically reduced.[28,34,37,38] Common withdrawal symptoms include rebound anxiety and insomnia, agitation, tension, dysphoria, sweating, irritability, impaired concentration, and weight loss.[2] More serious withdrawal symptoms have also been reported such as grand mal seizures,[39-41] nonconvulsive status epilepticus,[42] delirium,[39,40] and death.[40,43] The severity of benzodiazepine withdrawal and the inability to taper successfully can be attributed to factors associated with the benzodiazepine therapy along with individual patient characteristics[44-46] (Table 3) and to minimize the risk of withdrawal symptoms that benzodiazepines be discontinued gradually.[47]

Benzodiazepines are also commonly prescribed in clinically vulnerable populations for whom they are contraindicated or their efficacy has not been evaluated. Use of benzodiazepines in these clinically vulnerable populations is a controversial practice. Some experts recommend that benzodiazepines use be avoided in patients with a substance use disorder (SUD) history as they may exacerbate the preexisting SUD.[29,48] Additionally, patients with a SUD may be more likely to abuse prescribed benzodiazepines. According to a recent study in the Netherlands, patients with alcohol dependence are at an increased risk of developing benzodiazepine dependence.[49] Recent evidence also advises against the use of benzodiazepines among patients with very severe respiratory disease including chronic obstructive pulmonary disease (COPD) as use may lead to severe adverse events including respiratory depression[50] and mortality.[51] Furthermore, benzodiazepine use in the elderly population, has been associated with negative health outcomes including cognitive impairment, falls, and fractures.[52,53]

The purpose of this series of papers is to review current issues related to the medication misadventures as they pertain to benzodiazepines. More specifically, the goals of this series of papers is to quantify the prevalence of benzodiazepine misuse and abuse, examine health outcomes associated with the suboptimal use of benzodiazepines in clinically vulnerable populations, and test the impact of policies designed to reduce prescription drug abuse and diversion on the utilization of benzodiazepines. The specific aims of this literature review are to describe health outcomes associated with potentially inappropriate benzodiazepine use in specific populations, and to review policies that have been implemented to monitor transactions involving benzodiazepines and their impact on benzodiazepine prescribing and dispensing.

METHODS

The search engines of PubMed, Medline, and Google Scholar were used to search from combinations of the following key words and phrases: benzodiazepines, drug abuse, nonmedical prescription drug use, benzodiazepine poly-drug abuse, benzodiazepine misuse, health outcomes, medication misadventures, benzodiazepine monitoring, prescription drug monitoring program (PDMP), prescription monitoring program (PMP), and triplicate prescribing program (TPP). Searches of these databases were conducted between January and April 2014. Retrieved articles published in a language other than English were excluded from further review. Titles and abstracts of remaining articles were assessed for relevance to this review. Additionally, references cited in selected articles were examined and appropriate articles were considered based on their unique contribution to this review. The reviewed articles were grouped into two themes: prescription drug monitoring policies designed to mitigate consequences connected with prescription drug abuse and diversion, and health outcomes associated with potentially inappropriate benzodiazepine use.

FEDERAL AND STATE BENZODIAZEPINE POLICIES

Prescription drug abuse can be categorized as a type of medication misadventure leading to an adverse drug event or adverse drug reaction that can lead to injuries, a declined state of health, and death. Throughout history, several strategies have been implemented to address problems associated with the misuse, abuse, and diversion of psychoactive compounds. In the case of benzodiazepines, three strategies imposed by the US federal and state governments have had the most profound impact. First was the Controlled Substance Act of 1970 that classified potential drugs of abuse into Schedules and regulated transactions involving controlled substances (CS). Next, in 1989, New York became the first state to include

benzodiazepines on their TPP in order to monitor their prescribing and dispensing. Finally, in an effort to combat the problem of prescription drug abuse and diversion, many states have implemented PDMPs to track the prescribing and dispensing of CS, with the majority of states monitoring benzodiazepine transactions.

Controlled Substance Act of 1970

On October 27, 1970, President Richard Nixon signed into law the Comprehensive Drug Abuse Prevention and Control Act of 1970 in response to the increasing problem of illicit drug use, especially narcotics, which had become widespread in the late 1960s.[54] Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970, the Controlled Substance Act of 1970, created a complex regulatory system to control the distribution of drugs. The Controlled Substance Act created a classification system categorizing licit and illicit drugs into five categories called "Schedules" based on abuse potential, significance of abuse, dependence liability, the risk to public health, and scientific evidence regarding accepted medical use.[55] Substances classified as Schedule I currently have no accepted medical use in the United States with drugs included in Schedules II through V considered "necessary to maintain the health and general welfare of the American people."[55] Substances in the Schedule II category have been determined to have the greatest abuse potential while Schedule V CS have the least. The responsibility of adding drugs to CS Schedules and modifying the Schedules of already included substances falls upon the Drug Enforcement Administration (DEA) and the Food and Drug Administration. According to the criteria outlined by the Controlled Substance Act, benzodiazepines are defined as a Schedule IV CS. A description of the CS classification system and examples of drugs in each Schedule is provided in Table 3.

In addition to classifying CS into Schedules, the Controlled Substance Act also led to the regulation of transactions involving CS at the manufacturing and wholesale level. This aspect of the legislation was in response to the growing problem of illicit manufacturing and smuggling of CS from research laboratories to be sold on the black-market.[56] Individuals and firms who handle these drugs must register with the DEA and receive a registration number to be used on all transactions involving CS. Authorized handlers of CS include manufactures, distributors, hospitals, pharmacies, practitioners, and researchers. While all authorized handlers must maintain complete and accurate records of all their CS transactions only manufacturers are required to make periodic reports to the Attorney General.[57,58] An amendment to the Controlled Substance Act regarding the reporting of CS transactions occurred in 2008 as part of the Ryan Haight Online Pharmacy Consumer Protection Act. This legislation requires certain pharmacies distributing CS via the Internet to provide detailed reports of their CS transactions to the Attorney General.[59]

New York's Triplicate Prescription Program

Since the 1930s individual states have seen the need to collect and analyze prescribing and dispensing data pertaining to certain medications. In 1939, California became the first state to implement a PMP.[60] Early monitoring programs relied upon the use of multiple copy prescription forms and were implemented in nine states.[61] These monitoring programs required physicians to use government-issued serialized forms to write prescriptions for targeted drugs.[62] Ordering physicians would retain one copy of the prescription and give the remaining copies to the patient. Patients then would take their prescription to the pharmacy to be filled. At this point, the pharmacy would retain the other copies of the prescription, keeping one copy for their own records and submitting the remaining copy to the state surveillance unit.

On January 1, 1989, New York became the first state to include benzodiazepines in their list of targeted drugs monitored by the state's TPP with the primary objectives of reducing benzodiazepine diversion for illicit use and reducing inappropriate prescribing.[63-65] This program allowed regulatory agencies to track the prescribing, dispensing, and utilization of targeted drugs by providers, pharmacies, and patients suspected of misusing these medications.[66] With the exception of certain conditions, such as panic and convulsive disorders, the addition of benzodiazepines to the TPP limited prescriptions to a 30-day supply. In addition, refills were not permitted, requiring a patient to visit their provider when a new prescription was needed.[67]

Multiple copy prescription programs were strongly supported by the DEA, citing vast reductions of CS prescribing in states with an operational program.[68] Furthermore, it was emphasized these reductions were solely due to declines in inappropriate prescribing, in other words, there was no negative impact to CS access for patients with a legitimate CS need.[68] Early reports by the New York Department of Health proclaimed that adding benzodiazepines to the targeted drug list monitored by the state's TPP had not only succeeded in reducing the abuse of benzodiazepines and their diversion into the illicit market, but had done so without creating access limitations for legitimate users.[67] The success in reducing the abuse and diversion of benzodiazepines was supported by drastic increases in the street price of benzodiazepines (1mg of alprazolam rose from $1.50 to $8.50 and 10mg of diazepam went from $2.00-$2.50 to $4.50-$6.00), along with reduced mentions of benzodiazepines in the Drug Abuse Warning Network (DAWN), and a large decline in the number of Medicaid benzodiazepine prescriptions filled.[69] However, the claim of the TPP accomplishing these objectives without compromising benzodiazepine access for legitimate patients was widely challenged in a series of studies evaluating the change in policy.

A study by Reidenberg[70] compared the estimated number of benzodiazepine prescriptions written in New York and Pennsylvania for the years 1988, one year prior to, and 1989, one year after, the TPP implementation in New York. Pennsylvania was chosen as a comparator state as there was no policy change regarding benzodiazepine prescriptions during the study period. Findings showed a 57% decrease in the estimated number of benzodiazepine prescriptions in New York with only an 11% reduction occurring in Pennsylvania. The more interesting finding was the dramatic increase in the number of prescriptions during the study period for alternate sedative-hypnotics that are less effective in managing symptoms of anxiety and insomnia and/or have a higher abuse potential than benzodiazepines (i.e., meprobamate, buspirone, chloralhydrate, and hydroxyzine) in New York with no parallel changes observed in Pennsylvania. Similar findings were also reported by Weintraub et al.[71] Changes in the prescribing of alternate sedative-hypnotics from 1988 to 1989 in New York were assessed and compared them to nationwide trends using prescribing data from IMS America National Prescription Audit. While in New York the prescribing of benzodiazepine alternatives dramatically increased during the study timeframe, nationwide prescribing trends for these medications remained steady or declined. Hoffman et al.,[64] tested the presence of a substitution effect by examining the incident cases of overdoses reported to the New York City Poison Control Center for benzodiazepine and non-benzodiazepine sedative-hypnotics. The findings suggest that following the addition of benzodiazepines to the list of drugs targeted by the New York TPP the total number of sedative-hypnotic overdoses remained unchanged, but with a significant reduction in benzodiazepine overdoses concurrent with a significant rise in non-benzodiazepine sedative-hypnotic overdoses. As a result of the findings from the aforementioned studies, further questions were raised regarding the impact of benzodiazepine triplicate regulations on public health and patient care.

Four studies examining the effect of the benzodiazepine triplicate prescription policy on population subgroups suggested the triplicate prescription policy might have resulted in an unintended decrease in legitimate benzodiazepine use for patients in therapeutic need of this newly restricted medication.[65,72-74] A large controlled study conducted by Ross-Degnan et al.[65] examining the addition of benzodiazepines to the New York TPP on the dispensing of benzodiazepines observed a 50% reduction in dispensing to Medicaid beneficiaries. Furthermore, beneficiaries were classified as either problematic or non-problematic benzodiazepine users based on the indicators of long-term use (i.e., use greater than 120 days duration), excessive dosage (i.e., levels more than twice the recommended maximum), concurrent use (i.e., concurrent use of two long-acting or two short-acting benzodiazepines), pharmacy hopping (i.e., filling a prescription for the same benzodiazepine in two different pharmacies within seven days), and elderly use of long half-life benzodiazepine. Findings of the study showed that after benzodiazepines were added to the New York TPP the risk of discontinuing benzodiazepine therapy was twice as high in New York compared to New Jersey (relative risk (RR): 2.1; 95% confidence interval (CI): 2.1-2.1). Among New York Medicaid beneficiaries, the RR of benzodiazepine discontinuation was greater in those with problematic use compared to those with non-problematic use (RR: 1.3; 95% CI: 1.2-1.3). However, the authors suggested that overall, because at baseline the majority of benzodiazepine dispensing was identified as non-problematic the number of non-problematic users that had their benzodiazepine discontinued greatly exceeded that of problematic users. This conclusion implies that the inclusion of benzodiazepines on the list of drugs monitored by the TPP resulted in a barrier to appropriate medication therapy for patients with a legitimate need. Results also demonstrated a disproportionate impact on females, and residents of predominately urban, black, and poor areas, with these beneficiaries experiencing comparatively higher

benzodiazepine discontinuation rates after the policy change. However, differences in demographic characteristics between beneficiaries identified as problematic and non-problematic users were not provided. If problematic benzodiazepine dispensing at baseline were greater in these population subgroups then a high discontinuation rate among these beneficiaries would be expected and potentially appropriate.

Pearson et al.[74] further explored the issue of racial disparities in benzodiazepine access after the TPP policy change in a study of New York Medicaid beneficiaries. Changes in benzodiazepine use in white, black, Hispanic, and mixed race neighborhoods were examined and neighborhood racial composition was used as a predictor of benzodiazepine discontinuation. The study observed beneficiaries residing in black neighborhoods were consistently the most likely group to experience reduced access to benzodiazepines after the TPP policy change. This is a concerning observation as residents in black neighborhoods had the lowest baseline benzodiazepine utilization rates and the lowest baseline odds of problematic benzodiazepine use. Furthermore, this leads to concerns that health policies, in the process of achieving their intended goals, may disproportionally affect racial minorities, further widening health disparities between people of different racial backgrounds.

Evidence of a substantial impact on access to benzodiazepine therapy among clinically vulnerable populations was detected in two separate assessments. A 2003 evaluation by Wagner and colleagues[72] examined new benzodiazepine use among patients recently discharged from the hospital for either an acute cardiac event or cancer. Benzodiazepines are often prescribed to relieve anxiety associated with acute myocardial infarction and in cancer patients to reduce anticipatory anxiety and anxiety related effects associated with the administration of chemotherapy.[2] The study found new benzodiazepine use among New York

Medicaid beneficiaries recently discharged from the hospital for acute cardiac events and cancer declined 72.5% and 69.4%, respectively during the two-year observation period after the benzodiazepine triplicate regulation was implemented. Additionally, Simoni-Wastila et al.[73] studied patients who had a diagnosis of schizophrenia, epilepsy, or bipolar disorder, where benzodiazepines represent an effective first-line or adjunct treatment option, and demonstrated a nearly 50% decline in benzodiazepine use six months after the policy change. Patients with a seizure disorder experienced a 60% decline, the largest among the conditions assessed. However, while benzodiazepines are a first-line agent for status epilepticus and acute seizures their efficacy in treating chronic epilepsy is limited by the risk of side effects and development of tolerance[75] which may explain the significant decline in utilization among this population. Furthermore, clinical outcomes for the populations in both studies were not assessed. Therefore, it is unknown if patients for whom benzodiazepine therapy was not initiated, or discontinued, were adversely affected. However, the authors of these studies concluded access to appropriate pharmacotherapy had been restricted by the TPP policy change.

These studies highlight the potential for health policies to produce unintended consequences that create barriers to healthcare access for already disadvantaged individuals. While the addition of benzodiazepines to the New York TPP did not restrict physician prescribing of benzodiazepines, concerns existed of reduced access to appropriate pharmacological care, dubbed a “chilling effect”. The “chilling effect” describes a situation where a patient with a legitimate need for a CS is unable to acquire it either due to a physician’s unwillingness to prescribe or a pharmacist being unwilling or unable to dispense the CS. The unwillingness to prescribe or dispense a CS may be due to fear of legal investigations, fear of confidentially violations, increased administrative burden, or confusion between the patterns of addiction and pseudoaddiction, where patients who are not being adequately treated for their condition

appear, on paper, to be addicts.[76-79] Additionally, patients with a legitimate CS need may be unwilling to accept the medication due to concerns they may be labeled as a drug user in the surveillance system.[79]

The reviewed studies support the claim that benzodiazepine monitoring policies result in an immediate, significant, and sustained decline of overall benzodiazepine use. In addition, these studies identify reductions in problematic or inappropriate benzodiazepine use as a result of the benzodiazepine TPP regulation, a primary goal of the policy amendment. Evidence of unintended consequences, such as a "chilling effect" and a differential impact among certain population subgroups were also supported. However, the reviewed studies only assessed the effect of the New York TPP. Benzodiazepine monitoring policies in other states may affect patterns of benzodiazepine use differently based on physician prescribing practices, prevalence rates of mental illnesses, and variations in abused/misused substances. Furthermore, each of these studies exclusively relied upon data from a Medicaid population. Therefore, it is unknown how benzodiazepine monitoring programs affect use among privately insured populations. Moreover, clinical outcomes of the study populations after the TPP were not assessed. Without this information it is undetermined if patients who were discontinued from benzodiazepine therapy experienced adverse health outcomes as a result of the new regulation. Use of clinical outcomes would provide a more accurate depiction of the impact of the TPP on inappropriate and legitimate benzodiazepine use, as the proxy developed by the Advisory Panel described in Ross-Degnan et al.[65] does not contain diagnostic information, thus limiting the ability to distinguish between specific instances of appropriate and inappropriate use.

Prescription Drug Monitoring Programs

In the 1990s, states began to rely on electronic data transfer systems to track the prescribing, dispensing, and utilization of targeted medications in an effort to combat prescription drug abuse and diversion. Because of these electronic systems, states have repealed their multiple copy prescription programs in favor of PDMPs. In 2006, California became the last state to repeal their multiple copy prescription program, which they had been using concurrently with their electronic PDMP since 1997.[61] Prescription drug monitoring programs have an added advantage over multiple copy prescription programs as they provide prescribers and pharmacists with the ability to request and receive a patient's CS prescription history with quick turnaround, allowing treatment decisions to be made at the point of care. Reports detailing a patient's CS prescription history can be accessed upon request, or proactively distributed to specific healthcare providers and law enforcement officials, depending upon the regulations of the individual state's program. Pharmacies, along with dispensing physician and veterinarian offices submit CS dispensing data to the PDMP on a regular basis as mandated by state law. The majority of states require CS dispensing data to be submitted at least every seven days with some states requiring daily or "real-time" reporting.[80] Prescription data submitted to PDMPs follows a standard format and includes patient name, prescriber name, date of dispensing, and name, strength, and quantity of the CS medication dispensed. As of December 2014, 49 states have an operational PDMP. Missouri and Washington DC do not currently have a PDMP, however, Washington DC does have pending legislation.[80]

While all PDMPs were designed to facilitate collection, analysis and reporting of prescription controlled substance use, in practice they take several different forms based upon individual state legislation and differ in terms of objectives, design, and operations.[58] Housing

agencies of PDMPs vary between states with the majority of PDMPs housed within health departments, a single state authority (an entity designated as a state's administrative authority responsible for the planning and implementation of statewide systems that provides substance abuse services[81]), or Boards of Pharmacy.[80] Seven states house their PDMP within a law enforcement agency.[80] Variation exists across states in terms of authorized users and access to the PDMP system and PDMP reports. In most states healthcare professionals including prescribers and dispensers of CS, along with regulatory and licensing boards are authorized to receive the information contained within PDMP reports, however, access among law enforcement personnel is less uniform.[80] States also differ in the CS schedules monitored. While all state PDMPs track the dispensing of Schedule II CS, some states also monitor Schedules III, IV, and V. Some state PDMPs also have the authority to monitor non-CS under certain circumstances.[82] Relevant for this work, of the 49 operational PDMPs as a December 2014, 48 have the authority to monitor the prescribing and dispensing of Schedule IV CS which include benzodiazepines.[80,83] A list of states with active PDMPs and a description of CS Schedules monitored is provided in Table 4. Of note, Pennsylvania is the only state with a PDMP that does not monitor Schedule IV CS, including benzodiazepines.

The limited studies conducted regarding the effectiveness of PDMPs suggest these programs are successful in reducing the supply of CS. One study conducted by the United States General Accounting Office released in 2002 examined the presence of a PDMP in the ten states with the highest and lowest per capita OxyContin prescriptions. Among the ten states with the greatest number of OxyContin prescriptions per capita, only two (Kentucky and Rhode Island) had an active PDMP. Comparatively, six of the ten states with the lowest number of prescriptions per capita had a PDMP in place.[58] A 2006 evaluation of PDMPs by Simeone and Holland[84] used state and individual level models to estimate the relationship between the

presence of a PDMP, the supply of Schedule II CS, and the abuse of these medications. Using data from the Automation of Reports and Consolidated Orders System (ARCOS), which monitors the sale of CS through commercial channels, the per capita supply of Schedule II CS over the seven-year study period was found to be reduced in states with an active PDMP compared to states without a PDMP.

Conversely, PDMPs may not be associated with improved health outcomes as some studies suggest that PDMPs have a limited impact on overall opioid consumption and drug overdose mortality. Twillman[85] conducted a review of the ARCOS database and identified a decrease in the supply of Schedule II opioid analgesics along with a concurrent increase in Schedule III opioid analgesics among states with an active PDMP. Paulozzi, Kilbourne, and Desai[86] also analyzed the ARCOS database and noted that during the study period from 1999 to 2005, PDMPs were not associated with lower rates of overall opioid consumption and like Twillman[85] found PDMPs were associated with lower rates of Schedule II opioid analgesic use but not Schedule III opioid analgesics. Similar findings were reported in a 2012 cross sectional study conducted by Simoni-Wastila and Qian[87] who estimated the association between the presence of a PDMP and the probability of analgesic use by CS Schedule among older, privately insured adults. Results showed the odds of filling any opioid analgesic prescription were greater in states with a PDMP. More specifically, beneficiaries in states with an active PDMP had decreased odds of filling a prescription for a Schedule II opioid analgesic and increased odds for Schedule III opioid analgesics when compared to beneficiaries in states absent of a PDMP. Recently, Brady et al.[88] found that on a national level PDMPs are ineffective at significantly reducing the amount of opioids distributed per capita, but when examined at the state level there are marked variations among the effect of programs. Li et al.[89] found similar results when examining the impact of PDMPs on drug overdose mortality. On a national scale the presence of

a PDMP was associated with and 11% increase in drug overdose mortality, however, significant state variations were found ranging from a 35% decrease in Michigan to a 337% increase in Nevada. The findings presented by Brady et al. and Li et al. suggest that it is specific characteristics of PDMPs that have the greatest impact on prescription drug abuse and diversion as opposed to the presence of a program alone.

In clinical practice there is limited literature examining how PDMPs impact CS behaviors. Baehren et al.[90] studied how PDMP reports affected the prescribing decisions by emergency room physicians at a university hospital in Ohio for patients presenting with non-acute pain. In 41% of cases the physician chose to alter their initial CS pain medication prescribing decision after reviewing a patient's PDMP report with 60% of these cases resulting in fewer of no CS pain medications being prescribed. Green et al.[91] surveyed pharmacists in Connecticut and Rhode Island to understand how PDMPs influence their practice. Responding pharmacists reported they used reports generated by the PDMP to screen for abuse and doctor shopping but the effect on CS dispensing behavior was not evaluated. A 2010 independent study conducted by Blumenschein et al.[82] surveyed CS prescribers and dispensers in Kentucky and found that for 46% of prescribers and 34% of pharmacists the information contained within the PDMP report had altered their CS prescribing or dispensing decision.

To date, studies regarding current PDMP legislation have focused primarily on the impact concerning opioid analgesic prescribing and use. Focus on this medication class is understandable as opioid analgesics are the primary contributor to the increasing trend of drug overdose deaths in the United States.[92-94] However, other CS, specifically benzodiazepines, have been found to be a factor contributing to the substantial rise in unintentional poisoning deaths[92,95-97] likely related to the additive or synergistic effects when benzodiazepines are

combined with opioids.[98] In West Virginia, a forensic drug database review conducted by Shah et al.[97] found that the proportion of drug-related deaths where alprazolam was a contributing factor increased from 7.2% in 2005 to 27.5% in 2007. An analysis of medical examiner records from New York City found that benzodiazepine use concurrent with methadone maintenance therapy increased the odds of an accidental overdose by 1.66 (95 % CI: 1.12, 2.45).[99] Similar results were also reported in a study of opioid-related deaths in the United Kingdom. Interestingly, among the deaths primarily attributable to methadone in which benzodiazepines were detected, the blood concentration levels of methadone were considered to be within therapeutic ranges.[100]

Utilization of PDMPs can aid in the identification of potentially inappropriate prescribing and dispensing involving benzodiazepine medications. In the approximately 50% of drug-related deaths in West Virginia where opioids and benzodiazepines were identified through toxicology analysis, the deceased had a legal prescription for both medications.[97] Additionally, among the deceased with more than one benzodiazepine detected at the time of death, the majority (63%) had a valid prescription for each medication.[97] As many electronic PDMPs allow prescribers nearly instantaneous feedback of a patient's CS prescription history, use of these systems can alert prescribers to possible doctor shopping and inappropriate or risky adjunct CS prescribing. This information allows the prescriber to intervene in suspected cases of drug abuse and diversion by referring the patient to substance abuse treatment or conducting drug screens to ensure the patient is taking, and not diverting, the prescribed CS, thereby reducing the risk of unintentional poisonings.

Previous literature on benzodiazepine monitoring has centered on the New York TPP from the early 1990s. Given the noticeable absence of literature evaluating the impact of

current PDMP legislation on benzodiazepine prescribing, dispensing, and utilization studies in this area are warranted. Expanding the literature on current PDMP legislation to incorporate benzodiazepines is necessary to understand if these programs are effectively meeting their objectives of curbing the prescription drug abuse epidemic. Assessments of how PDMP policies affect benzodiazepines is also needed to ensure patient safety by not restring access to pharmacotherapy options among patients having a condition where benzodiazepine therapy is appropriate.

BENZODIAZEPINE USE AND HEALTH OUTCOMES

In the United States it is estimated that in a given year approximately one-quarter of adults 18 and older suffer from a diagnosable mental disorder.[101] Anxiety disorders, including panic disorder, post-traumatic stress disorder, generalized anxiety disorder, and phobias, are the most prevalent mental disorder in the United States affecting about 40 million Americans or 18% of the adult population.[101] Furthermore, patients who suffer from mental disorders, including anxiety disorders, are also likely afflicted with symptoms of insomnia.[102] Benzodiazepines are generally an effective pharmacological treatment option and are widely prescribed for the management of symptoms related to anxiety disorders and insomnia.[11,103]

Despite their benefits, benzodiazepine therapy is not optimal for all populations. Commission of benzodiazepine therapy has inherent risks and medication misadventures involving benzodiazepines are common when they are used in clinically vulnerable populations. The abuse potential of benzodiazepines and synergistic effect when coupled with opioid analgesics can lead to the risk of medication errors including concurrent use of benzodiazepines and opioid analgesics, duration of use exceeding that of proven efficacy, and escalation of dosage beyond that prescribed by a physician. While medication errors sometimes have little or

no potential for patient harm they can be linked with mild to severe adverse drug events and adverse drug reactions. Adverse drug events and adverse drug reactions may also present when benzodiazepines are used in patients with certain comorbid conditions. These avoidable incidents can lead to patient discomfort, progression of disease state, visits to the emergency department, hospitalizations, and death.

Misuse and abuse of benzodiazepines

The misuse and abuse of benzodiazepines is a prevalent issue. According to the 2012 National Survey of Drug Use and Health,[104] the estimated number of incident benzodiazepine abusers was 166,000. National estimates of drug-related visits to emergency departments collected by the Drug Abuse Warning Network[105] (DAWN) for the year 2011 reported that between 2004 and 2011 the number of emergency department visits for the non-medical use of benzodiazepines increased 149% from 143,500 to 357,800. Additionally, this report identified benzodiazepines as the second leading cause of all emergency department visits concerning nonmedical use of pharmaceuticals, as they were involved in 28.7% of all emergency department visits for this cause. Another recent study by Cai et al.[106] examining data from DAWN between 2004 and 2008 reported that benzodiazepines were identified in approximately 26% of all opioid related emergency department visits. These estimates suggest that benzodiazepine misuse and abuse can lead to serious adverse effects on individuals and caution must be exercised with their prescribing and use.

It has been suggested that patterns of benzodiazepine misuse and abuse can be separated into two categories: deliberate and unintentional.[15] Deliberate misuse and abuse of benzodiazepines entails taking the drug to achieve a euphoric effect, while unintentional misuse and abuse would include individuals with a valid prescription for the medication but take higher

than suggested doses or take it for a prolonged period of time.[15] Oftentimes benzodiazepines are deliberately abused in combination with other drugs, most commonly alcohol and opioids,[16] in order to enhance the effect provided by other substances. For example, in a survey of methadone maintenance patients, 72% of those who were also regular benzodiazepine users indicated that benzodiazepines were used in order to increase the effects of their daily methadone dose.[107] However, patients who are receiving methadone maintenance therapy and are also regular users of benzodiazepines experience a greater mean number of overdoses (3.3 ± 0.7) than occasional-users (1.8 ± 0.4) and non-users (0.7 ± 0.2; p=0.003).[108] The co-use of benzodiazepines and opioids is also common among patients treated for chronic pain with surveys estimating between 40-60% of chronic pain patients also regularly using benzodiazepines.[109] It is undetermined if chronic pain patients use benzodiazepines in order to enhance the pain relieving effects of opioids or to manage symptoms of anxiety and/or insomnia that frequently coexist with chronic pain.[110,111] Despite the frequency of concurrent use, the combination of benzodiazepines and opioids can have detrimental effects on physical and mental health. With this in mind, physicians should be aware of patterns that may signal deliberate drug misuse and abuse in patients using one or both of these medications.

Benzodiazepine use, mental illness, and substance use disorders

Among patients with severe mental illness, such as schizophrenia, bipolar disorder, and major depression, benzodiazepines are commonly prescribed to reduce symptoms of anxiety, insomnia, and agitation and to manage side effects of other medications.[112,113] The use of benzodiazepines in patients with mental illness is a controversial practice due to the high prevalence of SUDs in this population coupled with the abuse potential of benzodiazepines. The 2012 National Survey on Drug Use and Health found that 19.2% (8.4 million) of the 43.7 million

adults with any mental illness also met the criteria for a SUD as specified within the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).[114] Comparatively, only 6.4% (12.3 million) of adults without any mental illness were considered to have a SUD.[114] Despite concerns, benzodiazepine use is highly prevalent among individuals with mental illness and co-occurring SUDs.[112,113] Clark, Xie, and Brunette[112] reported that among Medicaid beneficiaries, the prevalence of benzodiazepine use is greater in patients with severe mental illness and co-occurring SUDs than in patients with a severe mental illness alone. Wixson and Brouwer[115] found that in a privately insured population, males infected with HIV were more likely (OR: 1.68; 95% CI: 1.05-2.67) to fill a benzodiazepine prescription compared to their uninfected counterparts. This finding is of notable concern as the HIV-infected population has high prevalence of mental illness and SUDs[116] and substance abuse has been linked to poor antiretroviral therapy adherence.[117] Furthermore, in patients with severe mental illness and co-occurring SUDs benzodiazepine use did not improve symptoms of anxiety and depression.[113] These findings suggest that further research into the appropriateness of benzodiazepine use in mental illness patients with and without a co-occurring SUD is warranted due to concerns regarding efficacy and abuse potential.

Benzodiazepines and adverse health outcomes

The use of benzodiazepines in certain clinically vulnerable populations carries a risk of negative effects on health outcomes. For example, studies examining patients with COPD have found evidence of a link between benzodiazepine use and several adverse respiratory outcomes such as decreased minute ventilation,[118,119] low levels of oxygen and high levels of carbon dioxide in the blood,[119,120] and a decrease in respiratory muscle strength.[118] Moreover, joint American Thoracic Society/European Respiratory Society guidelines recommend that hypnotics

such as benzodiazepines not be used in patients with severe COPD.[121] Despite these recommendations, a 2013 study by Vozoris et al.[122] examining benzodiazepine use in older patients with COPD in Ontario found that new benzodiazepine use is common, occurring in roughly one-third of the study population. The study also found that incident benzodiazepine use was more common in patients with severe COPD than less severe COPD, suggesting that patients who are most at risk of experiencing an adverse event related to benzodiazepine use are the patients most likely to receive this medication class. New benzodiazepine use among the COPD population was also found to increase the risk for outpatient respiratory exacerbations (RR: 1.45; 95% CI: 1.36-1.54) and emergency department visits for COPD and pneumonia (RR: 1.92; 95% CI 1.69-2.18) in a 2014 study conducted by Vozoris et al.[123] A 2007 study by Winkelmayer and colleagues[124] found a potential link between benzodiazepine use and an increased risk in mortality in patients with COPD.

The safety of benzodiazepines in the management of posttraumatic stress disorder has also been called into question. According to the *Veterans Affairs (VA)/Department of Defense Clinical Practice Guideline for Management of Post-Traumatic Stress*[125] regular benzodiazepine use in the PTSD population is discouraged due to insufficient evidence supporting avoidance and dissociation symptom improvement and concerns of safety, especially respiratory depression and over-sedation when used concurrently with other drugs acting on the CNS. Instead, it is recommended that SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs) are used as first line pharmacotherapy agents for treating PTSD. Even with these guidelines, Hawkins et al.[126] determined benzodiazepines were prescribed to nearly one-third (31%) of all VA patients diagnosed with PTSD in 2009. Their study examining the comparative safety of adjunct benzodiazepine therapy in addition to SSRIs/SNRIs versus SSRIs/SNRIs alone among VA patients diagnosed with PTSD found that compared with patients who only received SSRIs/SNRIs, those

who also concurrently used benzodiazepines had a significantly greater risk for a mental health hospitalization (adjusted hazard ratio (AHR): 1.87; 95% CI: 1.37-2.53) and for any hospitalization (AHR: 1.52; 95% CI: 1.16-2.00). The finding of increased adverse events in concurrent users of SSRIs/SNRIs and benzodiazepines supports the current guidelines discouraging benzodiazepine use for the management of PTSD due to safety concerns.

Benzodiazepine use in the elderly

In an elderly population adverse drug events can lead to increases in morbidity, mortality, and hospitalizations.[52,127] Often, such adverse events are associated with medications that are contraindicated for use in the elderly population. Benzodiazepines are identified by the *Beer's Criteria for Potentially Inappropriate Medication Use in Older Adults*[53] as one specific drug class that should be avoided in the elderly due to an increase of cognitive impairment, falls, and fractures. Furthermore, these guidelines state the quality of evidence for avoiding the use of benzodiazepines in the elderly is high and the strength of the recommendation is strong. The high quality of evidence means that consistent results have been found from well-designed and well-controlled studies, and the strong recommendation means the burden of the elderly population using this medication clearly outweighs the benefits.

Even though the recommendations against benzodiazepine use in the elderly exist, these drugs are still commonly prescribed in this population. It has been estimated that the prevalence of benzodiazepine use in the elderly ranges between 10-30%, significantly higher than the 2-5% prevalence ranges estimated in younger adults.[128-131] A 2014 study conducted by Olfson et al.[132] examining variations in rates of benzodiazepine use by age found the use of benzodiazepines, specifically long-term use defined as filling at least 120 days of supply during the study year of 2008, increases steadily with age. Of adults 65-80 years old, 31% were

identified as long-term benzodiazepine users compared to only 15% of those in the 18-35 age group.

Several studies have been conducted investigating relationships between benzodiazepine use in elderly populations and adverse health outcomes. Evidence suggests that physiological changes associated with aging make the elderly population more susceptible to side effects associated with benzodiazepines.[2] The use of benzodiazepines among elderly populations has been associated with an increased risk of cognitive and psychomotor impairment.

With an increasingly aging population, problems associated with cognitive impairment are a public health concern. Hanlon and colleagues[133] suggested current benzodiazepine use among community-dwelling elderly is associated with poorer performance on cognitive functioning tests. Furthermore, the study results suggested a dose response and a duration response relationship where patients taking higher dosages or who had a longer duration of use displayed greater cognitive decline than non-users of benzodiazepines. Similar results were also reported by Paterniti et al.[134] who found chronic benzodiazepine users had a significantly greater risk of cognitive decline than non-users (OR: 1.9; 95% CI: 1.0 – 3.5). In a large prospective study of elderly people in France, Billioti de Gage et al.[135] associated new benzodiazepine use with an approximate 50% increase in the risk of dementia. Most recently, Billioti de Gage and colleagues[136] reported any past benzodiazepine use was associated with an approximate 50% increase in the risk of Alzheimer's disease among community dwelling individuals in Quebec. The risk was increased when long-acting benzodiazepines were primarily used and as the duration of exposure increased.

Cutson et al.[137] conducted a double blind study assessing the effects of benzodiazepines on the balance of healthy older adults and found that after taking a single dose of diazepam, processes related to balance control were adversely affected. Several epidemiologic studies have been published suggesting benzodiazepine use in the elderly is strongly associated with an increased risk for falls and fractures. Bayesian adjusted odds ratios from a meta-analysis by Woolcott et al.[138] suggest benzodiazepine use among older individuals is associated with a 41% increase in the risk of falling. Furthermore, these falls are likely to be injurious, especially among individuals 80 years of age and older.[139] Xing et al.[140] conducted a meta-analysis examining the relationship between benzodiazepine use and risk of fractures in 18 studies where this relationship was investigated in an elderly population. Results of the meta-analysis suggest that benzodiazepine use in the elderly is associated with an overall relative risk of fractures of 1.26 (95% CI: 1.15 – 1.38). Additionally, an analysis of VA databases by French et al.[141] found a temporal association between outpatient benzodiazepine use and serious injuries resulting in inpatient stays, costing $2.89 million for 297 unique patients, and outpatient visits, costing $400,000 for 1,352 unique patients.[141] Additionally, studies have shown an association between benzodiazepine use in the elderly and an increase in the relative risk of motor vehicle accidents in this population.[142,143]

Benzodiazepine use in adolescents

To date, few studies have assessed the use of benzodiazepines in adolescent populations. Traditionally, benzodiazepines have been used in adolescent populations with anxiety disorders, sleep disorders, psychosis, and aggression despite a lack of sound evidence indicating benzodiazepines are an effective treatment option in this population.[144] In the United States the prescribing of CS to adolescents and children has nearly doubled over the previous

two decades.[145] At the same time that CS prescribing for adolescents has been increasing so has the nonmedical use of benzodiazepines in this population.[146] A recent study by McCabe and West[147] estimated that high school seniors the lifetime prevalence of medical benzodiazepine use to be 4.3% and 7.5% for nonmedical benzodiazepine use. In two separate studies of students enrolled in Detroit metropolitan area public secondary schools, medical use of controlled medications, including benzodiazepines, was associated with an increased likelihood of nonmedical prescription drug use compared to students who had never received a prescription for a CS.[148,149] Furthermore, the nonmedical use of benzodiazepines in adolescent populations is of significant concern as McCabe et al.[150] linked earlier initiation of nonmedical benzodiazepine use to an increased risk of developing a SUD compared to those whose initial nonmedical benzodiazepine use is later in life.

CONCLUSION

Benzodiazepines are an effective treatment option for many people suffering from a wide range of medical conditions including insomnia and anxiety. Due to the abuse liability of benzodiazepines and their synergistic effects when taken with other substances, clinicians should evaluate the benefits and risks of benzodiazepine therapy prior to prescribing in an effort to avoid medication misadventures associated with this drug class. The abuse liability of benzodiazepines has led to policies, most notably TPPs, and PDMPs, designed to monitor the distribution of benzodiazepines in an effort to reduce inappropriate use. Previous studies evaluating state monitoring programs suggest the supply of CS is drastically reduced upon implementation. However, the only studies evaluating the effect of state monitoring programs on benzodiazepine use focus on the New York TPP and the impact of current state PDMPs on benzodiazepine use is unknown. The available literature is also currently unable to definitively

evaluate the impact of prescription drug monitoring policies on health outcomes, an important aspect to determine the effect PDMPs have on inappropriate and legitimate benzodiazepine use.

Evaluations of health outcomes associated with benzodiazepine utilization in at-risk populations are warranted as many previous studies were conducted prior to the growth and notoriety of the prescription drug abuse epidemic. As a result, little is known about benzodiazepine use in populations at risk for SUDs. Furthermore, studies are needed to evaluate the use and safety of benzodiazepines in clinically vulnerable populations as inappropriate benzodiazepine use can increase the risk of medication misadventures involving adverse drug events and adverse drug reactions which can include increased healthcare resource utilization, morbidity, and mortality. Studies evaluating potentially inappropriate benzodiazepine use can help disseminate information regarding the effectiveness and suitability of benzodiazepines use in specific populations and thereby optimize health outcomes to the benefit of patients and society.

Motivated by the evidence suggesting medication misadventures pertaining to benzodiazepines are of significant concern, this dissertation will assess the issue in two clinically vulnerable populations (COPD and HIV) and examine the impact of a policy designed to mitigate their inappropriate use. The second chapter of this dissertation will examine the use of benzodiazepines in patients diagnosed with COPD and the risk of acute exacerbations requiring hospitalization. The objectives of this chapter will address the definition of a mediation misadventure by describing an iatrogenic hazard or incident created through by the administration of a medicine during which a patient may be harmed. Chapter 3 will determine whether individuals infected with HIV are more likely to fill a prescription for a benzodiazepine

compared to those who are uninfected with the disease. Additionally, Chapter 4 will continue the investigation pertaining to benzodiazepine use in the HIV infected population by examining whether individuals infected with HIV are more likely to engage in potentially problematic benzodiazepine use than their uninfected counterparts. In these two studies the inherent risk when medication therapy is indicated aspect of the medication misadventure definition will be addressed as the administration of benzodiazepines in the HIV infected population is controversial due to the abuse potential of the medication coupled with the high prevalence of SUDs in this population. In Chapter 5 the impact of a PDMP is evaluated using the example of South Carolina's program implementation and the subsequent effect on benzodiazepine dispensing. Chapter 6 will further elaborate on the topic of PDMPs by assessing their impact on benzodiazepine dispensing using a nationwide sample. These chapters will address a policy that has been implemented by states to curtail problems associated with prescription drug abuse, which can lead to negative health outcomes that are always unexpected or undesirable to the patient and healthcare professional. Examples of unexpected or undesirable health outcomes as they pertain to prescription drug abuse include: tolerance and/or addiction, overdose, and fatality. At the same time, these studies evaluate the possibility that PDMPs may induce a 'chilling effect' by limiting access to benzodiazepine therapy among patients who have a legitimate need for the medication. The inability of patients who have a legitimate need for a benzodiazepine to acquire it can lead to an iatrogenic hazard or incident that is created through the omission of a medication during which the patient may be harmed, another component of medication misadventures.

Table 1.1. List of benzodiazepines marketed in the United States as of January 2013.

Generic Name	*Trade Names*	*Dosage Forms*	*Year on Market*	*Indications*	*Diazepam Milligram Equivalent (DME)*[7,151]
Alprazolam	Niravam®; Xanax XR®; Xanax®	Solution, Tablet	1981	Treatment of generalized anxiety disorder (GAD); short-term relief of symptoms of anxiety; panic disorder, with or without agoraphobia; anxiety associated with depression	1
Chlordiazepoxide Hydrochloride	Librax®; Librium®; Limbitrol®; Limbitrol® DS	Capsule	1960	Management of anxiety disorder or for the short-term relief of symptoms of anxiety; withdrawal symptoms of acute alcoholism; preoperative apprehension and anxiety	50
Clobazam	Onfi®	Tablet	2011	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome	20
Clonazepam	Klonopin®; Klonopin® Wafers	Tablet	1975	Alone or as an adjunct in the treatment of petit mal variant (Lennox-Gastaut), akinetic, and myoclonic seizures; petit mal (absence) seizures unresponsive to succimides; panic disorder with or without agoraphobia	0.5
Clorazepate Dipotassium	GenXene®; Tranxene® T-TAB®	Capsule, Tablet	1972	Treatment of generalized anxiety disorder; management of ethanol withdrawal; adjunct anticonvulsant in management of partial seizures	15
Diazepam	Diastat® Rectal Delivery System; Valium®	Gel, Injection, Solution, Tablet	1963	Management of anxiety disorders; ethanol withdrawal symptoms; skeletal muscle relaxant; treatment of convulsive disorders; preoperative or preprocedural sedation and amnesia Rectal gel: management of selected, refractory epilepsy patients on stable regimens of antiepileptic drugs requiring intermittent use of diazepam to control episodes of increased seizure activity	10
Estazolam	ProSom®	Tablet	1990	Short-term management of insomnia	2

Table 1.1. List of benzodiazepines marketed in the United States as of January 2013 (cont'd).

Flurazepam Hydrochloride	Dalmane®	Capsule	1970	Short-term treatment of insomnia	30
Lorazepam	Ativan®	Injection, Solution, Tablet	1977	Oral: management of anxiety disorders or short-term (≤4 months) relief of the symptoms of anxiety, anxiety associated with depressive symptoms, or insomnia due to anxiety or transient stress IV: status epileptics, anterograde amnesia, sedation	2
Midazolam Hydrochloride	Versed®	Injection	1985	Preoperative sedation; moderate sedation prior to diagnostic or radiographic procedures; ICU sedation (continuous infusion); induction and maintenance of general anesthesia	15
Oxazepam	Serax®	Capsule, Tablet	1965	Treatment of anxiety; management of ethanol withdrawal	30
Quazepam	Doral®	Tablet	1985	Treatment of insomnia	15
Temazepam	Ristoril®	Capsule	1981	Short-term treatment of insomnia	20
Triazolam	Halcion®	Tablet	1982	Short-term generally (7-10 days) treatment of insomnia	0.25

Table 1.2. Characteristics of benzodiazepine therapy and individual patients that influence withdrawal severity and inability to taper off the medication.[44-46]

Characteristics of benzodiazepine therapy
Short half-life benzodiazepine
Higher benzodiazepine dosage
Longer duration of benzodiazepine therapy
Rapid taper
Characteristics of individual patients
Female
Higher baseline levels of anxiety and depression
Higher level personality pathology
History of mild to moderate alcohol or drug abuse

Table 1.3. United States Schedule of controlled substances.[55]

Schedule	*Definition of Controlled Substance Schedules*	*Examples*
Schedule I	No currently accepted medical use in the United States; lack of accepted safety for medical use; high potential for abuse	Heroin; lysergic acid diethylamide (LSD); marijuana
Schedule II	High potential for abuse potentially leading to severe psychological or physical dependence	Oxycodone; morphine; methamphetamine
Schedule III	Abuse potential is below that of Schedule I and II; abuse can lead to low to moderate physical dependence or high psychological dependence	Combination products containing <15mg of hydrocodone per dosage unit; products containing <90mg codeine per dosage unit; buprenorphine
Schedule IV	Low potential for abuse compared to Schedule III	All benzodiazepines; carisoprodol
Schedule V	Low potential for abuse compared to Schedule IV; primarily consists of substances containing limited quantities of certain narcotics	Cough medications with ≤ 200mg codeine per 100ml/100g

Table 1.4. States with an operational prescription drug monitoring program and controlled substance Schedules monitored as of December 2014.[80,83]

	Schedules Monitored					*Schedules Monitored*			
State	*II*	*III*	*IV*	*V*	*State*	*II*	*III*	*IV*	*V*
Alabama	X	X	X	X	Nebraska	X	X	X	X
Alaska	X	X	X	X	Nevada	X	X	X	
Arizona	X	X	X		New Hampshire	X	X	X	
Arkansas	X	X	X	X	New Jersey	X	X	X	X
California	X	X	X		New Mexico	X	X	X	X
Colorado	X	X	X	X	New York	X	X	X	X
Connecticut	X	X	X	X	North Carolina	X	X	X	X
Delaware	X	X	X	X	North Dakota	X	X	X	X
Florida	X	X	X		Ohio	X	X	X	X
Georgia	X	X	X	X	Oklahoma	X	X	X	X
Hawaii	X	X	X	X	Oregon	X	X	X	
Idaho	X	X	X	X	Pennsylvania	X			
Illinois	X	X	X	X	Rhode Island	X	X	X	
Indiana	X	X	X	X	South Carolina	X	X	X	
Iowa	X	X	X		South Dakota	X	X	X	
Kansas	X	X	X		Tennessee	X	X	X	X
Kentucky	X	X	X	X	Texas	X	X	X	X
Louisiana	X	X	X	X	Utah	X	X	X	X
Maine	X	X	X		Vermont	X	X	X	
Maryland	X	X	X	X	Virginia	X	X	X	
Massachusetts	X	X	X	X	Washington	X	X	X	X
Michigan	X	X	X	X	West Virginia	X	X	X	X
Minnesota	X	X	X		Wisconsin	X	X	X	X
Mississippi	X	X	X	X	Wyoming	X	X	X	
Montana	X	X	X	X					

CHAPTER 2: BENZODIAZEPINE USE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND THE RISK OF ACTUE EXACERBATIONS.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) refers to lung diseases, mainly emphysema and chronic bronchitis, which obstruct air flow and interfere with normal patterns of breathing.[152-154] Prevalence estimates suggest that 12.7 million adults in the US are afflicted with the disease.[153] Currently, COPD results in more than 800,000 hospitalizations annually[155] and is the third leading cause of death in the United States.[152,153] One of the trademarks of COPD is exacerbation, which is a sudden worsening of symptoms including shortness of breath or changes in the quantity and color of phlegm. Exacerbations typically occur in patients with COPD two to three times per year and their cause in largely unknown.[155]

Patients who suffer from COPD commonly experience symptoms related to insomnia,[156-159] anxiety and depression. Budhiraja et al.[159] estimated the prevalence of chronic insomnia in the COPD population to be approximately 27%, greater than the 10% prevalence in the general population. Symptoms related to insomnia frequently reported by patients with COPD include difficulty falling asleep, trouble staying asleep, and an increased feeling of sleepiness during the day.[156,160] Results from the Tucson Epidemiologic Study[157] found more than 50% of patients with COPD experience sleep related difficulties and 25% an excessive feeling of daytime sleepiness. Additionally, studies have found a higher prevalence of anxiety and depression in patients diagnosed with COPD compared to the general population. Utilizing a case-control study design, Di Marco et al.[161] estimated patients with COPD had a higher prevalence of anxiety (28% vs. 6%) and depression (19% vs. 6%) than controls without the disease. Kunik et al.[162] found a 51% prevalence of anxiety and a 39% prevalence of depression in patients diagnosed with COPD

receiving care through the Veteran's Affairs system. These estimates exceed those of the general population: 18% for anxiety[101] and 7% for depression.[163]

Benzodiazepines are generally an effective pharmacological treatment option and are widely prescribed for the management of symptoms related to anxiety disorders and insomnia.[11,103] Studies examining patients with COPD have found evidence of a link between benzodiazepine use and several adverse respiratory outcomes such as decreased minute ventilation,[118,119] low levels of oxygen and high levels of carbon dioxide in the blood,[119,120] and a decrease in respiratory muscle strength.[118] Moreover, joint American Thoracic Society/European Respiratory Society guidelines recommend that hypnotics such as benzodiazepines not be used in patients with severe COPD.[121]

To date there is little understanding regarding the impact benzodiazepine use on the risk of adverse respiratory outcomes among patients with COPD in the US. The current literature evaluating benzodiazepine use in this population relies on studies employing small sample sizes and patients with greater COPD severity. As a result, studies evaluating benzodiazepine use and their association with adverse respiratory outcomes at a population level are warranted. The goal of this research is to better understand how patients in the US with COPD are being treated when they have a psychiatric comorbid condition including anxiety, depression, and insomnia. This study will also provide clarity to concerns that the use of benzodiazepines in the COPD population may be associated with an elevated risk of adverse respiratory outcomes and thus impact the clinical care of these patients. The aims of this study are to estimate the prevalence of new benzodiazepine use among patients with COPD in the US and evaluate differences in the risk of acute exacerbations among patients with COPD who are identified as new users and nonusers of benzodiazepines.

METHODS

This study employs a new user, retrospective cohort using medical and pharmacy claims obtained from a large private insurer for beneficiaries in all 50 states and Washington DC between January 1, 2007 and December 31, 2009. This claims database includes de-identified information regarding beneficiary socio-demographics and codes related to interactions with the healthcare system. Beneficiaries were considered for inclusion if they had continuous medical and pharmacy benefits coverage for the duration of the study period, had a diagnosis code in the medical claims data for chronic bronchitis (ICD-9 code: 491.xx) emphysema (492.xx), or chronic airway obstruction, not elsewhere classified (496.xx), did not have a diagnosis of asthma (493.xx excluding 493.2), were at least 40 years of age, and did not have a prescription drug claim for a benzodiazepine during the 180 days prior to the index date.

Ascertainment of benzodiazepine use

Benzodiazepine exposure was evaluated using dispensing records from a pharmacy claims database and identified through the use of national drug codes. Beneficiaries were considered to be an incident benzodiazepine user if they had a prescription drug claim for the medications consisting of alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam, and trizolam following 180 days without a prescription drug claim for a benzodiazepine prior to the index date. The index date was defined as the date of the first prescription drug claim for a benzodiazepine following 180 days without a benzodiazepine prescription drug claim. Incident benzodiazepine use was only considered once during the study period, at the first occurrence, regardless if the beneficiary met the definition for incident benzodiazepine use multiple times.

Nonusers of benzodiazepines were identified based on not having a prescription drug claim for any of the benzodiazepine medications listed above. For these beneficiaries, index dates were randomly assigned based on the distribution of time to the first prescription drug claim for a benzodiazepine in those identified as incident benzodiazepine users.

The follow-up time for each beneficiary started on the index date and was extended until the earliest of an acute COPD exacerbation, 30 days after the index date, or the end of the study period. This approach was intended to emulate an intention-to-treat analysis similar to that employed by randomized controlled trials.

Propensity score matching

To account for baseline differences in the severity of COPD and to estimate the effect of incident benzodiazepine use on the risk of acute exacerbations in the COPD population, users and non-users of benzodiazepines were matched using propensity score matching methods. The propensity score for each patient in the study population was estimated through logistic regression as the probability of initiating benzodiazepine therapy during the study period, based on demographic characteristics, index date, measures of general health, and healthcare utilization intensity. Matching was performed using the Greedy Matching algorithm[164] without replacement and one-to-one and one-to-many matching methods were explored.

Ascertainment of acute exacerbation

The outcome of interest was the occurrence of an acute COPD exacerbation within 30 days following the index date. Acute exacerbations were identified in the medical claims database where the primary or admission diagnostic ICD-9 code was 491.21. Only the date of the first acute exacerbation within the 30-day follow-up timeframe after the index date was

utilized. The 30-day follow-up period was chosen as acute exacerbations related to benzodiazepine use were expected to occur relatively soon after their initiation.

Statistical analysis

Baseline characteristics of benzodiazepine users and nonusers were compared before and after propensity score matching. Standardized differences were calculated to compare users and nonusers on all covariates before and after propensity score matching. The rates of experiencing an acute exacerbation within 30 days after the index date were estimated and compared using cumulative incidence function curves. Tests of equality of the cumulative function curves were performed using Gray's method.[165] Cox proportional hazard models estimated the hazard ratio (HR) and accompanying 95% confidence interval (CI) of experiencing an acute exacerbation associated with incident benzodiazepine use within 30 days after initiation. Sensitivity analyses were conducted to test the robustness of the results. For beneficiaries who did fill a benzodiazepine prescription during the study period, those whose prescription was for seven days or less were excluded to examine if the restriction of non-acute benzodiazepine use was associated with an increased risk in an acute exacerbation. Additionally, a second sensitivity analysis was conducted where beneficiaries were also matched on the number of claims for an acute exacerbation in the database. Data use was approved by the Institutional Review Board at the University of Kentucky. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC). The a priori level of significance was set at 0.05.

RESULTS

A total of 92,461 beneficiaries with COPD met the inclusion criteria (Figure 2.1). Of these 15,723 (17.1%) were identified as incident benzodiazepine users. After propensity score matching 13,265 incident benzodiazepine users were matched to at least one benzodiazepine

nonuser. No propensity score match was found for 2,458 (15.6%) incident benzodiazepine users. Kernel density estimates of the propensity score distributions between the user and nonuser groups are shown in Figure 2.2a and Figure 2.2b. The distribution for the non-matched sample is depicted in Figure 2.2a while Figure 2.2b presents the matched sample. A comparison of baseline demographic and health characteristics between incident benzodiazepine users and nonusers is presented in Table 2.1. After matching incident benzodiazepine users and nonusers were well matched on all baseline characteristics with the exception of psychiatric disorders where the prevalence was greater among benzodiazepine users. Benzodiazepines are indicated and commonly prescribed for these conditions and to account for these observed differences the psychiatric disorders of anxiety, depression, and insomnia were considered in the hazard ratio calculation.

The logistic regression model used to derive propensity scores for the likelihood of initiating benzodiazepine therapy is presented in Table 2.2. The results indicate that among beneficiaries with COPD incident benzodiazepine use was more likely among females (AOR: 1.34; 95% CI: 1.24, 1.39) and those diagnosed with anxiety (AOR: 5.21; 95% CI: 4.94, 5.49), depression (AOR: 1.61; 95% CI: 1.53, 1.70), or insomnia (AOR: 3.18; 95% CI: 2.97, 3.40). Those taking oral corticosteroids also had increased odds of incident benzodiazepine use (AOR: 1.28; 95% CI: 1.20, 1.36). Beneficiaries were also more likely to be incident benzodiazepine users if they had a diagnosis for the comorbidities of other ischemic heart disease (AOR: 1.13; 95% CI: 1.08, 1.19), cerebrovascular disease (AOR: 1.14; 95% CI: 1.08, 1.20), lung cancer (AOR: 1.67; 95% CI: 1.50, 1.85), cancers excluding lung cancer (AOR: 1.17; 95% CI: 1.12, 1.22), weight loss (AOR: 1.12; 95% CI: 1.04, 1.22) or essential hypertension (AOR: 1.20; 95% CI: 1.02, 1.43). Beneficiaries with COPD who were black were less likely to be incident benzodiazepine users (AOR: 0.56; 95% CI: 0.52, 0.61). Additionally, increasing age was associated with a decreased likelihood of

incident benzodiazepine use (AOR: 0.98; 95% CI: 0.98, 0.98) as was a lower overall general health status as depicted by the Charlson Comorbidity Index (AOR: 0.69; 95% CI: 0.62, 0.71).

Prior to matching 148 (0.9%) of incident benzodiazepine users and 473 (0.4%) of nonusers had a claim for an acute exacerbation within 30 days of the index date. After matching 127 (1.0%) of incident benzodiazepine users and 272 (0.6%) of nonusers had an acute exacerbation claim within 30 days of the index date. Results of the Cox proportional hazard model are shown in Table 2.3. Compared to nonusers, incident benzodiazepine users with COPD were at a 26% higher risk (HR: 1.26; 95% CI: 1.01, 1.57) for having a claim for an acute exacerbation within the 30 days following the index date. The cumulative incidence of acute exacerbations during the 30-day follow-up was determined to be greater for incident benzodiazepine users versus nonusers ($p<0.01$) beginning immediately after benzodiazepine initiation and continuing onwards (Figure 2.3).

The findings from the sensitivity analyses are presented in Table 2.3. The finding from the model only examining non-acute benzodiazepine use supported the findings of this study. When compared to nonusers, non-acute incident benzodiazepine users were at a statistically higher risk (HR: 1.28; 95% CI: 1.01, 1.63) of having a claim for an acute exacerbation within 30 days of the index date. When all incident benzodiazepine users were considered but also matched on the number of claims for an acute exacerbation prior to the index date the association between incident benzodiazepine use and an acute exacerbation within 30 days was no longer statistically significant, however, the HR and most of the 95% CI were greater than 1 (HR: 1.11; 95% CI: 0.89, 1.39).

DISCUSSIONS

This study of a nationally representative sample of privately insured adults in the US with COPD showed that incident benzodiazepine use was associated with an increased risk of an acute exacerbation within 30 days of initiation. Findings from the sensitivity analyses supported this finding. However, the point estimates were attenuated and were no longer statistically significant suggesting the presence of confounding and selection bias related to these factors. This observed association is consistent with previous finding that have reported a relationship between benzodiazepine use and adverse respiratory outcomes in the COPD population. Vozoris et al.[123] recently evaluated the association between new benzodiazepine use and the risk of adverse health outcomes among older patients in Ontario with COPD. Their findings suggested that new benzodiazepine use is associated with a greater risk of outpatient respiratory exacerbations and emergency department visits for COPD or pneumonia.

An important finding in the present study was the observation that incident benzodiazepine use in the COPD population is common as we found it to occur in 17% of the study cohort despite American Thoracic Society/European Respiratory Society guidelines cautioning against their use.[121] While this finding is less than that reported by Vozoris et al.[122] where new benzodiazepine use was found in roughly one-third of COPD patients, that study examined older patients with COPD and existing evidence demonstrates than benzodiazepines are more likely to be prescribed to older individuals.[166]

The results of the logistic regression model indicate that receipt of an oral corticosteroid prescription was associated with an increase in the odds of new benzodiazepine use. It is possible that receipt of an oral corticosteroid prescription may be related to an acute

exacerbation[167] experienced in the outpatient setting where the patient did not utilize the healthcare system for treatment.

This study found that new benzodiazepine use was associated with an increased risk of experiencing an acute exacerbation within 30 days of benzodiazepine initiation; however, the absolute risk was small, occurring in 0.9% of new benzodiazepine users and 0.4% of nonusers. Furthermore, the sensitivity analyses revealed selection and confounding by factors related to benzodiazepine use. Due to the high prevalence of COPD in the US, especially in states such as Kentucky and Alabama where the prevalence is estimated to be greater than 9%, this small risk is clinically important at the population level.

Limitations to this study exist. Due to the observational nature of this study an association between variables does not imply causality as unmeasured difference between the benzodiazepine user and nonuser groups may have influenced the findings. Secondly, as this study employs data for a privately insured, continuously enrolled cohort the overall COPD population may not be accurately represented. This study also could not account for benzodiazepine medications acquired outside the healthcare system of paid for out of pocket. Another potential limitation is that dispensed benzodiazepine prescriptions may not be equivalent to benzodiazepines consumed. Not all patients who experienced an acute exacerbation may have sought treatment from a healthcare provider and thus were not documented in the data, however, it is expected that no systematic differences existed between the user and nonuser groups in their propensity to access the healthcare system for this event and thus the results would not be influenced.

The findings of this study identify benzodiazepines as a potential risk factor associated with the occurrence of an acute exacerbation in a large sample of privately insured adults with

COPD. This highlights concerns regarding the potential misuse of benzodiazepines in clinically vulnerable populations, including those with COPD. Given that patients with COPD are often afflicted with symptoms related to anxiety, depression, and insomnia, which are commonly managed with benzodiazepines, the potential of experiencing an acute exacerbation should be considered in treatment decisions. Inappropriate benzodiazepine use, especially in clinically vulnerable populations, can lead to adverse drug event and adverse drug reactions, which are potentially avoidable. These can result in a dramatic negative effect on a patient's health outcomes and quality of life. Based on the findings from this study further research is warranted regarding the relationship between benzodiazepine use in the COPD population, especially is it pertains to other COPD related health outcomes.

Table 2.1. Characteristics of benzodiazepine users and nonusers with COPD.

	Before Matching			*After Matching*		
	Benzodiazepine users	*Benzodiazepine nonusers*	*Std. Diff*[d]	*Benzodiazepine users*	*Benzodiazepine nonusers*	*Std. Diff*[d]
Beneficiaries[a]	15,723	76,738		13,265	37,828	
COPD Exacerbation						
Acute exacerbation within 30 days of index date	148 (0.9)	473 (0.4)	0.07	127 (1.0)	272 (0.7)	0.03
Sex						
Male	7,294 (46.4)	43,594 (56.8)		6,273 (47.5)	19,133 (50.4)	0.00
Female	8,429 (53.6)	33,142 (43.2)	0.21	6,992 (52.5)	18,695 (49.6)	0.00
Age						
Median age[b] (IQR[c])	71 (66-77)	72 (67-78)	-0.13	72 (67-78)	73 (68-78)	-0.06
Race						
White	12,806 (81.4)	59,790 (77.9)	0.11	11,932 (90.0)	33,871 (89.4)	0.01
Black	877 (5.6)	7,069 (9.2)	-0.15	847 (6.4)	2,598 (6.9)	-0.02
Other	523 (3.3)	2,191 (2.9)	0.03	486 (3.7)	1,359 (3.7)	0.00
Psychiatric Disorder						
Anxiety	4,954 (31.5)	4,403 (5.7)	0.70	3,581 (27.0)	4,025 (10.6)	0.43
Depression	4,516 (28.7)	8,177 (10.7)	0.47	3,439 (26.0)	6,588 (17.4)	0.21
Insomnia	2,309 (14.7)	2,709 (3.5)	0.40	1,645 (12.5)	2,427 (6.4)	0.21
Comorbidities						
Acute myocardial infarction	687 (4.4)	2,598 (3.4)	0.05	581 (4.4)	1,470 (3.9)	0.02
Other ischemic heart disease	6,475 (41.2)	25,928 (33.8)	0.15	5,575 (42.0)	15,293 (40.0)	0.03
Congestive heart failure	3,417 (21.7)	13,447 (17.5)	0.11	2,975 (22.5)	8,031 (21.0)	0.03
Cerebrovascular disease	3,788 (24.1)	13,427 (17.5)	0.16	3,212 (24.3)	8,373 (22.2)	0.05
Diabetes	5,724 (36.4)	25,533 (33.3)	0.07	4,970 (37.4)	13,994 (37.3)	0.01
Lung cancer	750 (4.8)	1,885 (2.5)	0.12	587 (4.4)	1,468 (3.9)	0.03
Cancers excluding lung cancer	6,371 (40.5)	25,129 (32.7)	0.16	5,310 (39.9)	14,662 (38.7)	0.03
Cardiac arrhythmia	4,397 (28.0)	17,527 (22.8)	0.12	3,745 (28.4)	10,140 (26.7)	0.03
Pulmonary circulation disorder	1,273 (8.1)	4,504 (5.9)	0.09	1,086 (8.1)	2,787 (7.4)	0.03
Weight loss	1,187 (7.5)	3,783 (4.9)	0.11	954 (7.2)	2,296 (6.1)	0.05
Essential hypertension	12,131 (77.2)	53,806 (70.1)	0.16	10,349 (78.1)	28,838 (76.0)	0.04
Any hypertension	12,322 (78.4)	54,946 (71.6)	0.16	10,522 (79.4)	29,387 (77.4)	0.04
Tobacco user	4,665 (30.0)	17,287 (22.5)	0.16	3,756 (28.2)	9,657 (25.7)	0.06
Medications used						
Short/long acting β-agonists	2,663 (16.9)	11,193 (14.6)	0.06	2,253 (17.0)	6,128 (16.4)	0.02
Inhaled corticosteroids	2,373 (15.1)	9,388 (12.2)	0.08	1,957 (14.9)	5,386 (14.3)	0.01
Oral corticosteroids	3,179 (20.2)	11,473 (15.0)	0.14	2,605 (19.8)	7,023 (18.7)	0.03
Theophylline	103 (0.7)	347 (0.5)	0.03	90 (0.7)	234 (0.6)	0.01
Healthcare utilization						
Median number of healthcare claims (IQR[c])	26 (14-49)	22 (11-43)	0.11	27 (14-50)	26 (13-49)	0.01
Median number of prescription claims (IQR[c])	51 (24-94)	44 (16-89)	0.11	53 (26-98)	53 (22-102)	0.00

[a] Data are presented at n(%) unless otherwise noted

[b] Median age assessed at index date

[c] Interquartile range

[d] A standardized difference of >0.10 is considered a potentially meaningful difference

Table 2.2. Propensity score model of incident benzodiazepine use.

Variable	*Odds Ratio*	*95% Confidence Interval*	
Year			
Index year[1]	1.05	1.02	1.09
Sex			
Male	Ref.		
Female	1.34	1.28	1.39
Race			
White	Ref.		
Black	0.56	0.52	0.61
Other	1.04	0.93	1.15
Age			
Age	0.98	0.98	0.98
Psychiatric Disorder			
Anxiety	5.21	4.94	5.49
Depression	1.61	1.53	1.70
Insomnia	3.18	2.97	3.40
COPD Medications			
Beta-agonists	0.96	0.90	1.03
Inhaled corticosteroids	1.03	0.97	1.11
Oral corticosteroids	1.28	1.20	1.36
Theophylline	1.19	0.93	1.54
Comorbidities			
Acute myocardial infarction	0.93	0.84	1.03
Other ischemic heart disease	1.13	1.08	1.19
Congestive heart failure	1.02	0.96	1.08
Cerebrovascular disease	1.14	1.08	1.20
Diabetes	0.99	0.94	1.03
Lung cancer	1.67	1.50	1.85
Cancers excluding lung cancer	1.17	1.12	1.22
Cardiac arrhythmia	1.02	0.97	1.07
Pulmonary circulation disorder	1.06	0.98	1.15
Weight loss	1.12	1.04	1.22
Essential hypertension	1.20	1.02	1.43
Any hypertension	0.88	0.74	1.05
Tobacco user	1.05	1.00	1.10
Healthcare Utilization			
Total number of medical claims	1.00	1.00	1.00
Total number of prescription claims	1.00	1.00	1.00
General Health State			
Charlson Comorbidity Index	0.69	0.62	0.77

[1] Reference year is 2007

Table 2.3. Comparison of hazard ratios.

Model	*Number of incident benzodiazepine users*	*Number of outcomes among incident benzodiazepine users*	*Number of non benzodiazepine users*	*Number of acute exacerbation among non benzodiazepine users*	*Hazard ratio*	*95% CI*
Study model	13,265	127	37,828	272	1.26	(1.01, 1.57)
Matching on acute exacerbation	13,265	125	37,763	288	1.11	(0.89, 1.39)
Elimination of acute benzodiazepine use	10,757	105	30,878	222	1.28	(1.01, 1.63)

Figure 2.1. Sample selection flow chart.

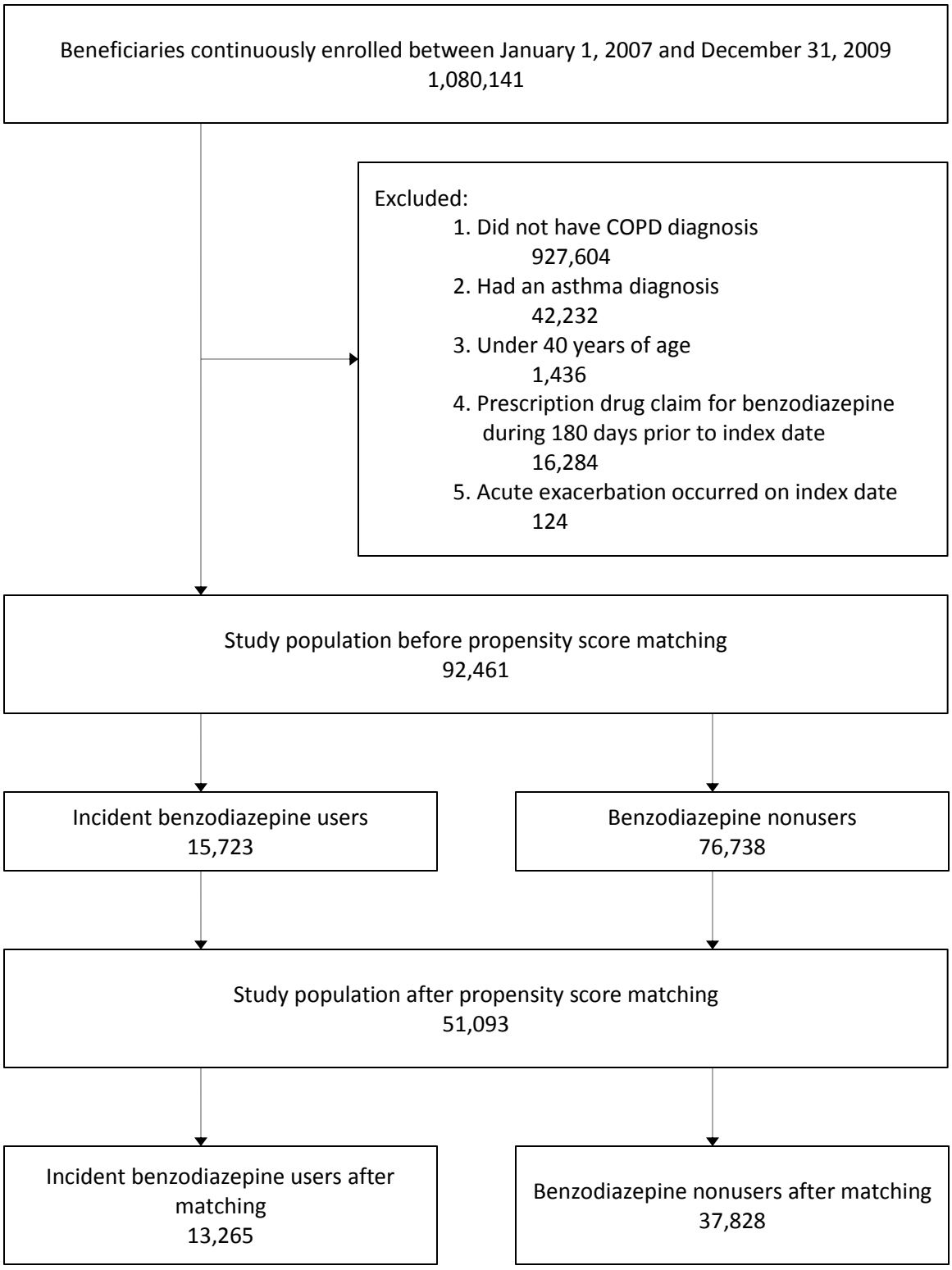


Figure 2.2a. Propensity score distributions for incident benzodiazepine users and nonusers before propensity score matching.

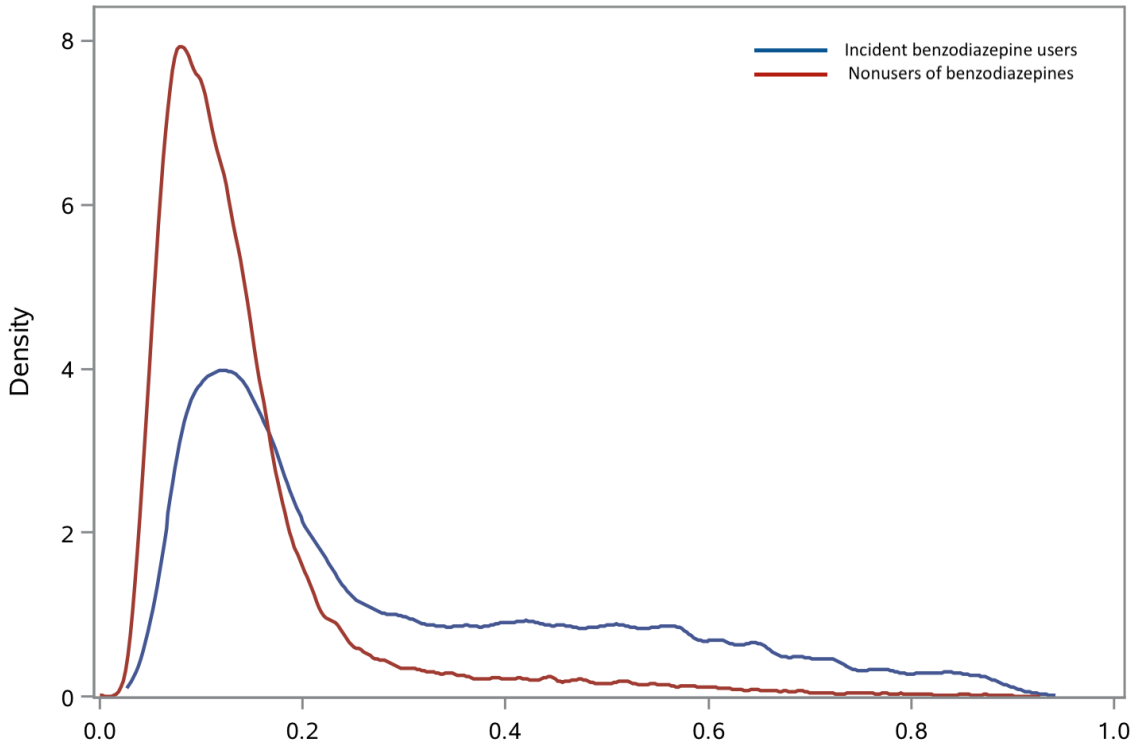


Figure 2.2b. Propensity score distributions for incident benzodiazepine users and nonusers after propensity score matching.

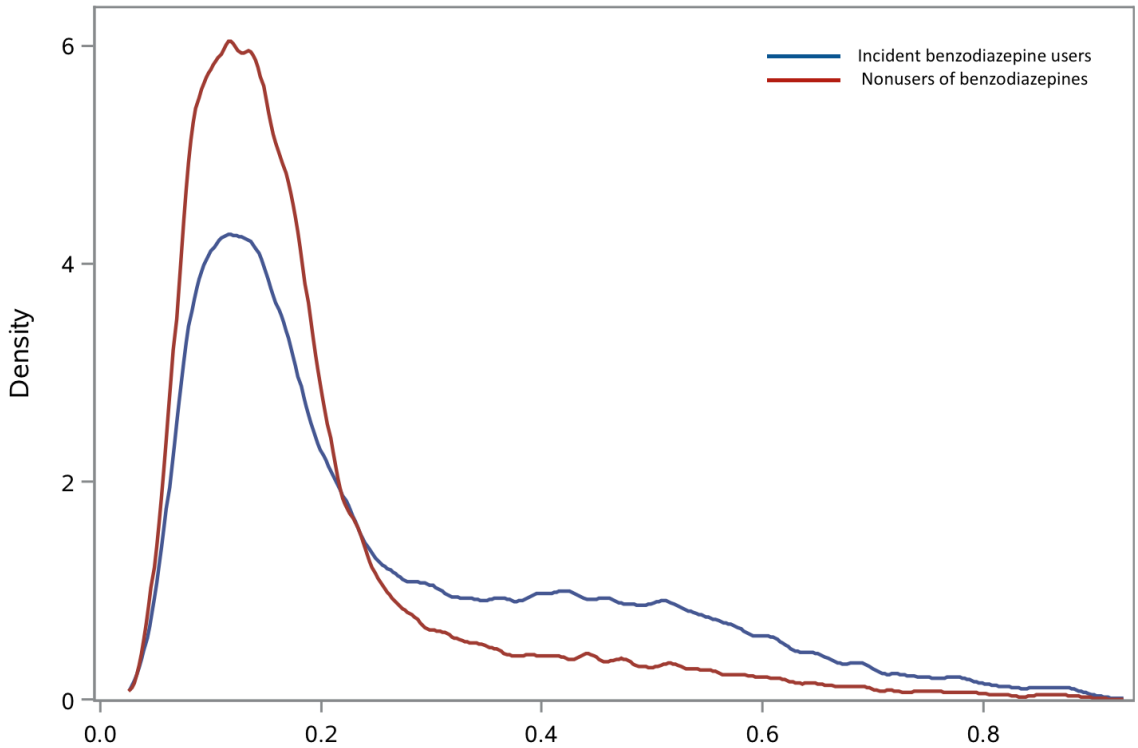
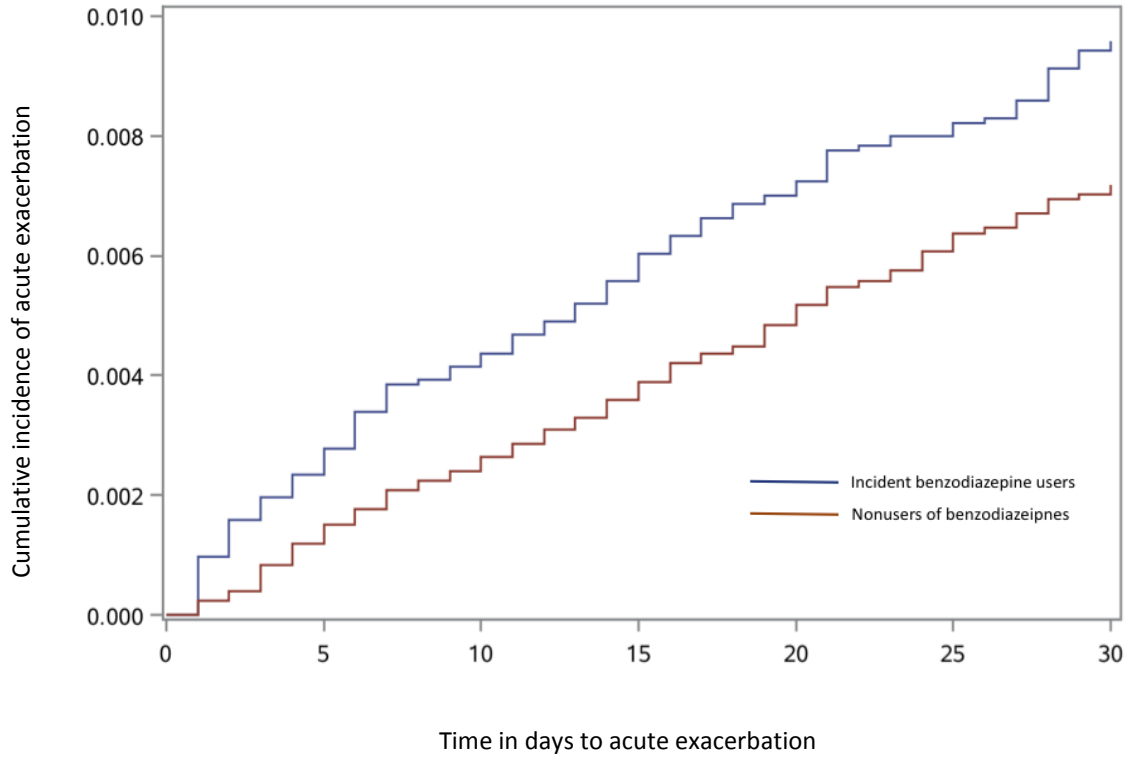


Figure 2.3. Cumulative incidence function curves for acute exacerbations among incident benzodiazepine users and nonusers occurring within 30 days of the index date.



CHAPTER 3: SEX DIFFERENCES IN BENZODIAZEPINE USE IN THE HIV-INFECTED POPULATION.

INTRODUCTION

The burden of psychiatric disorders in the HIV-infected population exceeds that of the general US population[116,168] and the 12-month prevalence of psychiatric disorders is estimated at 48%.[116] This estimate is nearly two times greater than the 26% prevalence rate estimated in the general population.[101] The most commonly detected psychiatric disorders in the HIV-infected population include major depression, dysthymia, and generalized anxiety disorder.[116] Additionally, patients who suffer from psychiatric disorders are likely afflicted with symptoms of insomnia.[102] The estimated prevalence rate for anxiety disorders may be as high as 38%,[169] 32% for depression,[116] and 78% for insomnia,[170] in the HIV-infected population. Each of these estimates exceeds those of the general population: 18% for anxiety,[101] 7% for depression,[163] and 30% for insomnia.[171] Managing symptoms of these comorbidities is especially important in HIV-infected patients as they are associated with suboptimal adherence to antiretrovirals.[117,168] High levels of adherence are necessary to achieve optimal viral load suppression and mitigate the development of drug-resistant HIV infection.[172,173]

Benzodiazepines are the most frequently used psychotropic drug class,[11] and are widely prescribed for the management of symptoms related to anxiety, insomnia, and depression.[103,174] Concerns exist regarding benzodiazepine use in the HIV-infected population due to potential interactions with antiretroviral therapy[175,176]. Moreover, due to their abuse/misuse potential, benzodiazepines are not recommended for patients with a substance abuse history, a common problem among the HIV-infected population.[116] To date, few studies have compared the prevalence of benzodiazepine use in the HIV-infected and uninfected populations. Furthermore, no studies have examined benzodiazepine usage by sex despite evidence suggesting prevalence

rates of psychiatric disorders differ between males and females in the general and HIV-infected populations.[163,177,178] The current study uses insurance claims data to examine whether HIV-infected patients are more likely to fill a benzodiazepine prescription than uninfected patients and, investigate sex differences in the likelihood of filling a benzodiazepine prescription among HIV-infected and uninfected patients.

METHODS

We established a four state nationally representative, population-based cohort using data from a large private insurance claims database from January 2007 to December 2009. This claims database includes patient socio-demographics and codes related to interactions with the healthcare system. Beneficiaries were included if they resided in Kentucky, Maryland, North Carolina, or Washington, were between 19 and 64 years of age, and had at least one healthcare claim in 2007 followed by a subsequent claim in either 2008 or 2009. Beneficiaries were identified as HIV-positive if they had at least one healthcare claim in 2007 with the ICD-9 code '042' (Human Immunodeficiency Virus (HIV) disease). The outcome of interest was filling a benzodiazepine prescription. Benzodiazepine fills during the study period were represented by a claim for any benzodiazepine identified using national drug codes. We considered the following covariates assessed in the year 2007: sex, age, race, education, state of residence, continuous insurance enrollment, substance abuse treatment (e.g. residential or non-residential treatment facility), and psychiatric disorders. Bivariate analysis examined the association between HIV-infection and benzodiazepine use. Multivariate logistic regression models adjusted for covariates identified above were used to estimate the adjusted odds ratio (AOR) of filling a benzodiazepine prescription for HIV-infected patients. We examined the presence of interaction between HIV-infection and the covariates using backwards elimination. Statistical significance

was considered using the Wald χ^2 p-value associated with the interaction term as well as clinically meaningful differences by comparing stratum specific odds ratios. Data use was approved by the XXXXX Institutional Review Board. Statistical analysis was conducted using Stata 12.0 (StataCorp., College Station, TX).

RESULTS

A total of 323,902 beneficiaries met the inclusion criteria for this study. Of these beneficiaries 106 were excluded due to duplicate or conflicting information. Overall, our study cohort consisted of 323,796 beneficiaries, 723 were identified as HIV-infected. Baseline characteristics and benzodiazepine utilization for HIV-infected and uninfected patients are shown in Table 1. Compared to the uninfected population the HIV-infected population had a greater proportion of men (80% versus 44%) and blacks (21% versus 7%). The HIV-infected population also had a greater proportion of patients with a diagnosis of depression (12% versus 8%) or insomnia (6% versus 3%). We observed a greater proportion of HIV-infected patients filled a benzodiazepine prescription during the study period (24% versus 19%) with alprazolam, diazepam, and lorazepam being the most commonly filled benzodiazepines.

Figure 1 shows the AOR of filling a benzodiazepine prescription for HIV-infected patients stratified by sex relative to the overall estimate of HIV-infected patients. The overall AOR demonstrates that without stratifying by sex, HIV-infected patients have 1.68 times greater odds of filling a benzodiazepine prescription than uninfected patients (95% CI: 1.39, 2.02). When stratified by sex, results from the multivariate regression showed HIV-infected males are 1.68 times more likely to fill a benzodiazepine prescription than uninfected males, adjusting for covariates (95% CI: 1.05, 2.67), while no statistical difference was observed between HIV-infected and uninfected females (AOR: 1.12, 95% CI: 0.73, 1.70). Interaction between HIV-

infection and age, race, education, substance abuse treatment, and psychiatric disorders was considered but statistical significance was not achieved at the 0.05 level nor were there any clinically meaningful differences between the strata.

In the overall population the likelihood of filing a benzodiazepine prescription is influenced by the patient's age, sex, and race, along with treatment for substance abuse and psychiatric disorder diagnosis. With each additional ten years patients age, their odds of filling a benzodiazepine prescription increase 21% (AOR: 1.21, 95% CI: 1.20, 1.22). Additionally, males are less likely than females (AOR: 0.62, 95% CI: 0.61, 0.63) and nonwhite patients are less likely than white patients to fill a benzodiazepine prescription (AOR: 0.72, 95% CI: 0.70, 0.74). Furthermore, treatment for substance abuse (AOR: 1.27, 95% CI: 1.14, 1.42), or having a diagnosis of anxiety (AOR: 5.99, 95% CI: 5.81, 6.18), depression (AOR: 2.48, 95% CI: 2.42, 2.56), or insomnia (AOR: 2.78, 95% CI: 2.65, 2.90) increase the odds of filling a benzodiazepine prescription.

DISCUSSIONS

This study demonstrates that HIV-infected patients are more likely to fill a benzodiazepine prescription than uninfected patients. Furthermore, we show HIV-infected males are more likely than uninfected males to fill a benzodiazepine prescription, with no observed difference between HIV-infected and uninfected females. This difference is notable as concerns exist regarding benzodiazepine use in the HIV-infected population due to their high abuse/misuse potential and the link between substance abuse and poor medication adherence.[179,180]

The overall difference in the odds of filling a benzodiazepine prescription between HIV-infected and uninfected patients may be related to the high prevalence of psychiatric disorders

in this population.[116] However, we adjusted for these conditions in our models suggesting additional factors shown to be associated with benzodiazepine use in this population and not captured within claims data, such as exposure to stressful events related to HIV serostatus and disclosure,[181] may explain the differences in benzodiazepine use between the HIV-infected and uninfected populations. The high prevalence of substance abuse and dependence in the HIV-infected population[116] should also be considered as an explanation of the observed differences in benzodiazepine use. Few studies have compared benzodiazepine use in the HIV-infected and uninfected populations and to our knowledge, this study is the first to examine differences in receipt of benzodiazepines by sex. Roux et al.[181] investigated factors associated with regular benzodiazepine use in HIV-infected patients but as this study included HIV-infected patients only, comparisons to the uninfected population were not made.

Reasons for observed differences between males and females in our study may be related to underlying differences in the prevalence of psychiatric disorders, differences in stigmatization, as well as differences in overall health care utilization between HIV-infected men and women. Lopes et al.[177] showed HIV-infected men were more likely than uninfected men to have a specific DSM-IV diagnosis with no observed differences among women. Our results support these findings as we found HIV-infected men more likely than uninfected men to fill a benzodiazepine prescription, with no observable differences between women. Additionally, Roux et al.[181] found that individuals belonging to the injecting drug use (IDU) and men who have sex with men (MSM) HIV-transmission groups were more likely than their heterosexual HIV-transmission group counterparts to report regular benzodiazepine use. This finding is likely associated with IDUs and MSM group members perceiving and facing greater discrimination and stigmatization.[182] Evidence exists of differences in healthcare utilization between HIV-infected

men and women. Hellinger and Encinosager[183] found HIV-infected men were more likely than HIV-infected women to receive antiretroviral therapy and costlier medications.

Limitations to this study exist. First, this study uses data from a private insurance claims database for four states, and may not accurately represent the overall HIV-infected or uninfected populations. Also, this study does not account for the number of benzodiazepine prescriptions filled or the quantity and dosages of those prescriptions. Additionally, we cannot account for prescriptions acquired through family and friends or paid for using cash. Finally, while our results show HIV-infected patients are more likely to fill a benzodiazepine prescription, we did not differentiate between appropriate and inappropriate use.

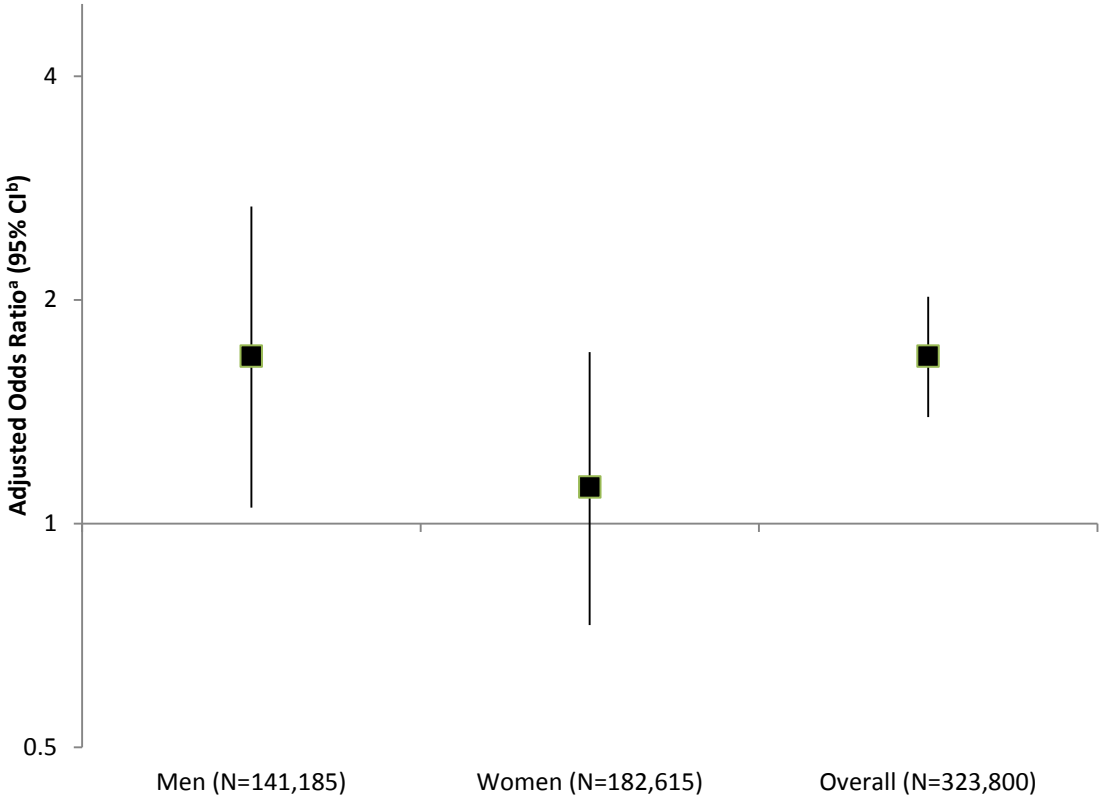
Despite these limitations, our findings demonstrate HIV-infected patients, especially HIV-infected males, are more likely to use benzodiazepines. Our findings, in combination with evidence demonstrating sex differences in psychiatric disorders, show the need for further research evaluating reasons for observed differences. Furthermore, intervention studies targeting this at-risk population to reduce the risk of substance abuse and improve HIV clinical care are warranted.

Table 3.1. Comparison of demographics of HIV-infected and HIV-uninfected patients.

	HIV N=723		*HIV-uninfected N = 323,073*		*p-value*
Variables	n	%	n	%	
Benzodiazepine Usage					
Filled Benzodiazepine Prescription	174	24%	60,420	19%	< 0.001
State of Residence					
Kentucky	67	9%	36,698	11%	0.077
Maryland	193	27%	59,635	18%	< 0.001
North Carolina	339	47%	177,680	55%	< 0.001
Washington	124	17%	49,060	15%	0.141
Sex					
Male	578	80%	140,605	44%	< 0.001
Age					
Mean Age (for year 2007), SD[a]	43.02	8.83	41.98	11.46	0.015
Race					
White	483	67%	255,735	79%	< 0.001
Black	155	21%	23,085	7%	< 0.001
Hispanic	32	4%	11,501	4%	0.209
Other	49	7%	29,917	9%	0.021
Education					
Less than High School	6	1%	2,023	1%	0.488
High School Graduate	237	33%	112,330	35%	0.262
Some College	345	48%	139,963	43%	0.017
College Graduate	118	16%	60,340	19%	0.104
Psychiatric Diagnosis					
Anxiety	47	7%	21,386	7%	0.989
Depression	84	12%	26,026	8%	< 0.001
Insomnia	44	6%	9,973	3%	< 0.001
Substance Abuse Treatment					
Receiving Substance Abuse Treatment	5	1%	1,941	1%	0.752
Enrollment Eligibility					
Continuously Eligible	284	39%	145,518	45%	0.002
Gaps in Coverage	439	61%	177,555	55%	0.002

[a]SD: Standard Deviation

Figure 3.1. Likelihood of filling a benzodiazepine prescription among HIV-infected individuals compared to HIV-uninfected individuals stratified by sex.



Strata	Odds Ratio[a]	(95% CI[b])
Men	1.68	(1.05, 2.67)
Women	1.12	(0.73, 1.70)
Overall	1.68	(1.39, 2.02)

[a]Adjusted for state of residence, age, race, education, and enrollment eligibility (e.g. continuous insurance coverage, gaps in insurance coverage).
[b]CI: Confidence Interval.

CHAPTER 4: PROBLEMATIC BENZODIAZEPINE USE AMONG COMMERCIALLY INSURED HIV-INFECTED INDIVIDUALS IN THE UNITED STATES.

INTRODUCTION

The misuse of prescription medications is a growing public health concern in the United States. Results from the 2013 National Survey on Drug Use and Health[184] found that prescription drug misuse is the second most prevalent drug problem in the United States trailing only marijuana. Prescription medications, including benzodiazepines, prescribed for the management of symptoms related to anxiety, depression, and insomnia, are increasingly being misused by patients who take them long-term or in larger than prescribed doses. National estimates of drug-related visits to emergency departments collected by the Drug Abuse Warning Network[105] (DAWN) for the year 2011 reported that between 2004 and 2011 the number of emergency department visits for the non-medical use of benzodiazepines increased 149% from 143,500 to 357,800 visits. The DAWN report also identified benzodiazepines as being involved in 29% of all emergency department visits concerning the nonmedical use of pharmaceuticals, trailing only opioids analgesics. These estimates suggest that benzodiazepine misuse can lead to serious adverse effects and caution must be exercised regarding their prescribing and use.

Existing evidence suggests that HIV-infected individuals are often afflicted with psychiatric comorbidities that are associated with prescription drug misuse.[53,185,186] A screening of a nationally representative sample of HIV-infected patients in the United States estimated approximately one-half have a diagnosable psychiatric disorder.[116] Managing symptoms of these conditions is important as they are associated with a lower quality of life and suboptimal adherence to antiretroviral therapy.[117,187] Symptom management is frequently accomplished through the prescribing and use of benzodiazepines. In the HIV-infected population the use of

benzodiazepines is controversial due to the high prevalence of substance use disorders in this population coupled with the abuse potential of benzodiazepines. Despite this, benzodiazepine use is highly prevalent among HIV-infected individuals. Vitello et al.[188] utilized the HIV Cost and Services Utilization Study (HCSUS) and found nearly one-quarter of HIV-infected patients with a co-occurring mental disorder reported benzodiazepine use. Wixson and Brouwer[115] found that in a privately insured population HIV infection was associated with a 68% increase in the odds of filling a benzodiazepine prescription relative to those uninfected. In a survey of HIV-infected patients conducted in France, Roux et al.[181] found regular benzodiazepine use in 16% of patients. Furthermore, results from this study determined that psychosocial factors, including disclosure of HIV status, are predictors of regular benzodiazepine use.

Prescription drug misuse is a common problem in the HIV-infected population. A survey conducted by Newville, Roley and Sorensen[189] of HIV-infected patients receiving antiretroviral therapy at a San Francisco hospital found 11% of patients acknowledged misuse of prescription medications. Most of the literature examining prescription drug misuse in the HIV-infected population has primarily focused on opioid analgesics. Hansen et al.[190] found a high prevalence of opioid analgesic misuse in a homeless and marginally housed sample of HIV-infected adults in San Francisco. Silverberg et al.[191] determined that long-term prevalent prescription opioid use, defined as longer than 90 days and associated with a greater than 120 total days' supply, or ten or more dispensed prescriptions in a year, was more common among individuals infected with HIV compared to those uninfected. An analysis of the HCSUS database by Tsao et al.[192] showed increased rates of opioid misuse in patients having a history of problematic substance use. Likewise, Robinson-Papp et al.[193] found an association between problematic opioid use and having a history of a substance use or dependence disorder. This study also demonstrated that a

current psychiatric disorder and poor antiretroviral adherence were linked to problematic opioid use.

While previous studies examining prescription drug misuse in the HIV-infected population have concentrated on opioid analgesics, this study focuses on the potentially problematic use of benzodiazepine medications. Potentially problematic benzodiazepine use describes instances when the medication may be used in a manner that has not been proven effective or may lead to patient harm. One measure of potentially problematic benzodiazepine use involves long-term continuous use exceeding 120 days duration. As their long-term (> 120 days) anxiolytic efficacy has not been evaluated, benzodiazepines are only recommended for short-term use, with the exception of managing symptoms related to panic or seizure disorders in some patients.[2] Additionally, long-term benzodiazepine use carries the risk of increasing tolerance to the drug's effects and the development of dependence.[28,35] Another measure of potentially problematic benzodiazepine use involves excessive daily dosages that are greater than 40 diazepam milligram equivalents (DME) per day. Current guidelines regarding the dosing of benzodiazepines in adults under 65 years of age recommend 20 DME per day as the maximum daily dose.[194] An expert panel has defined high daily dosage of benzodiazepines indicating potentially problematic benzodiazepine use as doses greater than two-times the recommended daily maximum (i.e. 40 DME).[65] Concurrent use of prescription benzodiazepine and prescription opioid medications for non-acute purposes also constitutes potentially problematic benzodiazepine use. Rarely are benzodiazepines the preferred or sole drug of abuse; instead abuse commonly occurs in conjunction with another substance, often opioids.[16] Clinical evidence shows that benzodiazepines and opioids, when used concurrently exert a synergistic effect by increasing the rewarding and reinforcing effects of opioids.[17-23] Other measures of potentially problematic benzodiazepine use include doctor shopping and pharmacy

hopping. Doctor shopping depicts a pattern of visiting multiple prescribers to obtain prescriptions for a controlled substance (CS) medication[95,195] and pharmacy hopping describes a pattern of having CS prescriptions filled at multiple pharmacies.[196] Each of these measures has previously been found to be associated with problematic prescription drug use.[197]

The aims of this study are to estimate the prevalence of potentially problematic benzodiazepine use in a commercially insured population of HIV-infected adults and, determine if HIV-infection is associated with an increased risk of potentially problematic benzodiazepine use. In addition, this study evaluated differences in patient characteristics including sex, age, race, education, presence of a psychiatric disorder, and substance use history on the likelihood of potentially problematic benzodiazepine use among HIV-infected and uninfected patients.

METHODS

This study utilized data from a population-based cohort of privately insured beneficiaries from all 50 states and the District of Columbia from January 2007 through December 2009. Beneficiaries were included in the study cohort if they were between the ages of 19 and 64 throughout the study period, resided in the same state the entire duration of the study period, had at least one healthcare claim in 2007 followed by a subsequent claim in either 2008 or 2009, and had a claim for a least one benzodiazepine prescription during the study period regardless of quantity, days' supply, or dosage form. Benzodiazepine fills during the study period were identified using national drug codes for the medications consisting of alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam, and triazolam. HIV-infection among beneficiaries was identified if they had at least one healthcare claim in 2007 in any position for HIV-infection (ICD-9 code: '042'). The outcome of interest was potentially problematic

benzodiazepine use. The following covariates were assessed during the first year of observation: sex, age, race, education, state of residence, substance abuse treatment (e.g. residential or nonresidential treatment facility), psychiatric disorders, and alcohol abuse.

Measures of potentially problematic benzodiazepine use were identified through reviews of the literature[65] and discussions with academic pharmacists. The measures employed in this study include: duration of benzodiazepine use exceeding 120 consecutive days, daily dosages greater than 40 DMEs, having filled a prescription for an opioid medication for a duration exceeding seven days during a benzodiazepine episode, having a benzodiazepine prescription written by a minimum of four different prescribers during the study period, and filling a benzodiazepine prescription at a minimum of four different pharmacies during the study period. The duration of a benzodiazepine episode was defined as a chronological sequence of benzodiazepine dispensing with a break of no more than seven days between the end date of the prescription and the subsequent benzodiazepine prescription fill. The end date of a prescription was calculated by taking the fill date of the prescription and adding to it the days' supply of that prescription. For each benzodiazepine prescription DMEs per day were calculated based on equivalency rates proposed by Shader et al.[7] and The American Pharmacists Association.[151] Conversion to DME dosages allowed for therapeutic comparisons between each benzodiazepine dispensed. To calculate the per day dosage the equivalency rates were multiplied by the quantity and strength of the prescribed benzodiazepine and then divided by the total days' supply. Prescription opioid fills were identified through the use of national drug codes. The dispensing of an opioid medication where the days supply was less than or equal to seven days were not considered as short-term concurrent benzodiazepine and opioid use may be appropriate (i.e. opioid use for the management of acute pain in a person taking

benzodiazepines to manage symptoms of a psychiatric disorder). Individual prescribers and pharmacies were identified using unique identifiers within the database.

The distributions of baseline covariates between the HIV-infected and uninfected samples were examined. Bivariate analyses tested the association between HIV-infection and potentially problematic benzodiazepine use defined by the measures above. Multivariate logistic regression models adjusted for covariates were used to estimate the adjusted odds ratio (AOR) of potentially problematic benzodiazepine use for HIV-infected patients. The covariates described previously were added to the multivariate model based on their bivariate association with potentially problematic benzodiazepine use and were operationalized as categorical variables. Age was segregated into two categories, ages 19 to 44 years and 45 to 64 years, based on the mean age of the study population years. Race was divided into two categories, white and nonwhite. The nonwhite category was comprised of beneficiaries identified in the claims data as black, Hispanic, or other. Education was separated into two categories: high school graduate or less and more than high school education. Effect modification between HIV and the covariates was examined using the Breslow-Day test and added to the model based on clinically meaningful differences between the stratums. Data use was approved by the University of Kentucky Institutional Review Board. Statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). Statistical significance was set a priori at the 0.05 level.

RESULTS

A total of 835,025 beneficiaries met the inclusion criteria for this study. Of these beneficiaries, 3,555 were excluded due to duplicate information (i.e., multiple states of residence, conflicting years of birth), 181 were excluded because they resided outside the US at some point during the study period, and eight were excluded due to incomplete benzodiazepine

dispensing information. Overall, the study cohort consisted of 831,281 beneficiaries with 3,447 identified as HIV-infected. Baseline characteristics of the HIV-infected and uninfected populations are presented in Table 4.1. Compared to the uninfected population the HIV-infected population had a greater proportion of males (84% vs. 32%) blacks (8% vs. 4%) Hispanics (11% vs. 7%). The HIV-infected population also had a greater proportion of beneficiaries with a diagnosis of depression (24% vs. 20%) and insomnia (11% vs. 8%) compared to those uninfected with HIV.

At least one indicator of potentially problematic benzodiazepine use was found in 45% of HIV-infected patients and 31% of uninfected patients (Figure 4.1). Of these indicators, long-term continuous use exceeding 120 days duration was the most common measure of potentially problematic benzodiazepine use and was observed in 28% of HIV-infected patients compared to 16% of uninfected patients. Patients infected with HIV also were more likely than their uninfected counterparts to have benzodiazepine prescriptions written by at least four different providers (10% vs. 7%), filled by at least four different pharmacies (6% vs. 3%), have the daily dosage exceed 40 DMEs (7% vs. 5%), and have non-acute opioid use during a benzodiazepine episode (25% vs. 19%).

Results from the multivariate model suggest differences in the likelihood of potentially problematic benzodiazepine use by any measure between the HIV-infected and uninfected populations stratified by level of education and the presence of a depression or insomnia diagnosis (Figure 4.2). In this model HIV-infection alone was associated with a significant increase in the odds of potentially problematic benzodiazepine use by any measure (AOR: 1.32; 95% CI: 1.20, 1.45). Stratum-specific results show that HIV-infected patients with less education (i.e. high school graduate or less) were 1.37 times more likely (95% CI: 1.20, 1.56) to have

potentially problematic benzodiazepine use compared to HIV-infected patients who had more than a high school education while in the uninfected population those with less education were less likely to have potentially problematic benzodiazepine use (AOR: 0.76; 95% CI: 0.76, 0.77). Results show that in both the HIV-infected and uninfected populations having received a diagnosis of depression was associated with an increased likelihood of potentially problematic benzodiazepine use, however, in the HIV-infected population the likelihood was greater than that observed in the uninfected population. HIV-infected patients who had received a depression diagnosis were twice as likely (AOR: 1.99; 95% CI: 1.71, 2.32) to have potentially problematic benzodiazepine use than HIV-infected patients without a depression diagnosis while in the uninfected population those who received a diagnosis of depression, compared to those without, were only 20% more likely (AOR: 1.20; 95% CI: 1.18, 1.21) to have potentially problematic benzodiazepine use. Having been diagnosed with insomnia was also found to increase the likelihood of potentially problematic benzodiazepine use in the HIV-infected and uninfected populations. In the HIV-infected population a diagnosis of insomnia was associated with an 87% increase (AOR: 1.87; 95% CI: 1.49, 2.35) in the likelihood of potentially problematic benzodiazepine use but in the uninfected population a diagnosis of insomnia was only associated with a 23% increase in the odds (AOR: 1.23; 95% CI: 1.21, 1.25).

DISCUSSIONS

To our knowledge this is the first study to examine potentially problematic benzodiazepine use in the HIV-infected population. The present study demonstrates that HIV infection is associated with an increase in the likelihood of potentially problematic benzodiazepine use. Furthermore, among the HIV-infected population those with less education or who were diagnosed with depression or insomnia were more likely to display signs of

potentially problematic benzodiazepine use compared to those with more education or absent a depression diagnosis. In the uninfected population lower education was associated with a decrease in the odds of potentially problematic benzodiazepine use, and even though having received a diagnosis of depression or insomnia was associated with an increase in the likelihood of potentially problematic benzodiazepine use it was not as great as the association observed in the HIV-infected population. The observed findings are notable as concerns exist regarding benzodiazepine use in the HIV-infected population due to their high abuse/misuse potential. Substance abuse has been linked to poor adherence of antiretroviral therapy[179,180] and problematic benzodiazepine use may lead to increases in the cost of treating the HIV-infected population and poor clinical outcomes.

Reasons for the observed finding of HIV-infection being a risk factor of potentially problematic benzodiazepine use may be related to the high prevalence of substance abuse in this population. Evidence also suggests that chronic pain is undertreated among HIV-infected patients as physicians may have a difficult time managing chronic pain in HIV-infected patients due to the high prevalence of substance abuse concerns.[198-200] As a result of undertreated pain, HIV-infected patients may seek pain relief by concurrently taking benzodiazepines with opioid analgesics in an effort to enhance the pain relieving effects of opioids. Our finding that one quarter of HIV-infected patients had evidence of non-acute opioid use during a benzodiazepine episode lends support to this explanation; however, it is not possible to ascertain the reasons for the concurrent use.

This study also found that HIV-infected patients with less education were more likely that their more educated counterparts to have potentially problematic benzodiazepine use while the reverse was found in the uninfected population where less educated patients had a

decreased likelihood of potentially problematic benzodiazepine use. Lower educational attainment has been shown to be associated with both prescription drug misuse[201] and HIV-infection.[202] The increased odds of potentially problematic benzodiazepine use among those with less education in the HIV-infected population may be explained by links that have been shown to exist between education and health related quality of life. Murri et al.[203] showed that lower education levels were associated with poorer mental health where symptom management may involve benzodiazepine use. Lower education levels may also lead to difficulties in understanding complex HIV treatment regimens that may cause additional stress and anxiety for the patient.[203]

The differences in the odds of potentially problematic benzodiazepine use between the HIV-infected and uninfected populations based on the presences of depression may be related to demographic or behavioral factors that are unable to be captured in the claims data (i.e., HIV-related stigmas, psychosocial burdens, and the overall encumbrance of being HIV-infected). Surveys using a sample of the general US population found that men who have sex with men and injecting drug users perceive and face a greater degree of discrimination and stigmatization associated with their HIV serostatus.[182] The level of social support has also been found to be directly related to depressive symptoms experienced by patients infected with HIV.[204] Another possible explanation is HIV-infected patients with depression may be more concerned about their health status and life expectancy thus making them more likely to engage with treatment providers who monitor their medications[205] leading to increased opportunities to acquire a benzodiazepine prescription. Benzodiazepines are not specifically indicated for the management of depression however, anxiety, a condition for which benzodiazepines are indicated, is associated with depressive symptoms.[116]

In the HIV-infected population managing symptoms related to insomnia is important as they have been linked with adverse effects on the immune system[206] and medication adherence,[207,208] both which can impact disease outcomes. This may offer explanation to the finding that among HIV-infected individuals those diagnosed with insomnia were more likely than those without to have at least one indicator of potentially problematic benzodiazepine use. Estimates of the rate of sleep disturbances in the HIV-infected population vary widely (29-97%)[209] but mostly exceed that estimated in the general population (33%).[210] Existing evidences also points to a direct relationship between sleep disturbances and advanced HIV disease stage[211-213] and longer duration of HIV-infection.[206,209,214] Furthermore, a relationship between antiretroviral therapy, specifically nonnucleoside reverse transcriptase inhibitor (NNRTI), and sleep disturbances has been shown in several studies.[215-217] These previous studies may provide explanation for the finding that in the HIV-infected population the likelihood of potentially problematic benzodiazepine use among those diagnosed with insomnia is greater than the odds observed in the uninfected population.

Limitations to this study should be recognized. First, as this study employs data from a private insurance claims database the overall HIV-infected and uninfected populations may not be accurately represented. Additionally, we are unable to account for medications acquired from family or friends or prescriptions paid for with cash. Due to the observational nature of this study an association between variables does not imply causality. Another potential limitation is that dispensed medications may not be equivalent to medications consumed. More generous definitions of continuous benzodiazepine use have been employed elsewhere in the literature[65] however, when applied results from the present study were unchanged.

Despite these limitations the findings presented provide valuable information on potentially problematic benzodiazepine use in the HIV-infected population. This study supports the idea that caution should be exercised in the prescribing of benzodiazepines and other potentially abused medications in this population. Additionally, these findings highlight the need to adequately manage symptoms of depression and insomnia among this clinically vulnerable population. Furthermore, social factors including perceived stigmas and social support systems may have a valuable role in the management of HIV related symptoms. Future research should highlight HIV related health outcomes associated with potentially problematic benzodiazepine use. Interventions designed to reduce potentially problematic benzodiazepine use in this population are also warranted. Healthcare providers should take care in an effort to adequately manage symptoms of pain in the HIV-infected population while also being mindful of concerns regarding the risk of prescription drug misuse. Additionally, decreasing stigmas associated with HIV infection and mitigating daily stressors for HIV-infected patients may also reduce potentially problematic benzodiazepine use in this population. As the lifespan of the HIV-infected population continues to approach that of the uninfected population adequately managing symptoms associated with HIV and curtailing prescription drug misuse would benefit patients, payers, and society.

Table 4.1. Comparison of demographics of HIV-infected and uninfected patients.

	HIV-infected n = 3,447		*HIV-uninfected n = 827,834*	
Variable	*n*	*%*	*n*	*%*
Sex				
Male	2,886	84%	267,077	32%
Race				
White	2,463	71%	657,722	79%
Black	292	8%	31,526	4%
Hispanic	389	11%	56,018	7%
Other	289	8%	75,404	9%
Age				
Mean age (for year 2007), SD[a]	44.1	(8.4)	43.9	(11.0)
Education				
High school graduate or less	1,044	30%	282,203	34%
Some college or college graduate	2,304	67%	520,314	63%
Location				
Northeast	419	12%	84,623	10%
Midwest	494	14%	198,531	24%
South	1,943	56%	423,821	51%
West	590	17%	120,822	15%
Psychiatric disorders				
Anxiety	676	20%	178,947	22%
Depression	844	24%	169,143	20%
Insomnia	375	11%	68,739	8%
Substance abuse				
Alcohol abuse	120	3%	15,802	2%
Substance abuse treatment	35	1%	7,396	1%

[a] Standard deviation

Percentage values presented may not add to 100% due to rounding or missing values.

Figure 4.1. Measures of potentially problematic benzodiazepine use in the HIV-infected and uninfected samples.

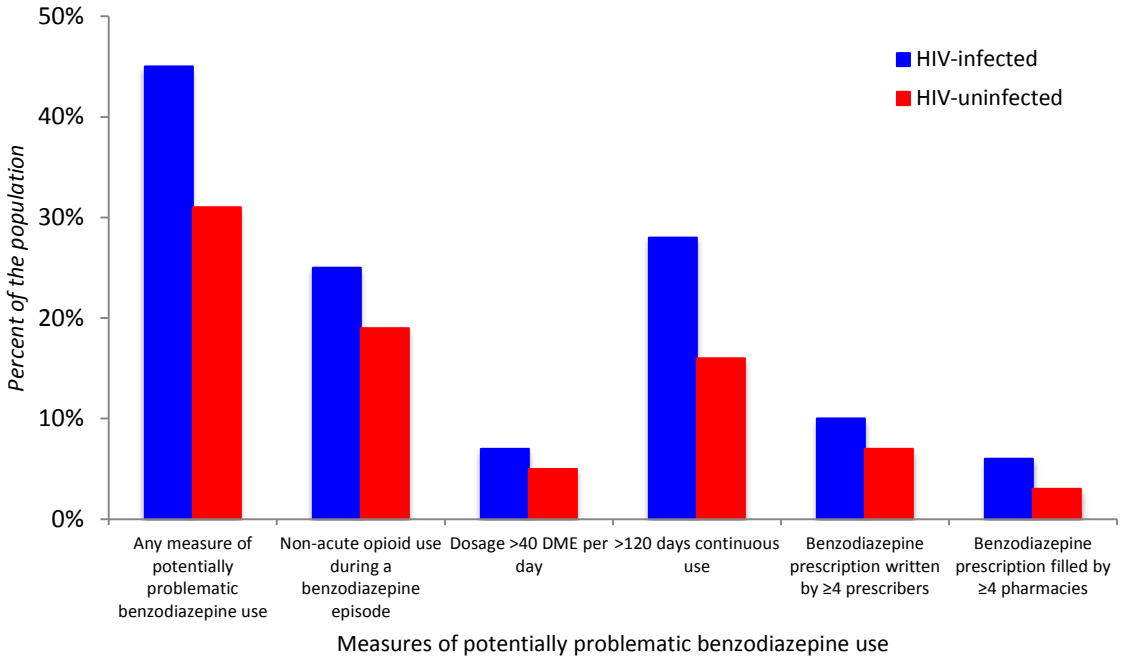
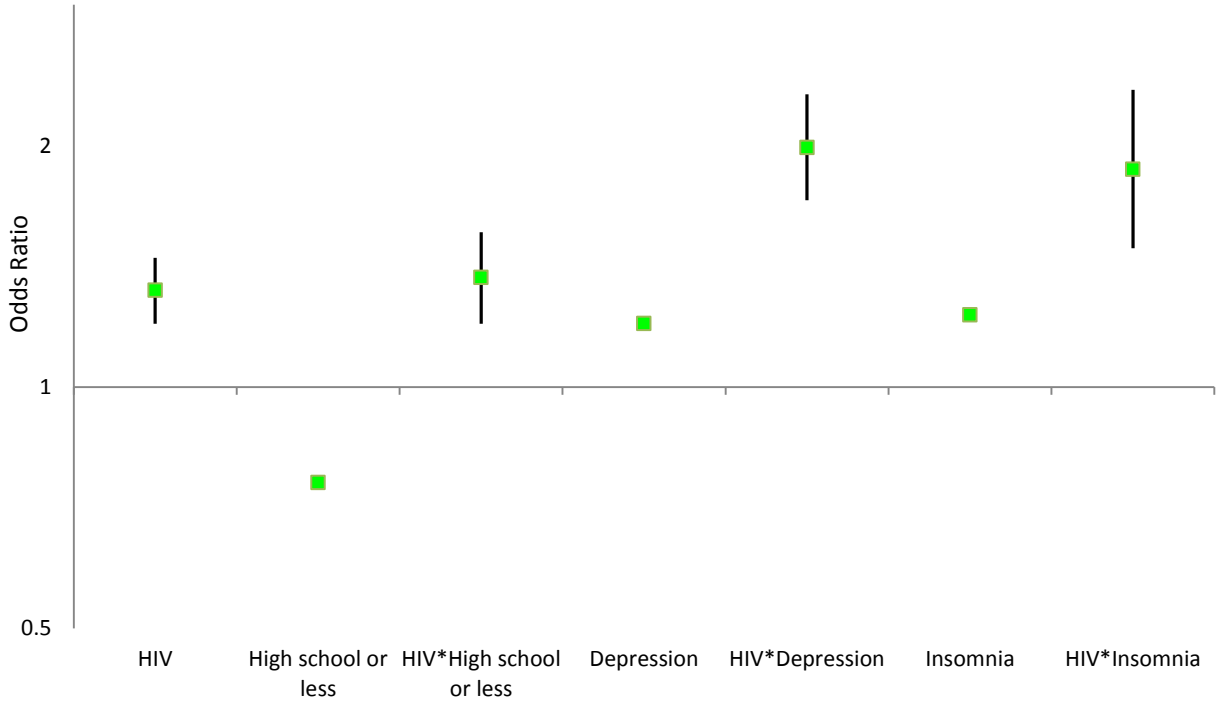


Figure 4.2. Likelihood of potentially problematic benzodiazepine use among HIV-infected patients compared to HIV-uninfected patients stratified by presence of anxiety diagnosis and age.



Strata	Odds Ratio[a]	(95% CI[b])
HIV	1.32	(1.20, 1.45)
High school or less	0.76	(0.76, 0.77)
HIV*High school or less	1.37	(1.20, 1.56)
Depression	1.20	(1.18, 1.21)
HIV*Depression	1.99	(1.71, 2.32)
Insomnia	1.23	(1.21, 1.25)
HIV*Insomnia	1.87	(1.49, 2.35)

[a] Adjusted for sex, education, race, psychiatric disorder diagnosis, substance use disorder (e.g., alcohol abuse diagnosis, treatment for substance use).
[b] CI: Confidence interval.

CHAPTER 5: IMPACT OF SOUTH CAROLINA'S PRESCRIPTION DRUG MONITORING PROGRAM ON THE USE OF BENZODIAZEPINES IN A COMMERCIALLY INSURED POPULATION.

INTRODUCTION

For patients afflicted with symptoms of anxiety and insomnia, benzodiazepines are a generally safe and effective pharmacological treatment option. Benzodiazepines are indicated for use as anxiolytics, sedatives, hypnotics, anticonvulsants, and/or skeletal muscle relaxants[2,103] and are the most frequently prescribed psychotropic drug class.[11] In 2012 benzodiazepines were the 10th most prescribed drug class in the United States with approximately 94 million prescriptions dispensed.[12] Alprazolam was the most commonly dispensed benzodiazepine with 49 million prescriptions dispensed in 2012 and ranked as the 13th most commonly dispensed medication in the United States.[13]

Although considered safer than other sedative-hypnotics drugs, such as barbiturates and meprobamate,[2,3,6] the potential exists for benzodiazepines to be abused and are therefore classified as a Schedule IV controlled substance (CS). According to the 2012 National Survey of Drug Use and Health, the estimated number of incident benzodiazepine abusers was 166,000.[104] National estimates of drug-related visits to emergency departments collected by the Drug Abuse Warning Network (DAWN) for the year 2011 reported that between 2004 and 2011 the number of emergency department visits for the non-medical use of benzodiazepines increased 149% from 143,500 to 357,800.[105] Additionally, this report identified benzodiazepines as the second leading cause of all emergency department visits concerning nonmedical use of pharmaceuticals as they were involved in 28.7% of all emergency department visits for this cause.[105] Another recent study examining data from DAWN between 2004 and 2008 reported that benzodiazepines were identified in approximately 26% of all opioid-related emergency

department visits.[106] These estimates suggest that inappropriate benzodiazepine use can lead to serious adverse effects and caution must be exercised regarding their prescribing and use.

Concerns about the growing trend of prescription drug abuse and diversion have prompted states to enact legislation to track the prescribing and dispensing of targeted CS. In 1989, New York became the first state to monitor the prescribing and dispensing of benzodiazepines through the state's triplicate prescribing program (TPP).[63-65] Several studies have since evaluated the effectiveness of the New York TPP on the state's Medicaid population and discovered that following implementation there was an immediate, significant, and sustained reduction in overall benzodiazepine use.[65,73,74] Other studies of the New York TPP highlighted concerns that policies monitoring benzodiazepine prescribing and dispensing may result in a chilling effect where patients with a chronic psychiatric disorder and/or a legitimate need for benzodiazepine therapy are unable to acquire the medication.[73] Patients may be unable to obtain appropriate CS medications either due to a physician's unwillingness to prescribe or a pharmacist being unwilling to dispense the CS. The unwillingness to prescribe or dispense a CS may be due to fear of legal investigations, fear of confidentiality violations, increased administrative burden, or confusion between the patterns of addiction and pseudoaddiction, where patients who are not being adequately treated for their condition appear, on paper, to be addicts.[76-79]

More recently, states have relied on electronic data transfer systems, more commonly referred to as prescription drug monitoring programs (PDMPs), to track the prescribing, dispensing, and utilization of targeted medications in an effort to mitigate prescription drug abuse and diversion. Reports detailing a patient's CS prescription history can be accessed upon request by healthcare providers, allowing for treatment decisions to be made at the point of

care. Additionally, because many PDMPs allow healthcare providers nearly instantaneous access to a patient's CS prescription history, use of PDMPs can alert them to possible cases of prescription drug abuse and diversion by patients. As of December 2014, 49 states have an operational PDMP.[80]

In 2006, the South Carolina state legislature signed into law legislation authorizing the state's Department of Health and Environmental Control (DHEC) Bureau of Drug Control to establish and maintain a PDMP with the intent of improving the ability to identify and prevent prescription drug diversion in an efficient and cost effective manner without impeding access to licit CS medications for patients with a legitimate need.[218] The South Carolina Reporting and Identification Tracking System (SCRIPTS) started collecting data from CS dispensers on January 1, 2008, and reporting began on February 1, 2008.[219]

All dispensing of Schedule II-IV CS in community pharmacy and outpatient settings are maintained in the SCRIPTS electronic database.[218] Dispensers, including pharmacists, physicians, and veterinarians, are required to submit their CS dispensing data for Schedule II-IV at least every 30 days, between the 1st and 15th of the month.[218] Controlled substance prescription data submitted to SCRIPTS follows a standard format and includes patient's name, address, and date of birth, prescriber's Drug Enforcement Administration (DEA) number, dispenser's (i.e., pharmacy's) DEA number, date the prescription was issued, date the drug was dispensed, National Drug Code (NDC), quantity, and approximate number of days supply of the CS medication dispensed.[218] Physicians and pharmacists may request a patient's CS prescription history report from SCRIPTS, which is usually available within minutes,[219] in order to make treatment decisions at the point of care; however, physicians and pharmacists are not required to do so.[218] Prior to accessing the SCRIPTS database, physicians and pharmacists are required to

complete an online training course and granted access by the DHEC.[220,221] Law enforcement and prosecutorial officials may also request reports from the SCRIPTS database as long as they are officially engaged in a drug-related investigation.[218,221] However, these parties cannot access the database directly. Instead, they must mail a request form to the DHEC who must approve the request before reports will be mailed via certified U.S. Mail to the requesting official.[222] In the first complete fiscal year following the implementation of SCRIPTS (July 1, 2008 – June 30, 2009) more than nine million prescription records were collected and more than 51 thousand SCRIPTS reports were produced.[223]

Policies designed to curtail the abuse, misuse, and diversion of prescription drugs (i.e., PDMPs) should be evaluated to determine if they are effectively meeting their objectives. Assessments of these policies are also necessary to ensure patient safety (i.e., permitting access to CS medication for appropriate medical care). To date, studies regarding current PDMP legislation have focused primarily on the impact concerning opioid analgesic prescribing and use. Focus on this medication class is understandable as opioid analgesics are the primary contributor to the increasing trend of drug overdose deaths in the United States.[92-94] However, other CS, specifically benzodiazepines, have been found to be a factor contributing to the substantial rise in unintentional poisoning deaths.[92,95-97] Despite the role of benzodiazepines in the US prescription drug abuse epidemic, no studies have evaluated the impact of current PDMP legislation on benzodiazepine use. Of the 49 operational PDMPs, as of December 2014, 48 have the authority to monitor the prescribing and dispensing of Schedule IV CS which includes benzodiazepines.[224]

The aim of this study is to evaluate the effect of South Carolina PDMP implementation on the dispensing of benzodiazepines. This will be accomplished by testing the following

hypotheses: 1.) Implementation of the PDMP in South Carolina will not result in a change in the rate of benzodiazepine use 2.) Implementation of the PDMP in South Carolina will not result in a chilling effect, defined as a reduction in the likelihood of filling a benzodiazepine prescription among patients with a legitimate need for the medication. Results of this study will expand the literature on PDMPs and their influence on benzodiazepine utilization.

METHODS

Using data from a large private insurance claims database containing beneficiary socio-demographic information and codes related to interactions with the healthcare system, two identically defined cohorts, one from South Carolina (study), the other from Tennessee (control), were extracted for the time period between January 2007 and December 2009. This time period constitutes the 12 months prior to and 24 months after the South Carolina PDMP was implemented. Tennessee was selected as a control state because had a PDMP in place during the entire study period and, with the exception of race, is it similar demographically to South Carolina[225] (Table 5.1). Beneficiaries were included in the analyses if they resided in South Carolina or Tennessee, were between 19 and 64 years of age during the entire study period, and were continuously enrolled (≥1090 days) during the study period. Beneficiaries under the age of 19 were excluded because the prescribing of benzodiazepines in children is an uncommon practice[65] while those 65 and older were excluded because benzodiazepines are not recommended for use in this population due to an increased risk of cognitive impairment, falls, and fractures.[52,53] Psychiatric disorders for which benzodiazepines are commonly prescribed including anxiety[103] (ICD-9 codes: 300.xx, excluding 300.4), insomnia[103] (307.41, 307.42, and 780.52), and depression[174] (296.2x, 296.3x, 300.4, and 311) were also identified in the database. These conditions were used as an indicator of legitimate benzodiazepine use to test for the

presence of a chilling effect. Beneficiaries were considered to have a specific psychiatric disorder if they had a claim at any time during the study period with a diagnosis including one of the ICD-9 diagnostic codes listed above. Benzodiazepine dispensing during the study period was represented by a claim for any benzodiazepine during a given month of the study period and identified using national drug codes.

To evaluate whether or not the implementation of the South Carolina PDMP had a greater impact on the rate of benzodiazepine use than any underlying secular trend, interrupted time series methods were employed. Time series analyses using autoregressive integrated moving average (ARIMA) models estimated changes in the level and trend of the percent of beneficiaries in each state who filled a benzodiazepine prescription during each of the 12 months prior to and 24 months after the South Carolina PDMP was implemented. According to Wagner, Soumarai, Zhang, and Ross-Degnan (2002), a change in level is described as the jump or drop in the outcome after an intervention, while a change in the trend is defined by an increase or decrease in the slope of the trend line after the intervention compared to the trend line prior to the intervention.[226] Because some prescriptions written in 2007 may not have been filled immediately and because reporting did not begin until February 1, 2008, January 2008 was excluded from this analysis. The exclusion of this time period is consistent with the methods used by Ross-Degnan et al. (2004) to evaluate the impact of the New York TPP on benzodiazepine use.[65] Moreover, a sensitivity analysis was performed to test the robustness of the results using the proportion of the continuously eligible sample who filled an opioid prescription during each of the 12 months prior to and 24 months after the South Carolina PDMP was implemented.

Panel data methods were employed to examine the effect that South Carolina PDMP implementation had on the likelihood of filling a benzodiazepine prescription. Multivariate logistic regression models using random effects and adjusted for presence of a PDMP, sex, age, race, presence of psychiatric disorders, state and month specific unemployment rates, time in months, and state of residence were used to estimate the adjusted odds ratio (AOR) and associated 95% confidence intervals (CI) of filling a benzodiazepine prescription. The covariates, with the exception of the monthly unemployment rates and the time trend variable, were operationalized as categorical variables. Age was calculated based on the beneficiary's year of birth and segregated into two categories based on the median age of the study sample, age 19 to 44 and 45 to 64. Race was divided into three categories: white, black, and other. The other race category was comprised primarily of beneficiaries identified in the database as Hispanic, or other. These beneficiaries were considered together due to their individually small representation in the study population. State and month specific unemployment rates acquired from the US Bureau of Labor Statistics were used to adjust for the economic climate that was especially volatile during the study period.[227] The unemployment variable was operationalized as a continuous variable representing the percentage of the states' workforce who were without a job, actively seeking employment, and available for work during a given month. The monthly time trend variable was operationalized as an ordinal variable taking the values 1 through 36 and included in the analysis to capture the effects that trend in one direction over time.

The first multivariate logistic regression model takes a linear form to determine factors that influence the likelihood of filling a benzodiazepine prescription among beneficiaries in the study population. This model takes the form of

$$BZD_{ikt} = \beta_0 + \beta_1 PDMP_{kt} + \beta_2 State_i + \beta_3 X_i + \beta_4 Y_i + \beta_5 Unemploy_{kt} + \beta_6 Time_t + \varepsilon$$

Where BZD_{ikt} is the odds of filling a benzodiazepine prescription for beneficiary i residing in state k in month t. The variable $PDMP_{kt}$ indicates the presence of an operational PDMP in state k in month t. $State_i$ represents the state of residence for beneficiary i. The matrix X identifies demographic characteristics for beneficiary i including sex, race, and age, and the matrix Y represents the presence of a psychiatric disorder diagnosis including anxiety, depression, and insomnia for beneficiary i. The variable $Unemploy_{kt}$ is the unemployment rate for state k in month t and $Time_t$ is the monthly time trend variable. Finally, ε is a normal independent identically distributed (i.i.d.) error term.

A difference in difference (DD) estimator, obtained by interacting the variables indicating the beneficiary's state of residence and the presence of a PDMP, estimated the effect the South Carolina PDMP had on the odds of filling a benzodiazepine prescription among South Carolina beneficiaries compared to their counterparts in Tennessee. To evaluate if the South Carolina PDMP implementation had a differential impact on specific subgroups in the population, difference in difference in difference (DDD) estimators were employed. These second order interactions were obtained by interacting the DD estimator with each of the demographic and psychiatric disorder covariates listed previously. This model takes the form of

$$BZD_{ikt} = \beta_0 + \beta_1 PDMP_{kt} + \beta_2 State_i + \beta_3 X_i + \beta_4 Y_i + \beta_5 Unemploy_{kt} + \beta_6 Time_t + \beta_7 PDMP_{kt} * State_i + \beta_8 PDMP_{kt} * State_i * X_i + \beta_9 PDMP_{kt} * State_{kt} * Y_i + \varepsilon$$

Linear combinations of coefficients estimated the odds of filling a benzodiazepine prescription among subgroups in South Carolina during the two years after the PDMP implementation compared to the odds in the year preceding the program. Statistical significance was considered using the Wald χ^2 p-value associated with the interaction term. The a priori level of significance for all analyses was set at 0.05. Data use was approved by the University of Kentucky

Institutional Review Board. Statistical analyses was conducted using Stata 13.0 (StataCorp., College Station, TX).

RESULTS

A total of 69,738 beneficiaries met the inclusion criteria of this study. Of these, 19,034 (27.3%) resided in South Carolina and 50,965 (72.7%) in Tennessee. Baseline characteristics and benzodiazepine utilization by state of residence are shown in Table 5.2. Due to the large sample sizes, differences in the demographic characteristics between the states are statistically significant but the proportions in the distributions are similar for most characteristics. A sizable difference exists between the individual state cohorts with regards to race, with the South Carolina cohort having a higher proportion of nonwhite beneficiaries, particularly black beneficiaries (11.85% vs. 6.57%), compared to the Tennessee cohort. The South Carolina cohort, compared to the Tennessee cohort, also had a greater proportion of beneficiaries with at least some college education or a college degree (52.1% vs. 48.5%).

Overall, 18% of the South Carolina cohort and 17% of the Tennessee cohort filled a benzodiazepine prescription between January 2007 and December 2009. During this timeframe 12,297 unique beneficiaries filled a total of 101,036 benzodiazepine prescriptions. Alprazolam (47,501 unique prescriptions filled), clonazepam (19,612), lorazepam (13,624), and diazepam (11,836) were the most commonly filled benzodiazepine prescriptions. The number of beneficiaries who filled a benzodiazepine prescription in each month of the study period is presented in Appendix 5.1.

Interrupted Time Series Analysis

Throughout 2007, the percentage of South Carolina beneficiaries who filled a prescription for a benzodiazepine was increasing monthly by a rate 5% (0.05; 95% CI: 0.03, 0.07; p<0.01; Table 5.3). After the PDMP was implemented in South Carolina in January 2008, the percentage of beneficiaries filling a benzodiazepine prescription increased at a rate of 4% (0.04; 95% CI: 0.03, 0.07; p<0.01). This change in trend of the percent of South Carolina beneficiaries filling a benzodiazepine prescription each month was not significant (-0.01; 95% CI: -0.03, 0.02; p=0.46). Additionally, there was no change observed in the level (0.10; 95% CI: -0.33, 0.12; p=0.38) of the percent of South Carolina beneficiaries who filled a benzodiazepine prescription immediately after the PDMP was implemented (Figure 5.1). In the control state of Tennessee, no change was observed in the slope of the trend line of the percentage of beneficiaries filling a benzodiazepine prescription each month (-0.01; 95% CI: -0.03, 0.01; p=0.25). There was also no change observed in the level of filled benzodiazepine prescriptions (0.13; 95% CI: -0.30, 0.04; p=0.13) among Tennessee beneficiaries at the time of the South Carolina PDMP implementation.

The relative effect of the South Carolina PDMP based on 2007 predicted values initially after the program was implemented was 3.1% (95% CI: -8.92%, 3.58%; p=0.36) reduction in the percent of beneficiaries who filled a benzodiazepine prescription and not statistically significant (Figure 5.2). In January 2009, one year after the program began, the relative effect was a 5.3% (95% CI: -13.91%, 5.41%; p=0.31) reduction in the percent of beneficiaries who filled a benzodiazepine prescription and also not determine to be significant. By the end of 2009 the relative effect of the PDMP implementation was a 7% (95% CI: -18.44, 8.33%; p=0.34) reduction

in the percent of beneficiaries who were predicted to fill a benzodiazepine prescription and not statistically significant.

The results from the sensitivity analysis performed determined that there was no change in trend or level of the percentage of South Carolina beneficiaries who filled an opioid prescription after the PDMP was implemented in January 2008 (Appendix 5.2). Similar findings were observed in Tennessee where there was no change in trend or the level of the percent of beneficiaries who filled an opioid prescription. Furthermore, the relative effect of the South Carolina PDMP on the percentage of beneficiaries who filled an opioid prescription was not significant throughout the follow-up period (Appendix 5.3).

Multivariate Logistic Regression Analysis

In the overall study population, the odds of filling a benzodiazepine prescription were influenced by sex, race, age, presence of a psychiatric disorder, state of residence, unemployment rate, and time (Table 5.4). The odds of filling a benzodiazepine prescription were greater for beneficiaries residing in South Carolina compared to those in Tennessee (AOR: 1.29; 95% CI: 1.18, 1.40; $p<0.01$), females compared to males (AOR: 2.45; 95% CI: 2.26, 2.66; $p<0.01$) and beneficiaries between the ages of 45 and 64 compared to those 19 to 44 (AOR: 1.64; 95% CI: 1.54, 1.73; $p<0.01$). Having a diagnosis of anxiety (AOR: 31.39; 95% CI: 28.58, 34.48; $p<0.01$), depression (AOR: 4.68; 95% CI: 4,27, 5.13; $p<0.01$), or insomnia (AOR: 5.65; 95% CI: 5.09, 6.28; $p<0.01$) also increased the odds of filling a benzodiazepine prescription during the study period. Furthermore, the time trend variable included in the regression suggests that as time progressed during the study period the odds of a beneficiary filling a benzodiazepine prescription also increased (AOR: 1.02; 95% CI: 1.02, 1.03; $p<0.01$). Conversely, beneficiaries identified as black (AOR: 0.35; 95% CI: 0.30, 0.42; $p<0.01$) or other race (AOR: 0.55; 95% CI: 0.49,

0.67; p<0.01) were less likely than white beneficiaries to have filled a benzodiazepine prescription. The unemployment rate was also inversely related to the odds of filling a benzodiazepine prescription (AOR: 0.98; 95% CI: 0.97, 0.99; <0.01). Results also suggest the presence of a PDMP did not have an effect on the odds of beneficiaries filling a benzodiazepine prescription during the study period (AOR: 0.98; 95% CI: 0.94, 1.02; p=0.37).

Table 5.5 presents results from the DDD model evaluating whether the South Carolina PDMP implementation had a differential impact on the likelihood of having a benzodiazepine prescription filled among specific subgroups in South Carolina. The DD estimator was omitted from the final interaction model due to collinearity as the correlation between the DD estimator and the state of residence variable was determined to be 76 percent.

Adjusted for the covariates described previously, results from the DDD model suggested the implementation of the PDMP in South Carolina differentially impacted the likelihood that certain subgroups in the population would fill a benzodiazepine prescription. Linear combinations of effect estimates (Table 5.6) demonstrated that in the 24 months after the PDMP in South Carolina went into effect females and beneficiaries 45 and older experienced a significant reduction in the odds of filling a benzodiazepine prescription compared to the 12 months prior to the program. The South Carolina PDMP implementation resulted in females only having 85% (AOR: 0.85; 95% CI: 0.77, 0.91; p<0.01) of the odds of filling a benzodiazepine prescription while beneficiaries 45 and older only had 87% (AOR: 0.87; 95% CI: 0.80, 0.95; p<0.01) of the odds of filling a benzodiazepine prescription in 2008 and 2009 than they did prior to the program in 2007.

Conversely, beneficiaries in South Carolina with a diagnosis of insomnia during the study period had greater odds of filling a benzodiazepine prescription in the two years after the PDMP

was implemented than they did in the year prior. South Carolina beneficiaries diagnosed with insomnia during the study period experienced a 16% increase (AOR: 1.16; 95% CI: 1.03, 1.30; p=0.02) in their odds of filling a benzodiazepine prescription after the PDMP was implemented.

DISCUSSIONS

In this sample of continuously eligible, privately insured beneficiaries in South Carolina the implementation of SCRIPTS did not impact the rate of benzodiazepine use or create a chilling effect by decreasing the likelihood of filing a benzodiazepine prescription during the two years following the program's implementation for beneficiaries having a diagnosis of insomnia, a condition for which benzodiazepines are indicated. This finding is a contrast from previous findings in New York,[65] which suggested that benzodiazepine monitoring programs cause a sudden and sustained decrease in the rate of benzodiazepine use. The findings of the present study show that in the two years after SCRIPTS was implemented there was no change in the in the level nor the trend of benzodiazepine dispensing when compared to the year prior to the program. One possible explanation for this finding is that during the study period use of SCRIPTS was voluntary among physicians and pharmacists. Physicians may not have accessed the SCRIPTS database due to time constraints often present with evaluating patients. Another deterrent to SCRIPTS use by physicians may be the perception that the information contained in the report is incomplete and would therefore not impact their CS prescribing decisions. The perception of the report being incomplete may be based on the knowledge that CS dispensers were only required to submit their CS dispensing data once every 30 days. Of note, in June 2014 legislation passed the South Carolina General Assembly requiring daily reporting of CS dispensing data by dispensers.[228] Pharmacists may not have accessed the SCRIPTS database to request a patient's CS prescription history due to workflow issues and limited access to the

Internet, especially in chain pharmacy settings. Pharmacists may have also assumed that physicians were accessing the SCRIPTS database and therefore there was no reason for them to do so.

Findings from this study did show that the presence of SCRIPTS differentially impacted certain subgroups of the population. Results show that among South Carolina beneficiaries the likelihood of filling a benzodiazepine prescription after SCRIPTS went into effect were significantly decreased for females and beneficiaries 45 and older. However, even after SCRIPTS was implemented females remained nearly three times more likely than males to fill a benzodiazepine prescription and those 45 and older were nearly twice as likely to fill a benzodiazepine prescription as their younger counterparts. As this study evaluated the impact of SCRIPTS on the dispensing of benzodiazepines it cannot be determined if the discontinuation of benzodiazepine therapy among female beneficiaries in South Carolina was appropriate or if there were any adverse outcomes experienced as a result.

This study also demonstrated that having received a diagnosis of insomnia during the study period significantly increased the likelihood of filling a prescription for a benzodiazepine after the PDMP was implemented compared to beneficiaries without a diagnosis. As benzodiazepines are indicated to manage symptoms associated with this condition, the finding suggests that PDMPs, as they pertain to benzodiazepines, do not induce a chilling effect by restricting access to pharmacotherapy options among those with a diagnosis of insomnia, a condition where benzodiazepine therapy is appropriate.

Limitations to this study exist. First, this study does not distinguish between appropriate or potentially inappropriate benzodiazepine dispensing to beneficiaries. However, the use of diagnostic codes for conditions for which benzodiazepines are indicated and/or commonly

prescribed can be used as a proxy for appropriate dispensing. Also, even though benzodiazepines are often prescribed for the treatment of seizure disorders, they are generally not the first-line therapy option. Because of this and the necessity of tailoring seizure disorder treatments to individual patients seizure disorder conditions were not assessed. This study does not account for the number of benzodiazepine prescriptions filled or the quantity and dosage of these prescriptions. As this study utilized prescription drug claims from a private insurance claims database, prescriptions acquired from family and friends or paid for using cash cannot be accounted for. Additionally, this study could not account for utilization of the SCRIPTS program by physicians and pharmacists who make treatment decisions. Finally, this a sample of continuously enrolled, privately insured beneficiaries may not adequately represent the populations of South Carolina or Tennessee as a whole and may not be generalizable to other populations.

Findings from this study demonstrate that the presence of SCRIPTS did not induce a chilling effect with regards to benzodiazepines in the overall sample of continuously enrolled, privately insured beneficiaries in South Carolina with a diagnosis of insomnia. However, benzodiazepine dispensing to females and beneficiaries 45 and older in South Carolina were more impacted by the presence of the program than they were to males and younger adults. As this study did not explicitly differentiate between appropriate and potentially inappropriate benzodiazepine dispensing it cannot be determined if the reduction in benzodiazepine dispensing to females and beneficiaries 45 and older was focused on those who may have been misusing or diverting benzodiazepines or if discontinuation occurred in those who were using the medication appropriately. Future research focusing on PDMPs and their impact on benzodiazepine utilization should consider employing methods to identify appropriate and potentially inappropriate benzodiazepine use in claims databases in order to evaluate if PDMPs

are achieving their goal of reducing prescription drug abuse and diversion without impeding access for those with a legitimate need. Additionally, exploring clinical outcomes among patients who have had their benzodiazepine therapy discontinued can assist in evaluating costs associated with the presence of a PDMP. Finally, future studies should explore the impact of PDMPs on benzodiazepine use by expanding the number of states to allow for specific characteristics of PDMPs to be analyzed and understand how they impact benzodiazepine use. In addition, the time period analyzed should be expanded in order to observe the long-term impact of PDMPs on benzodiazepine utilization. Considerable potential exists for PDMPs to become a powerful tool to combat prescription drug abuse and diversion heightening the need for more research to understand their clinical utility and ensure they do no obstruct access to legitimate pharmacotherapies.

Table 5.1. United States Census demographic information for South Carolina and Tennessee.[225]

	South Carolina	*Tennessee*
2010 Population	4,625,364	6,346,105
Sex		
Male	48.7%	48.8%
Female	51.3%	51.2%
Age		
Under 18 years of age	22.6%	23.0%
Age 65 and older	15.2%	14.7%
Race		
White	63.9%	74.9%
Black	27.9%	17.0%
Hispanic	5.3%	4.9%
Education		
High School or more	84.5%	84.4%
Bachelor's or more	25.1%	23.8%

Table 5.2. Demographic characteristics of continuously enrolled[a] adult beneficiaries in South Carolina and Tennessee.

	South Carolina		*Tennessee*		
Sample Size	19,043		50,695		p-value
Benzodiazepine use					
Filled benzodiazepine prescription	3,515	18.46%	8,782	17.32%	<0.01
Sex					
Female	9,727	51.08%	25,738	50.77%	0.47
Age[b]					
Median age (IQR[c])	44	(35 – 53)	44	(34 – 52)	<0.01
Race					
White	15,165	79.64%	42,875	84.57%	<0.01
Black	2,257	11.85%	3,332	6.57%	<0.01
Hispanic	421	2.21%	1,199	2.37%	0.23
Other	1,053	5.53%	2,987	5.89%	0.07
Education					
High school diploma or less	8,422	44.23%	25,003	49.32%	<0.01
Some college or college degree	9,911	52.05%	24,604	48.53%	<0.01
ICD-9 Diagnosis					
Anxiety	2,205	11.58%	6,310	12.45%	<0.01
Depression	2,165	11.37%	6,559	12.94%	<0.01
Insomnia	1,489	7.82%	3,854	7.60%	0.34

[a] Continuously enrolled defined as ≥1090 days eligibility between Jan 1, 2007 & Dec 31, 2009

[b] Median age was evaluated for the year 2007

[c] Interquartile range

Table 5.3. Interrupted time series analysis examining the percentage of South Carolina and Tennessee beneficiaries filling a benzodiazepine prescription by month.

	South Carolina			*Tennessee*		
	Coefficient	*p-value*	*95% Confidence Interval*	*Coefficient*	*p-value*	*95% Confidence Interval*
Monthly rate of increase in benzodiazepine in 2007	0.05	<0.01	0.03, 0.07	0.04	<0.01	0.03, 0.06
Monthly rate of increase in benzodiazepine in 2008 & 2009	0.04	<0.01	0.02, 0.05	0.03	<0.01	0.03, 0.04
Change in the rate of increase of benzodiazepine use	-0.01	0.43	-0.03, 0.01	-0.01	0.25	-0.03, 0.01
Change in the level one month after PDMP implementation	-0.11	0.35	-0.34, 0.12	-0.13	0.13	-0.30, 0.04

Table 5.4. Odds of filling a benzodiazepine prescription between January 2007 and December 2009 among continuously enrolled adult beneficiaries in South Carolina and Tennessee.

Variable	*Odds Ratio*	*p-value*	*95% Confidence Interval*
PDMP			
No operational PDMP	Ref.		
PDMP operational	0.98	0.37	0.94 – 1.02
State of Residence			
Tennessee	Ref.		
South Carolina	1.29	<0.01	1.18 – 1.40
Sex			
Male	Ref.		
Female	2.45	<0.01	2.26 – 2.66
Race			
White	Ref.		
Black	0.35	<0.01	0.30 – 0.42
Other	0.58	<0.01	0.49 – 0.67
Age			
Age 44 and under	Ref.		
Age 45 and over	1.64	<0.01	1.54 – 1.73
Diagnosis of a Psychiatric Disorder			
No psychiatric disorder diagnosis	Ref.		
Anxiety	31.39	<0.01	28.58 – 34.48
Depression	4.68	<0.01	4.27 – 5.13
Insomnia	5.65	<0.01	5.09 – 6.28
Economic Climate			
Unemployment rate[a]	0.98	<0.01	0.97 – 0.99
Time Trend			
Month[b]	1.02	<0.01	1.02 – 1.03

[a] Unemployment rate interpretation is the effect of a one percentage point increase in the unemployment rate

[b] Month interpretation is the effect of time progressing forward one additional month

Table 5.5. Odds of South Carolina adult beneficiaries filling a benzodiazepine prescription after the implementation of the state's PDMP.

Variable	*Odds Ratio*	*p-value*	*95% Confidence Interval*
Presence of PDMP			
No operational PDMP	Ref.		
PDMP operational	0.92	0.09	0.83 – 1.01
State of Residence			
Tennessee	Ref.		
South Carolina	1.26	<0.01	1.12 – 1.41
Sex			
Male	Ref.		
Female	2.49	<0.01	2.29 – 2.71
Race			
White	Ref.		
Black	0.35		0.29 – 0.42
Other	0.57	<0.01	0.48 – 0.66
Age			
Age 44 and under	Ref.		
Age 45 and over	1.65	<0.01	1.55 – 1.75
Diagnosis of a Psychiatric Disorder			
No psychiatric disorder diagnosis	Ref.		
Anxiety	30.55	<0.01	27.78 – 33.60
Depression	4.64	<0.01	4.23 – 5.10
Insomnia	5.40	<0.01	4.85 – 6.00
Economic Climate			
Unemployment rate[a]	0.98	<0.01	0.97 – 0.99
Time Trend			
Month[b]	1.02	<0.01	1.02 – 1.03
DDD[c] Estimators			
PDMP * SC * Female	0.92	0.04	0.85 – 0.99
PDMP * SC * Black	1.03	0.73	0.89 – 1.18
PDMP * SC * Other	1.08	0.34	0.92 – 1.26
PDMP * SC * Over 45	0.95	0.19	0.88 – 1.03
PDMP * SC * Anxiety	1.15	<0.01	1.06 – 1.25
PDMP * SC * Depression	1.05	0.25	0.97 – 1.14
PDMP * SC * Insomnia	1.26	<0.01	1.15 – 1.37

[a] Unemployment rate interpretation is the effect of a one percentage point increase in the unemployment rate

[b] Month interpretation is the effect of time progressing forward one additional month

[c] Difference in difference in difference estimators

Table 5.6. Linear combinations of effect estimates comparing odds of subgroups of South Carolina adult beneficiaries filling a benzodiazepine prescription before and after PDMP implementation.

Variable	Odds of filling a benzodiazepine prescription before South Carolina PDMP p-value (95% CI)	Odds of filling a benzodiazepine prescription after South Carolina PDMP p-value (95% CI)	Comparison of odds after the South Carolina PDMP implementation to before p-value (95% CI)
Female	3.13 <0.01 (2.70, 3.64)	2.65 <0.01 (2.19, 3.20)	0.85 <0.01 (0.77, 0.92)
Black	0.44 <0.01 (0.36, 0.54)	0.41 <0.01 (0.32, 0.54)	0.94 0.47 (0.80, 1.11)
Other	0.71 <0.01 (0.58, 0.87)	0.70 0.01 (0.54, 0.92)	0.99 0.92 (0.83, 1.18)
Age 45 and over	2.07 <0.01 (1.81, 2.37)	1.81 <0.01 (1.51, 2.16)	0.87 <0.01 (0.80, 0.95)
Anxiety	38.40 <0.01 (32.90, 44.83)	40.64 <0.01 (32.99, 50.05)	1.06 0.28 (0.95, 1.17)
Depression	5.84 <0.01 (5.02, 6.80)	5.63 <0.01 (4.51, 7.03)	0.96 0.57 (0.85, 1.09)
Insomnia	6.79 <0.01 (5.79, 7.96)	7.85 <0.01 (6.29, 9.80)	1.16 0.02 (1.03, 1.30)

Figure 5.1. Percent of sample who filled a benzodiazepine prescription each month during the study period among continuously enrolled, privately insured beneficiaries in South Carolina and Tennessee.

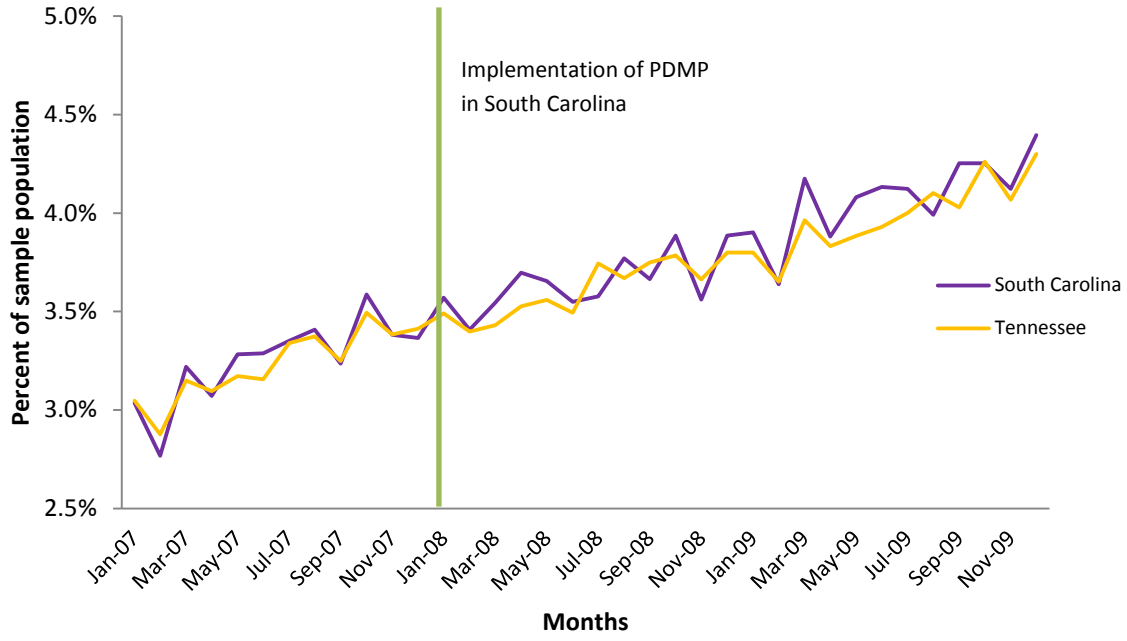
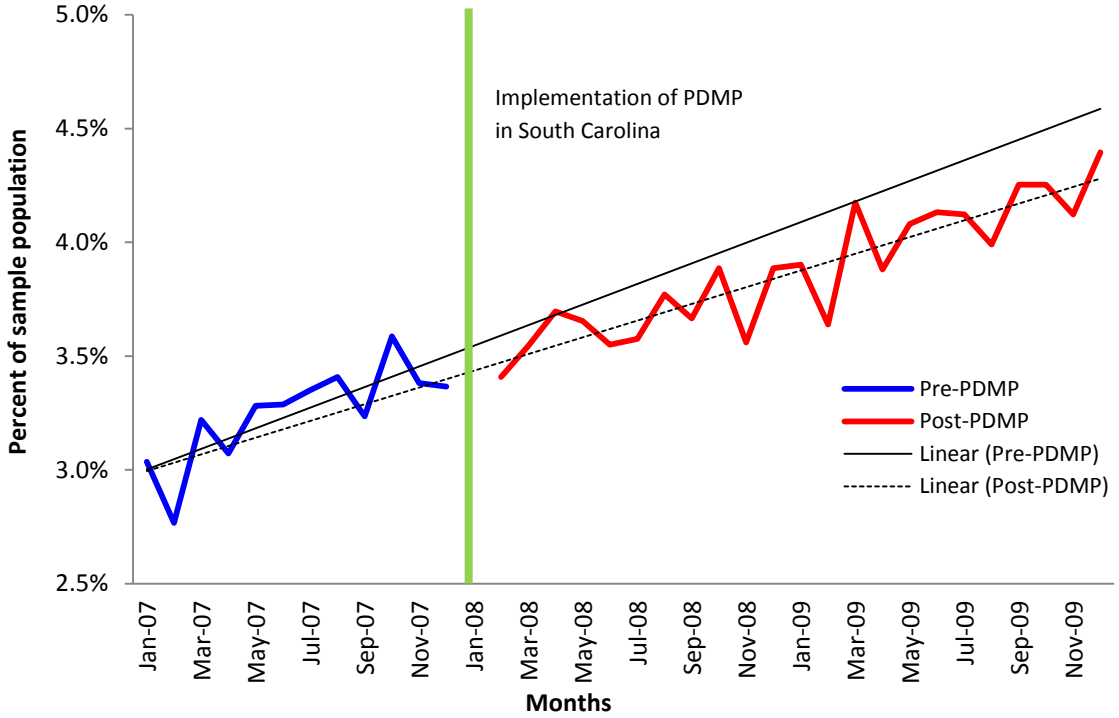


Figure 5.2. Relative effect of South Carolina PDMP on percentage of sample population filling a benzodiazepine prescription.



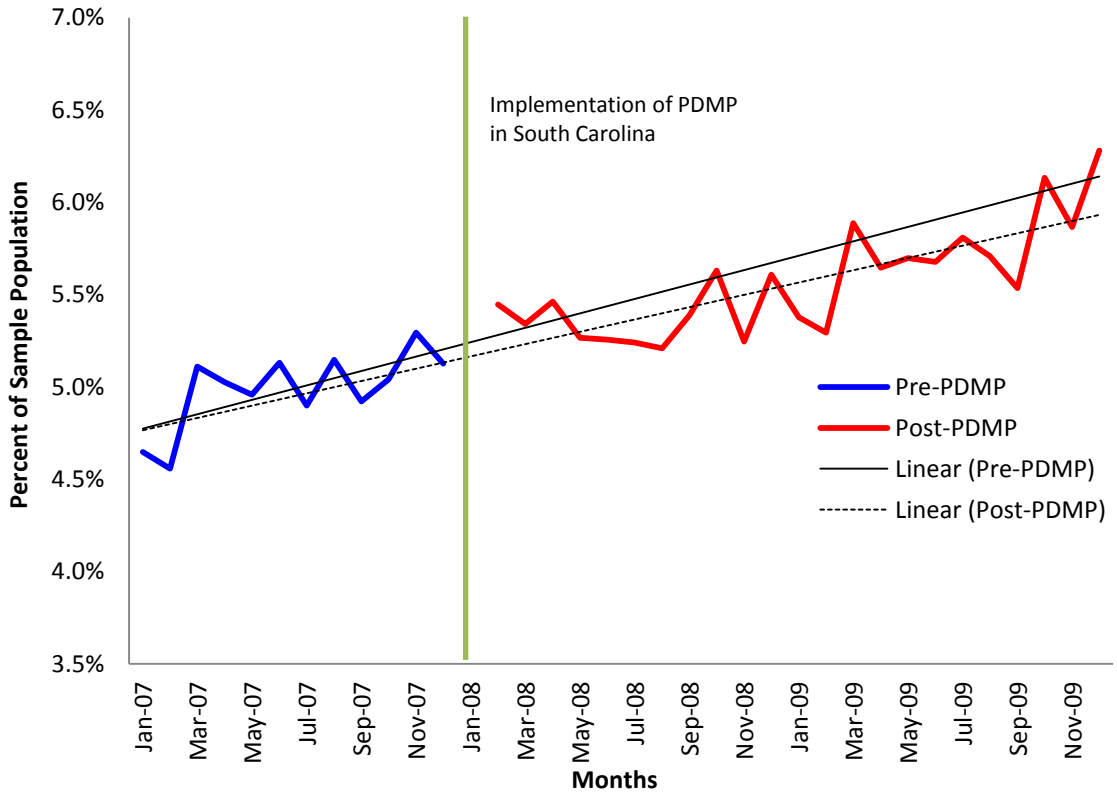
Appendix 5.1. Number and percentage of continuously enrolled beneficiaries in South Carolina and Tennessee who filled a benzodiazepine prescription by month.

		South Carolina		*Tennessee*	
Sample Size		19,043		50,695	
2007	January	578	3.04%	1545	3.05%
	February	527	2.77%	1458	2.88%
	March	613	3.22%	1597	3.15%
	April	585	3.07%	1569	3.09%
	May	625	3.28%	1608	3.17%
	June	626	3.29%	1600	3.16%
	July	638	3.35%	1693	3.34%
	August	649	3.41%	1710	3.37%
	September	616	3.23%	1647	3.25%
	October	683	3.59%	1771	3.49%
	November	644	3.38%	1715	3.38%
	December	641	3.37%	1730	3.41%
2008	January	680	3.57%	1770	3.49%
	February	649	3.41%	1723	3.40%
	March	675	3.54%	1739	3.43%
	April	704	3.70%	1788	3.53%
	May	696	3.65%	1804	3.56%
	June	676	3.55%	1771	3.49%
	July	681	3.58%	1898	3.74%
	August	718	3.77%	1860	3.67%
	September	698	3.67%	1901	3.75%
	October	740	3.89%	1919	3.79%
	November	678	3.56%	1857	3.66%
	December	740	3.89%	1926	3.80%
2009	January	743	3.90%	1926	3.80%
	February	693	3.64%	1851	3.65%
	March	795	4.17%	2009	3.96%
	April	739	3.88%	1943	3.83%
	May	777	4.08%	1969	3.88%
	June	787	4.13%	1992	3.93%
	July	785	4.12%	2028	4.00%
	August	760	3.99%	2079	4.10%
	September	810	4.25%	2042	4.03%
	October	810	4.25%	2160	4.26%
	November	785	4.12%	2062	4.07%
	December	837	4.40%	2180	4.30%

Appendix 5.2. Interrupted time series analysis examining the percentage of South Carolina and Tennessee beneficiaries filling an opioid prescription by month.

	South Carolina			*Tennessee*		
	Coefficient	*p-value*	*95% Confidence Interval*	*Coefficient*	*p-value*	*95% Confidence Interval*
Monthly rate of increase in benzodiazepine in 2007	0.04	0.03	0.00[a], 0.08	0.02	0.25	-0.02, 0.07
Monthly rate of increase in benzodiazepine in 2008 & 2009	0.03	<0.01	0.02, 0.04	0.03	<0.01	0.02, 0.05
Change in the rate of increase of benzodiazepine use	-0.01	0.73	-0.04, 0.03	0.01	0.68	-0.03, 0.05
Change in the level one month after PDMP implementation	-0.08	0.67	-0.45, 0.03	0.11	0.55	-0.25, 0.48

Appendix 5.3. Relative effect of South Carolina PDMP on percentage of sample population filling an opioid prescription.



CHAPTER 6: A NATIONWIDE STUDY OF THE IMPACT OF PRESCRIPTION DRUG MONITORING PROGRAMS ON THE DISPENSING OF BENZODIAZEPINES AMONG COMMERCIALLY INSURED ADULTS.

INTRODUCTION

For the millions of American afflicted with symptoms of anxiety and insomnia benzodiazepines are a generally safe and effective pharmacologic treatment option. Benzodiazepines are the most frequently prescribed psychotropic drug class.[11] In 2012 they were the 10th most prescribed drug class in the United States with approximately 94 million prescriptions dispensed.[12] Benzodiazepines are considered a safer alternative compared to other sedative-hypnotics drugs, such as barbiturates and meprobamate,[2,3,6] however the potential remains for benzodiazepines to be abused due to their addictive nature. Due to evidence regarding the abuse potential of benzodiazepines they are classified as a Schedule IV controlled substance (CS).

The role of benzodiazepines in the United States prescription drug abuse epidemic is prominent. National estimates of drug-related visits to emergency departments collected by the Drug Abuse Warning Network[105] (DAWN) for the year 2011 reported that between 2004 and 2011 the number of emergency department visits for the non-medical use of benzodiazepines increased 149% from 143,500 to 357,800. Additionally, this report identified benzodiazepines as the second leading cause of all emergency department visits concerning nonmedical use of pharmaceuticals, as they were involved in 28.7% of all emergency department visits for this cause. Another recent study by Cai et al.[106] examining data from DAWN between 2004 and 2008 reported that benzodiazepines were identified in approximately 26% of all opioid related emergency department visits. These estimates suggest that benzodiazepine misuse and abuse

can lead to serious adverse effects on individuals and caution must be exercised with their prescribing and use.

To address the prescription drug abuse epidemic in the United States, individual states have taken the lead in creating and implementing prescription drug monitoring programs (PDMPs) with the purpose of identifying and mitigating prescription drug abuse and diversion. These programs permit healthcare providers, including prescribers and pharmacists, the ability to request and receive a patient's controlled substance (CS) prescription history with quick turnaround, allowing treatment decisions to be made at the point of care. Reports detailing a patient's CS prescription history can be accessed upon request, or proactively distributed to authorized PDMP users, depending upon the regulations of the individual state's program. Pharmacies, along with dispensing physician and veterinarian offices submit CS dispensing data to the PDMP on a regular basis as mandated by state law. The majority of states require CS dispensing data to be submitted at least every seven days with some states requiring daily or "real-time" reporting.[80] Prescription data submitted to PDMPs follows a standard format and includes patient name, prescriber name, date of dispensing, and name, strength, and quantity of the CS medication dispensed. As of December 2014, 49 states have an operational PDMP. Missouri and Washington DC do not currently have a PDMP, however, Washington DC does have pending legislation.[80]

While all PDMPs were designed to facilitate collection, analysis, and reporting of prescription CS use, in practice they take several different forms based upon individual state legislation and differ in terms of objectives, design, and operations.[229] Housing agencies of PDMPs vary between states with the majority of PDMPs housed within and agency having primarily a public health mission (e.g. health professional boards, departments of health);

however some states house their PDMP within a law enforcement agency and while others are part of another housing authority.[80] The housing agency of the PDMP may have an effect on the overall mission of the program and how authorized PDMP users interact with the system. For example, states that house their PDMP within a law enforcement agency may perceive prescription drug abuse as a safety concern and those who abuse and divert CS as criminals while a state that houses their PDMP in a public health department may view prescription drug abuse and diversion as a condition for which people need programs and treatment options to help them overcome their problem. Variation also exists across states in terms of groups authorized to access the PDMP system and subsequent reports. In most states healthcare professionals including prescribers and pharmacists are authorized to receive the information contained within PDMP reports, however, access among law enforcement personnel is less uniform.[80] States also differ in the CS Schedules monitored. While all state PDMPs track the dispensing of Schedule II CS, some states also monitor Schedules III, IV, and V. Some state PDMPs also have the authority to monitor non-CS under certain circumstances.[82] The frequency with which CS prescription dispensing data is transmitted to the PDMP is another source of variation between programs with the majority of states require CS dispensing data to be submitted at least every seven days, however, some states require daily or "real-time" reporting.[80]

Policies designed to curtail the abuse, misuse, and diversion of prescription drugs (i.e., PDMPs) should be evaluated to determine if they are effectively meeting their objectives. Assessments of these policies are also necessary to ensure patient safety (i.e., permitting access to CS medication for appropriate medical care). To date, studies regarding current PDMP legislation have primarily focused on the impact concerning opioid analgesic prescribing and use. Emphasis on this medication class is understandable as opioid analgesics are the primary

contributor to the increasing trend of drug overdose deaths in the US.[92-94] The role of other CS medications, specifically benzodiazepines, has also been found to contribute substantially to the rise in unintentional poisoning deaths.[92,95-97]

Previous studies assessing the impact of benzodiazepine monitoring have concentrated on the New York triplicate prescription program (TPP) from the early 1990s. In 1989, New York became the first state the track the prescribing, dispensing, and utilization of benzodiazepines when they were added to the list of medications to be targeted by the state's TPP with the goal of reducing diversion for illicit use and inappropriate prescribing.[63-65] Evaluations of the effectiveness of the New York TPP policy change suggested that immediately following implementation there was a significant and sustained reduction in overall benzodiazepine use.[65,73,74] There were also concerns that this policy change may have induced a 'chilling effect' by restricting access to benzodiazepine therapy among patients with chronic psychiatric disorders, and/or a legitimate need for the medication were also highlighted. A 2003 evaluation by Wagner and colleagues[72] examined new benzodiazepine use among patients recently discharged from the hospital for either an acute cardiac event or cancer. Benzodiazepines are often prescribed to relieve anxiety associated with acute myocardial infarction and in cancer patients to reduce anticipatory anxiety and anxiety related effects associated with the administration of chemotherapy.[2] The study found new benzodiazepine use among New York Medicaid beneficiaries recently discharged from the hospital for acute cardiac events and cancer declined 72.5% and 69.4%, respectively during the two-year observation period after the benzodiazepine triplicate regulation was implemented. Additionally, Simoni-Wastila et al.[73] studied patients who had a diagnosis of schizophrenia, epilepsy, or bipolar disorder, where benzodiazepines represent an effective first-line or adjunct treatment option, and demonstrated

a nearly 50% decline in benzodiazepine use six months after the policy change. Patients with a seizure disorder experienced a 60% decline, the largest among the conditions assessed.

Despite the prominent role of benzodiazepines in the US prescription drug epidemic, there is a notable absence of the studies evaluating how current PDMP legislation impacts benzodiazepine behaviors. Of the 49 operational PDMPs as of December 2014, 48 have the authority to monitor Schedule IV CS which includes benzodiazepines.[80,83] The aim of this study is to understand the impact of PDMPs on the dispensing of benzodiazepines by quantifying the impact of having a PDMP become operational on the percentage of beneficiaries who fill a benzodiazepine prescription, estimating the relationship between the presence of a PDMP monitoring Schedule IV CS an the likelihood of filling a benzodiazepine prescription, testing for evidence of a chilling effect in the presence of a PDMP, and identifying the association between the presence of a PDMP monitoring Schedule IV CS and potentially inappropriate benzodiazepine dispensing.

METHODS

Data were extracted from a large private insurance claims database for the time period between January 2007 and December 2009 for continuously eligible beneficiaries (≥1090 days) from all 50 states and the District of Columbia who were between 19 and 64 years of age throughout the duration of the study period. The claims database includes patient socio-demographic information and codes related to interactions with the healthcare system. Benzodiazepine dispensing during the study period was represented by a claim for any benzodiazepine during a given month of the study period and identified using national drug codes. Psychiatric disorders for which benzodiazepines are indicated or commonly prescribed including anxiety[103] (ICD-9 codes: 300.xx, excluding 300.4), insomnia[103] (307.41, 307.42, and

780.52), and depression[174] (296.2x, 296.3x, 300.4, and 311) were also identified in the database. These conditions were used as a proxy for legitimate benzodiazepine use to test of the presence of a chilling effect. Beneficiaries were considered to have a specific psychiatric disorder if they had a claim in any position at any time during the study period with a diagnosis including one of the ICD-9 diagnostic codes listed above.

The operational status of PDMPs was considered monthly. The monthly time period was chosen because PDMP implementations take immediate effect (i.e., beginning on a specified date all dispensing of monitored CS must be reported to the system). The use of monthly time periods also allowed for the observation of short-term (<12 months) and long-term (≥12 months) trends related to the dispensing of benzodiazepines associated with the implementation of a PDMP. To be considered operational PDMPs had to be actively collecting CS dispensing data and authorized users able to generate CS dispensing reports. For the purpose of this study, states were divided into categories based on their PDMP status during the study period. States that had an operational PDMP and also monitored Schedule IV CS the entire duration of the study were grouped together as were states that did not have an operational PDMP or did not monitor Schedule IV CS throughout the study period. States that had a PDMP become operational or started monitoring Schedule IV CS during the study period were considered individually as the dates the PDMPs became operational varied. The month each state's PDMP became operational was excluded from all analyses as some benzodiazepine prescriptions written prior to the PDMP becoming operational may not have been filled immediately. The exclusion of this time period is consistent with the methods applied by Ross-Degnan et al.[65] to evaluate the impact of the New York TPP on benzodiazepine use.

To evaluate if having a PDMP monitoring Schedule IV CS become operational impacted the proportion of beneficiaries who filled a benzodiazepine prescription, interrupted time series methods were employed. States were considered for individual analysis if they had a PDMP become operational during the study period, had a minimum observation period of 12 months before and after PDMP implementation to allow for adequate trend analysis and, on average, had more than 30 beneficiaries fill a benzodiazepine prescription each month. Time series analyses using autoregressive integrated moving average (ARIMA) models estimated changes in the level and trend, in addition to 95% confidence intervals (CI), of the percent of beneficiaries in each state who filled a benzodiazepine prescription during each of the months prior to and after the PDMP became operational. A change in level is described by Ramsay et al.[230] as the difference between the observed level at the first intervention time point and that predicted by the pre-intervention time trend, and a change in trend as the difference between post- and pre-intervention slopes. States that did not have the operational status of their PDMP change throughout the study period were used as controls to account for any underlying secular trends that may have concurrently affected the dispensing of benzodiazepines. States that did not have a PDMP monitoring Schedule IV CS in place throughout the study and those states that did were evaluated separately to determine if other underlying and unobserved factors related to either having or not having an operational PDMP monitoring Schedule IV CS may have partially accounted for the results observed in the state implementing the PDMP.

Panel data methods using random effects were employed to examine the effect PDMPs monitoring Schedule IV CS had on the likelihood of beneficiaries filling a benzodiazepine prescription during the study period. Random effects models were used to control for factors unobserved in the data that may have impacted the dispensing of benzodiazepines (i.e., alternate prescription drug abuse policies, changes in news coverage surrounding prescription

drug abuse, changing attitudes towards treatments for anxiety, depression, and insomnia). Multivariate logistic regression models adjusted for presence of a PDMP, sex, age, race, presence of psychiatric disorders, state and month specific unemployment rates, and time in months were used to estimate the adjusted odds ratio (AOR) and associated 95% CI of filling a benzodiazepine prescription. The covariates, with the exception of the monthly unemployment rates and the time trend variable, were operationalized as indicator variables. Age was segregated into two categories based on the study population's median age, 19 to 44 and 45 to 64, and was calculated based on the beneficiary's year of birth. Race was divided into four categories: white, black, Hispanic, and other race. State and month specific unemployment rates acquired from the US Bureau of Labor Statistics[227] were used to adjust for the economic climate that was especially volatile during the study period and included in the model because unemployment has previously been shown to be associated with benzodiazepine use.[164] The unemployment variable was operationalized as a continuous variable representing the percentage of the states' workforce who were without a job, actively seeking employment, and available for work during a given month. The monthly time trend variable was operationalized as an ordinal variable taking the values 1 through 36, with 1 representing January 2007 and 36 representing December 2009, and included to capture the effects that trend in one direction over time.

The first multivariate logistic regression model used a linear form to determine factors that influence the likelihood of filling a benzodiazepine prescription among beneficiaries in the study population. This model took the form of

$$BZD_{ikt} = \beta_0 + \beta_1 PDMP_{kt} + \beta_2 X_i + \beta_3 Y_i + \beta_4 Unemploy_{kt} + \beta_5 Time_t + \varepsilon$$

Where BZD_{ikt} is the odds of filling a benzodiazepine prescription for beneficiary i residing in state k in month t. The variable $PDMP_{kt}$ indicates the presence of an operational PDMP in state k in month t. The matrix X identifies demographic characteristics for beneficiary i including sex, race, and age, and the matrix Y represents the presence of a psychiatric disorder diagnosis including anxiety, depression, and insomnia for beneficiary i and the occurrence of a combination of these psychiatric disorders. The variable $Unemploy_{kt}$ is the unemployment rate for state k in month t and $Time_t$ is the monthly time trend variable. Finally, ε is a normal independent identically distributed (i.i.d.) error term.

To better understand the effect of PDMPs on the likelihood of filling a benzodiazepine prescription an interaction model was estimated. This model estimated the effect of PDMPs in conjunction with the beneficiary specific predictor variables to understand how subgroups within the population are potentially differentially impacted by the presence of a PDMP. The interaction model utilized took the form of

$$BZD_{ikt} = \beta_0 + \beta_1 PDMP_{kt} + \beta_2 X_i + \beta_3 Y_i + \beta_4 Unemploy_{kt} + \beta_5 Time_t + \beta_6 PDMP_{kt} * X_i + \beta_7 PDMP_{kt} * Y_i + \varepsilon$$

Linear combinations of coefficients estimated the likelihood of filling a benzodiazepine prescription among subgroups within the population in the presence of an operational PDMP monitoring Schedule IV CS. The odds of filling a benzodiazepine prescription in the presence of a PDMP monitoring Schedule IV CS was compared to the likelihood of doing so in the absence of such a program.

A third multivariate regression model was estimated to determine if the presence of a PDMP alone, or if instead, individual program characteristics has the greatest impact on benzodiazepine dispensing. This model analyzing PDMP characteristics took the form of

$$BZD_{ikt} = \beta_0 + \beta_1 PDMP_{kt} + \beta_2 S_{kt} + \beta_3 T_{kt} + \beta_5 U_{kt} + \beta_6 V_{st} + \beta_6 W_{st} + \varepsilon$$

In this model $PDMP_{kt}$ represents the presence of an operational PDMP monitoring Schedule IV CS in state k in month t. The matrix S_{kt} denotes the housing agency of the PDMP in state k in month t. Housing agencies were grouped together based on the primary focus of the agency in which the PDMP was housed. For the purpose of this analysis housing agencies were categorized as "health focused" (e.g., departments of public health), "safety focused" (e.g., law enforcement agencies or agencies with a safety focused mission), and "licensing boards" (e.g., Boards of Pharmacy). Health focused agencies were identified by observing if the work 'health' was in the name of the housing agency. Likewise, safety focused agencies were identified if the word 'safety' or 'protection' was present in the housing agency's name. Law enforcement housing agencies were initially considered separately from safety focused agencies. Due to lack of variation between states housed in law enforcement agencies the variable was dropped from the model. The decision was made to combine safety focused agencies and law enforcement agencies as their primary mission is to protect and serve the public. Licensing boards were evaluated separately because even though they may be health centric their primary purpose is to serve the profession they represent. Controlled substance Schedules monitored by the PDMP are represented by the matrix T. The authority to monitor non-controlled substances are denoted in matrix U. Groups authorized to access the PDMP and obtain information from the system are represented by the matrix V. Groups of authorized users included in this analysis are pharmacists and law enforcement agents who were able to access the system without requiring a warrant. Physicians were not included to avoid the issue of collinearity as all states with a PDMP monitoring Schedule IV CS also allowed physician access to the system. Finally, the W matrix characterizes the frequency with which CS dispensing was required to be reported to the PDMP and includes monthly, bi-monthly, weekly, and daily reporting frequencies.

Statistical significance was considered using the Wald χ^2 p-value associated with the interaction term. The a priori level of significance for all analyses was set at 0.05. Data use was approved by the University of Kentucky Institutional Review Board. Statistical analyses was conducted using Stata 13.0 (StataCorp., College Station, TX).

RESULTS

A total of 2,827,874 beneficiaries met the inclusion criteria of this study. Baseline characteristics and benzodiazepine utilization are described in Table 6.1. The population was divided evenly between males and females (48% vs. 52%) and the median age assessed in 2007 was 44 years (interquartile range (IQR) 35-52). Nearly two-thirds (63%) of the population had received at least some college education or had earned a college degree. The study population was also predominately white (74%) with blacks (5%) Hispanics (8%) and beneficiaries of other races (12%) comprising only one-quarter of the sample. Anxiety and depression diagnoses were each found in 12% of the study population with 6% of beneficiaries having had received an insomnia diagnosis during this timeframe. Throughout the study period the proportion of beneficiaries who filled a benzodiazepine prescription in each month increased steadily (Figure 6.1) with a total of 443,380 (16%) unique beneficiaries having filled at least one prescription for a benzodiazepine.

Overall, 19 states had an operational PDMP monitoring Schedule IV CS during the entire study period. Eighteen states did not have an operational PDMP throughout the study duration. Four states had an operational PDMP in place during the study period but did not monitor Schedule IV CS. An additional nine states had a PDMP become operational during the study, and one state had a PDMP in place during the entire study period but began monitoring Schedule IV

CS during the study period. A description of the states and their PDMP status from January 2007 through December 2009 are presented in Table 6.2.

Interrupted Time Series Analysis

Tables 6.3a-6.3f present results from the interrupted time series analyses. All values in the tables are interpreted as percentages. The first column of results in each of the tables shows the rate of increase in the trend of benzodiazepine dispensing before and after the PDMP was implemented in the state of interest, the change in the rate of benzodiazepine dispensing after the PDMP was implemented compared to before, and the change in the level of benzodiazepine dispensing in the month immediately following the implementation of the PDMP compared to the month immediately preceding the PDMP implementation. The second column of the results shows the results of the interrupted time series analysis for states without an operational PDMP monitoring Schedule IV CS throughout the duration of the study period. The last column shows the results for states that did have a PDMP in place monitoring Schedule IV CS during the entire study period. These last two columns were analyzed and included to determine if other underlying and unobserved factors related to either having or not having an operational PDMP monitoring Schedule IV CS may have partially accounted for the results observed in the state of interest.

Among the states that had a PDMP become operational during the study period, six (Arizona, Connecticut, Illinois, Iowa, Louisiana, and South Carolina) met the requirements for individual trend analysis. Of these states only Iowa experienced a changed in the trend of beneficiaries who filled a benzodiazepine prescription after their PDMP became operational. Prior to January 2009 when the PDMP was implemented in Iowa, the percentage of beneficiaries in that state who filled a benzodiazepine prescription was increasing by a rate of 3% (0.03; 95%

CI: 0.02, 0.04; p<0.01; Table 6.3d) each month. After the PDMP was implemented the percentage of beneficiaries who filled a benzodiazepine prescription increased at a rate of 6% each month (0.06; 95% CI: 0.04, 0.08; p<0.01). The observed increase in the slope of the trend line of Iowa beneficiaries filling a benzodiazepine prescription after the PDMP became operational was determined to be statistically significant (0.03, 95% CI: 0.01, 0.05; p<0.01). At the same time there was no change observed in the percent of beneficiaries who filled a benzodiazepine prescription in states with an operational PDMP monitoring Schedule IV CS throughout the study period (0.00; 95% CI: 0.00, 0.01; p=0.31) or without an operational PDMP monitoring Schedule IV CS throughout the study period (-0.01; 95% CI: -0.03, 0.00; p=0.12).

A change in the level of beneficiaries who filled a benzodiazepine prescription was observed in Connecticut and Iowa. In the August 2008, the first month after the Connecticut PDMP became operational, there was a statistically significant decrease the proportion of beneficiaries who filled a benzodiazepine prescription (-0.15; 95% CI: -0.30, -0.01; p=0.04). At the same time, no change in the level was observed in states that throughout the study period monitored Schedule IV CS (-0.01; 95% CI: -0.13, 0.11; p=0.89) or did not monitor Schedule IV CS (-0.02; 95% CI: -0.18, 0.15; p=0.84). A similar finding was observed in Iowa where in February 2009, the first month after the PDMP became operational, there was a statistically significant decrease in the proportion of beneficiaries who filled a benzodiazepine prescription (-0.28; 95% CI: -0.48, -0.08; p=0.01). Additionally, there was no observed change in the level of beneficiaries who filled a benzodiazepine prescription among states that throughout the duration of the study period monitored Schedule IV CS (-0.04, 95% CI: -0.12, 0.05; p=0.39) or did not monitor Schedule IV CS (-0.12; 95% CI: -0.25, 0.01; p=0.08).

Results from the interrupted time series analyses also suggest that while the beginning of Schedule IV monitoring in Illinois and PDMP implementation in South Carolina occurring in January 2008 did not have a direct effect on the trend or level of the proportion of beneficiaries who filled a benzodiazepine prescription (Tables 6.3c and 6.3f), states that did not have a PDMP monitoring Schedule IV CS throughout the study period had a statistically significant increase in the level of the proportion of beneficiaries who filled a benzodiazepine prescription during this timeframe (0.26; 95% CI: 0.16, 0.37; $p<0.01$). Also of note was that states that did not monitor Schedule IV CS throughout the study period experienced a decline in the rate of increase of the proportion of beneficiaries who filled a benzodiazepine prescription during the same timeframe when the PDMPs in Arizona, Connecticut, and Louisiana became operational, however, a similar change in these states was not observed (Tables 6.3a, 6.3b, and 6.3e).

In most states that implemented a PDMP monitoring Schedule IV CS during the study period the relative effect of the program, based on pre-PDMP predicted values, was not statistically significant (Figures 6.3a-6.3f). Two states, Connecticut (Figure 6.2b) and Iowa (Figure 6.2d), had significant reductions in the proportion of beneficiaries who filled a benzodiazepine prescription. In each instance the significance of this effect was negated after only three months. In Connecticut the PDMP resulted in a 5.26% (95% CI: -9.71%, -0.35%; p=0.04) reduction in the proportion of beneficiaries who filled a benzodiazepine prescription in the first month after implementation based on pre-PDMP predicted values. This was followed by a 5.22% (95% CI: -9.93%, 0.00%; p=0.04) and 5.17% (95% CI: 10.11%, 0.00%; p=0.05) reduction in the second and third months before becoming insignificantly different from pre-PDMP predicted values. In Iowa the relative effect of the PDMP in the first month based on pre-PDMP predicted values was a 9.74% (95% CI: -15.96%, -2.11%; p=0.01) reduction in the proportion of beneficiaries who filled a benzodiazepine prescription. This was followed by a 7.96% (95% CI: -

14.14%, -1.22%; p=0.02) and 6.74% (95% CI: 12.63%, 0.00%; p=0.05) reduction in the subsequent months before the relative effect of the PDMP was no longer significant.

Multivariate Logistic Regression Analysis

In the overall study population, the odds of filling a benzodiazepine prescription were influenced by the presence of an operational PDMP monitoring Schedule IV CS, sex, race, age, presence of a psychiatric disorder, the unemployment rate, and time (Table 6.4). The odds of filling a benzodiazepine prescription were two times greater for females compared to males (AOR: 2.07; 95% CI: 2.04-2.10) and 2.5 times higher for beneficiaries 45-64 years of age than beneficiaries 19-44 (AOR 2.52; 95% CI: 2.49-2.55). Having received a diagnosis for a psychiatric disorder during the study period also significantly increased the likelihood of filling a benzodiazepine prescription during the study period. Among beneficiaries having received a diagnosis of anxiety, the odds of filling a benzodiazepine prescription were 48 times greater (AOR: 47.92; 95% CI: 46.84-49.02) compared to beneficiaries without a diagnosis. Having received a diagnosis for insomnia increased the likelihood of filling a benzodiazepine prescription 10 times (AOR: 10.23; 95% CI: 10.00-10.46) and among those with depression the odds of filling a benzodiazepine prescription were nearly 10 times greater than those without a diagnosis (AOR: 9.91; 95% CI: 9.70-10.13). Additionally, the time trend variable included in the model suggests that as time progressed during the study period, the odds of a beneficiary filling a benzodiazepine prescription in a given month were also increasing (AOR: 1.02; 95% CI: 1.02-1.02).

Conversely, beneficiaries identified and black, Hispanic, or other race were less likely than white beneficiaries to have filled a benzodiazepine prescription during the study period. The odds of Hispanic (AOR: 0.63; 95% CI: 0.61-0.64) and beneficiaries of other race (AOR: 0.64;

95% CI: 0.63-0.65) filling a benzodiazepine prescription were only about 60% of that of white beneficiaries while black beneficiaries were only half as likely to fill a benzodiazepine prescription compared to their white counterparts (AOR: 0.49; 95% CI: 0.48-0.51). Beneficiaries diagnosed with multiple psychiatric comorbidities were significantly less likely to fill a benzodiazepine prescription than beneficiaries without any diagnosis of a psychiatric disorder (AOR: 0.22; 95% CI: 0.21-0.22). Also, the presence of an operational PDMP monitoring Schedule IV CS lowered the odds of filling a benzodiazepine prescription. When such a PDMP was present the odds of filling a benzodiazepine prescription were only 92% (AOR: 0.92; 95% CI: 0.92-0.93) of that compared to instances where one was not.

Results from the interaction model determining whether PDMPs have a differential impact on specific subgroups of beneficiaries by interacting the PDMP indicator variable with beneficiary specific predictor variables are presented in Table 6.4. Adjusted for the covariates described previously, results from the interaction model infer that the presence of a PDMP monitoring Schedule IV CS differentially impacts the likelihood that specific subgroups within the population fill a prescription for a benzodiazepine. For the reference group of white males, between the ages of 19 and 44, and absent a diagnosis of anxiety, depression or insomnia, the presence of a PDMP monitoring schedule IV CS decreased the likelihood of filling a benzodiazepine prescription to 97% (AOR: 0.97; 95% CI: 0.95-0.98) of what they were when one is not present or monitoring Schedule IV CS. For females, non-white beneficiaries, and those between 45 and 64 years of age, the odds were further decreased. When a PDMP was operational and monitoring Schedule IV CS females were only 95% (AOR: 0.95; 0.94-0.97) as likely to fill a benzodiazepine prescription compared to the reference group, blacks 93% (AOR: 0.93; 95% CI: 0.90-0.97), Hispanics 91% (AOR: 0.91; 95% CI: 0.88-0.94), beneficiaries of another race 92% (AOR: 0.92; 95% CI: 0.89-0.94), and those between 45 and 64 years of age 90% (AOR:

0.90; 95% CI: 0.88-0.91). Conversely, those beneficiaries who had received an anxiety diagnosis were 12% more likely (AOR: 1.12; 95% CI: 1.10-1.14) to fill a benzodiazepine prescription when there was an operational PDMP monitoring Schedule IV CS than the reference group. Beneficiaries who had been diagnosed with insomnia had 11% (AOR: 1.11; 95% CI: 1.08-1.13) greater odds of filling a benzodiazepine prescription in the presence of a PDMP monitoring Schedule IV CD than the reference group, and beneficiaries diagnosed with depression were 2% more likely (AOR: 1.02; 95% CI: 1.00-1.05) to fill a benzodiazepine prescription.

Linear combinations of effect estimates (Table 6.5) demonstrate that in the presence of a PDMP monitoring Schedule IV CS, females, beneficiaries identified as black, Hispanic, or other race, those 45 and older, and who had multiple psychiatric disorder diagnoses experienced reduced odds of filling a benzodiazepine prescription. In the presence of a PDMP monitoring Schedule IV CS the odds of filling a benzodiazepine prescription for females was 92% (AOR: 0.92; 95% CI: 0.90-0.94) what they were when no program was operational. For blacks the odds were reduced to 90% (AOR: 0.90; 95% CI: 0.86-0.94), Hispanics 88% (AOR: 0.88; 95% CI: 0.85-0.91), beneficiaries of other races 89% (AOR: 0.89; 95% CI: 0.86-0.91), and those 45 and older only had 87% (AOR: 0.87; 95% CI: 0.85, 0.88) of the odds of filling a benzodiazepine prescription in the presence of PDMP monitoring Schedule IV CS compared to when no program was operational. Of note, females (AOR: 1.94; 95% CI: 1.90-1.98) and those 45 and older (AOR: 2.27; 95% CI: 2.22-2.31) were still approximately two times more likely to fill a benzodiazepine prescription in the presence of a PDMP monitoring Schedule IV CS than their male and younger counterparts. However, the presence of a PDMP monitoring Schedule IV CS further reduced the odds of black (AOR: 0.45; 95% CI: 0.43-0.47), Hispanic (AOR: 0.57; 95% CI: 0.55-0.59), and beneficiaries of other race (AOR: 0.59; 95% CI: 0.57-0.60) filling a benzodiazepine prescription to nearly half that of white beneficiaries. Likewise, those with multiple psychiatric disorder diagnoses were only

94% (AOR: 0.94; 95% CI: 0.91-0.98) as likely to fill a benzodiazepine prescription when there was a PDMP monitoring Schedule IV CS further reducing the odds of filling a benzodiazepine prescription to only 20% (AOR: 0.21; 95% CI: 0.20-0.22) of those absent any psychiatric disorder diagnosis.

In the presence of a PDMP monitoring Schedule IV CS, beneficiaries who had received an anxiety or insomnia diagnosis during the study period experienced greater odds of filling a benzodiazepine prescription compared to when no program was operational. Beneficiaries who had received an anxiety diagnosis were 8% (AOR: 1.08; 95% CI; 1.06–1.11) more likely to fill a benzodiazepine prescription. Likewise, those who had been diagnosed with insomnia experienced a 7% increase (AOR: 1.07; 95% CI: 1.04–1.10) increase in their odds of filling a benzodiazepine prescription.

Characteristics of PDMPs during the study period between January 2007 and December 2009 are presented in Table 6.7. Results from the model testing whether the presence of a PDMP alone or instead individual characteristics of the program affect benzodiazepine dispensing are reported in Table 6.8. The findings indicate that it is individual characteristics of the PDMP, and not the presence of the PDMP alone, that have an effect on the likelihood of filling a benzodiazepine prescription. The model found that beneficiaries residing in a state where the PDMP was housed in a safety focused agency were less likely (AOR: 0.70; 95% CI: 0.68, 0.73) to fill a benzodiazepine prescription. There was no observed effect on the likelihood of filling a benzodiazepine prescription in states were the PDMP was housed in a health focused agency (AOR: 0.97; 95% CI: 0.93, 1.01) or a licensing board (AOR: 1.00; 95% CI: 0.97, 1.04). Authorized access to a beneficiary's CS history report by pharmacists and law enforcement officials resulted in an increase in the odds of filling a benzodiazepine prescription. When

pharmacists were allowed to access CS history reports, in addition to submitting CS dispensing records, there was a 24% increase (AOR: 1.24; 95% CI: 1.21, 1.27) in the odds of filling a benzodiazepine prescription. When law enforcement officials hand the ability to access a beneficiary's CS history report there was a 3% increase (AOR: 1.03; 95% CI: 1.01, 1.05) in the odds of filling a benzodiazepine prescription. Regarding the CS Schedules monitored by the PDMP, there was no effect observed on the odds of filling a benzodiazepine prescription when the program only monitored Schedule II & III CS (AOR: 1.03; 95% CI: 0.99, 1.06) or Schedule II-IV CS (AOR: 1.01; 95% CI: 0.95, 1.07) compared to Schedule II CS monitoring only. When the CS Schedules monitored included Schedule II-V there was a 17% increase (AOR: 1.17; 95% CI: 1.12, 1.24) in the likelihood of filling a benzodiazepine prescription. The addition of the authority to monitor non-controlled substances, however, resulted in a decrease in the odds of filling a benzodiazepine prescription (AOR: 0.91; 95% CI: 0.89, 0.93). When compared beneficiaries in states with PDMPs that only required CS dispensing to be reported monthly, those residing in states that mandated bi-monthly (AOR: 0.87; 95% CI: 0.85, 0.88) or daily (AOR: 0.74; 95% CI: 0.66, 0.83) experienced decreased odds of filling a benzodiazepine prescription. However, a 10% increase in the odds (AOR: 1.10; 95% CI: 1.07, 1.13) of filling a benzodiazepine prescription was found among those residing in states where weekly reporting of CS dispensing to the PDMP was required.

DISCUSSIONS

In this sample of continuously eligible adult beneficiaries in the United States, PDMPs monitoring Schedule IV CS impacted benzodiazepine dispensing. The findings of the interrupted time series analyses suggested that in the month following the PDMP implementations in Connecticut and Iowa there was a significant decrease in the level of the percentage of each

states' beneficiaries who filled a benzodiazepine prescription. Results also indicated that in the year after the PDMP in Iowa became operational the proportion of beneficiaries who filled a benzodiazepine prescription each month was increasing at a faster rate than it was prior to the PDMP going into effect. This finding was at least partially negated by the decrease in the level of the proportion of beneficiaries who filled a benzodiazepine prescription which resulted in the relative effect of the PDMP being a significant reduction in the proportion of beneficiaries who filled a benzodiazepine prescription in the first three months following implementation with no significant difference detected thereafter.

The PDMP implementation in Connecticut and Iowa created a shock to the system and the trend of benzodiazepine dispensing to beneficiaries as the percentage of the population who filled a benzodiazepine prescription was significantly lower in the month following the PDMP implementation compare to the month prior to the program. The relative effect of these shocks in each of these two states were only observed for three months before the observed percentage of the population who filled a benzodiazepine prescription approached their predicted values as no PDMP been implemented. These results from Connecticut and Iowa in conjunction with the other states that had a PDMP implemented during the study period suggest that with regards to benzodiazepine dispensing PDMP implementation may have a modest short-term effect on the percentage of the beneficiaries who fill a prescription, however there is not significant long-term impact as healthcare providers and patients will adjust to the new policy and the proportion of beneficiaries who fill a benzodiazepine prescription will approach their pre-PDMP predicted values.

Furthermore, benzodiazepine dispensing was indirectly impacted in some states by the implementation of a PDMP monitoring Schedule IV CS. In Illinois and South Carolina, two states

that began monitoring Schedule IV CS in January 2008, having the PDMP become operational may have prevented the rate of benzodiazepine dispensing from increasing at a faster rate. States that did not monitor Schedule IV CS during 2008 and 2009 experienced an increase in the trend of the proportion of beneficiaries who filled a benzodiazepine prescription in each month whereas there was no evidence of a change in the trends observed in Illinois and South Carolina. This result suggests that there may have been an unobserved factor occurring at this time that was associated with an increasing proportion of beneficiaries who filled a benzodiazepine prescription but the effect of this factor was mitigated by the presence of a PDMP as states that had a PDMP throughout the study period, in addition to Illinois and South Carolina, did not have a significant change in the trend of the proportion of beneficiaries who filled a benzodiazepine prescription between January 2008 and December 2009 compared to January through December of 2007.

Of interest is the finding after PDMPs were implemented in Arizona, Connecticut, and Louisiana there was no evidence of a change in the trend regarding the proportion of beneficiaries who filled a benzodiazepine prescription each month, however, in states that did not have a PDMP monitoring Schedule IV CS during this time experienced a decline in the trend. One explanation is that there was an alternative intervention occurring concurrently that targeted states without Schedule IV CS monitoring, as states that had a PDMP in place throughout also did not experience a decline in the trend of benzodiazepine dispensing.

Results from the linear logistic regression model found an association between an operational PDMP monitoring Schedule IV CS and a reduction in the odds of filling a benzodiazepine prescription. Furthermore, the interaction model provided evidence that PDMPs may differentially influence the likelihood of filling a benzodiazepine prescription among certain

subgroups within the population. Females, blacks, Hispanics, beneficiaries of other races, those between the ages of 45 and 64, and those with more than one psychiatric condition were significantly less likely to fill a benzodiazepine prescription during the study period when Schedule IV CS were being monitored by a PDMP. Even with having an operational PDMP, females and beneficiaries between 45 and 64 remained more likely to fill a benzodiazepine prescription than their male and younger counterparts, a finding that is in line with existing evidence demonstrating that in the general US population, benzodiazepines are more likely to be prescribed to females and older individuals.[166] The finding that having an operational PDMP was associated with black, Hispanic, and beneficiaries of other races being even less like to fill a benzodiazepine prescription is consistent with findings reported by Pearson et al.[74] who found Medicaid beneficiaries residing in predominately black, Hispanic, or mixed race neighborhoods were consistently more likely to have their benzodiazepine therapy discontinued after they were added to the list of medications monitored by the New York TPP.

No evidence of a chilling effect was detected among beneficiaries who received a diagnosis of anxiety or insomnia during the study period. Moreover, the odds of beneficiaries with these diagnoses filling a benzodiazepine prescription were greater when a PDMP monitoring Schedule IV CS was operational. As benzodiazepines are indicated to manage symptoms associated with these conditions, this suggests that PDMPs, as they pertain to benzodiazepines, do not induce a chilling effect by restricting access to pharmacotherapy options among those with a diagnosis of anxiety or insomnia, two conditions where benzodiazepine therapy is appropriate. An explanation for this finding is that prescribers and dispensers may have felt more confident in their decisions surrounding benzodiazepine use in a patient with these conditions in the presence of a PDMP. This potential increase in confidence may be because the information contained within a patient's CS history report could give a more

comprehensive depiction of the patient's CS use history and allow for a quick determination of the appropriateness of benzodiazepine in the patient ad their propensity to abuse or divert the medication.

Of interest was the result that patients with multiple psychiatric diagnoses were significantly less likely to fill a benzodiazepine prescription than those without any psychiatric diagnoses, and furthermore, the presences of a PDMP monitoring Schedule IV CS further depressed these odds. This finding indicates that benzodiazepines are not prescribed and dispensed to patients with more severe and complex psychiatric illness. This could be because alternate therapeutic options are being utilized in these patients as severe psychiatric disorders have been acknowledged as a risk factor for substance use disorders.[231] The finding that PDMPs monitoring Schedule IV CS further reduces the likelihood of filling a benzodiazepine prescription indicates that prescribers and dispensers may be using a patient's CS history report to identify those most at risk of inappropriate benzodiazepine use.

After adjusting for individual characteristics of PDMPs, it was determined that it is individual characteristics of these programs, and not the presence of the program itself, that impact the likelihood of filling a benzodiazepine prescription. An interesting finding was that safety focused housing agencies of PDMPs were associated with a significant decrease in the likelihood of filling a benzodiazepine prescription. This finding may be due to increased reluctances of prescribing and dispensing benzodiazepines, and other CS, by healthcare providers due to fears of investigations and prosecutions related to CS prescribing and dispensing behaviors. Also of interest was that more frequent reporting requirements, with the exception of weekly reporting, was associated with lower odds of filling a benzodiazepine prescription. During the timeframe of this study only North Dakota had a mandate requiring

dispensers to report daily their CS dispensing records. Therefore, the finding of weekly reporting of CS dispensing requirements being associated with an increase in the odds of filling a benzodiazepine prescription may be related to healthcare providers feeling they had a comprehensive insight into the patient's history of CS behaviors and thus an increase confidence in the prescribing and dispensing of benzodiazepines to their patients.

Of note is the result that law enforcement access to PDMPs was associated with a slight increase in the odds of filling a benzodiazepine prescription. This categorization does not take into account the types of law enforcement officials who have access to information from the PDMP or the process necessary for them to acquire that information. For example, in some states law enforcement officials may be required to be pursuing an active investigation in order to obtain a CS history report while in other states only a select few law enforcement officials are allowed to directly access and obtain CS history reports from the PDMP. These officials are then responsible for disseminating that report or the information contained within to other law enforcement officials as needed. These variations in laws pertaining to law enforcement access should be considered when evaluating the meaningfulness of this particular finding.

Limitations to this study exist. First, this study employs data for a nationally representative sample extracted from private insurance claims database and may not accurately represent the overall US population. Due to the utilization of a claims database this study could not account for prescription medications acquired from sources outside the healthcare system or paid for using cash. Additionally, this study utilized diagnostic codes for psychiatric comorbidities for which benzodiazepines are indicated and/or commonly prescribed as proxies for appropriate benzodiazepines use. While these proxies may not encompass all facets of appropriate benzodiazepine use they are consistent with the goals of PDMPs in mitigating

prescription drug abuse and its consequences while maintaining access to those with a legitimate need for CS medications. Also, this study did not account for the number of benzodiazepine prescriptions filled or the quantity and dosage of these prescriptions. However, as the aim of this study was to understand the impact of PDMPs on the likelihood of filling a benzodiazepine prescription among privately insured beneficiaries this information was not required. Differences may exist between what was written in PDMP legislation and what was practiced. For example, even though some states had the authority to monitor non-controlled substances they may not have been actively doing so. Additionally, variability in the operationalization of PDMPs housed within the same type of housing agency is possible, (e.g., types of PDMP requestor accounts, requirements for determining the necessity of requesting a report) and may impact the observed findings, however, decisions on how individual PDMPs are operationalized are made in order to achieve the overall goals and mission of the program, which are likely similar among programs housed within the same type of agency.

The findings presented in this study indicated that PDMPs monitoring Schedule IV CS have an impact on the dispensing of benzodiazepines. Using an interrupted time series model evidence was provided that indicated having a PDMP monitoring Schedule IV CS become operational directly and indirectly impacted benzodiazepine dispensing trends. The presence of a PDMP monitoring Schedule IV CS was found to decrease the likelihood of filling a benzodiazepine prescription, especially for those beneficiaries who were female, black, Hispanic, of another race, between 45 and 64 years of age, or who had multiple psychiatric disorders. On the other hand, beneficiaries diagnosed with only anxiety or insomnia during the study period experienced an increase in their odds of filling a benzodiazepine prescription suggesting that for beneficiaries diagnosed with these conditions there was no “chilling effect” induced by a PDMP. Furthermore, specific characteristics of PDMPs were found to have a

significant effect on the odds of filling a benzodiazepine prescription, and should be considered when amending current PDMPs laws in order to assist effort of mitigating the prescription drug abuse crisis.

The findings in this study provide support for PDMPs as an effective tool to address the prescription drug abuse epidemic in the US as it pertains to benzodiazepines. Future studies regarding the relationship between PDMPs and benzodiazepines should explore clinical outcomes experienced by those who have their benzodiazepine therapy discontinued to better understand the economic and societal costs associated with PDMPs. Future policy amendments should focus on reducing the potential for disparities in benzodiazepine access among vulnerable groups within the population. As PDMPs become a more widely utilized tool to combat prescription drug abuse and diversion more research is needed to understand their clinical utility and ensure they do no obstruct access to legitimate pharmacotherapies.

Table 6.1. Demographic characteristics of continuously enrolled, commercially insured adults in the United States.

	Number of beneficiaries (%)
Sample size	*2,827,874*
Benzodiazepine utilization	
Filled benzodiazepine prescription	443,380 (16%)
Gender	
Male	1,354,884 (48%)
Female	1,472,990 (52%)
Age	
Median[a] (IQR)	44 (35-52)
Education	
High school diploma or less	955,281 (34%)
Some college or college degree	1,787,429 (63%)
Race	
White	2,085,190 (74%)
Black	146,165 (5%)
Hispanic	240,090 (8%)
Other	331,325 (12%)
Psychiatric disorder diagnosis	
Anxiety	325,107 (12%)
Depression	352,750 (12%)
Insomnia	175,090 (6%)
Multiple psychiatric disorder diagnoses	206,112 (7%)

[a] Median age was evaluated for the year 2007

Table 6.2. Prescription drug monitoring programs tracking the dispensing of Schedule IV controlled substances for the period January 2007 – December 2009.[31]

PDMP operational throughout study period	*No PDMP operational throughout study period*	*PDMP operational but Schedule IV CS not monitored*	*PDMP became operational during study period (date of PDMP implementation)*
Alabama	Alaska	Massachusetts	Arizona
California	Arkansas	Pennsylvania	(October 2008)
Hawaii	Delaware	Rhode Island	Colorado
Idaho	District of Columbia	Texas	(July 2007)
Indiana	Florida		Connecticut
Kentucky	Georgia		(July 2008)
Maine	Kansas		Illinois[a]
Michigan	Maryland		(January 2008)
Mississippi	Minnesota		Iowa
Nevada	Missouri		(January 2009)
New Mexico	Montana		Louisiana
New York	Nebraska		(November 2008)
Ohio	New Hampshire		North Carolina
Oklahoma	New Jersey		(July 2007)
Tennessee	Oregon		North Dakota
Utah	South Dakota		(September 2007)
Virginia	Washington		South Carolina
West Virginia	Wisconsin		(January 2008)
Wyoming			Vermont
			(January 2009)

[a] Prior to Jan. 2008 Illinois had a PDMP in place but only electronically monitored Schedule II CS

Table 6.3a. Interrupted time series analysis examining the percentage of beneficiaries filling a benzodiazepine prescription by month (Arizona).

	Arizona	*States with no PDMP throughout the study period*	*States with a PDMP throughout the study period*
	Coefficient p-value 95% Confidence Interval	Coefficient p-value 95% Confidence Interval	Coefficient p-value 95% Confidence Interval
Monthly rate of increase in beneficiaries filling a benzodiazepine prescription prior to PDMP	0.02 <0.01 0.02, 0.03	0.04 <0.01 0.04, 0.05	0.02 <0.01 0.01, 0.03
Monthly rate of increase in beneficiaries filling a benzodiazepine prescription after PDMP implementation	0.03 <0.01 0.02, 0.03	0.03 <0.01 0.03, 0.05	0.02 <0.01 0.02, 0.03
Change in the rate of increase of beneficiaries filling a benzodiazepine prescription pre/post PDMP	0.00 0.29 0.00[a], 0.01	-0.01 0.04 -0.03, 0.00[a]	0.00 0.51 -0.01, 0.01
Change in the level one month after PDMP implementation	-0.06 0.17 -0.14, 0.03	-0.08 0.11 -0.17, 0.02	-0.01 0.43 -0.30, 0.13

[a] Confidence interval contains 0.00 due to rounding

Table 6.3b. Interrupted time series analysis examining the percentage of beneficiaries filling a benzodiazepine prescription by month (Connecticut).

	Connecticut	States with no PDMP throughout the study period	States with a PDMP throughout the study period
	Coefficient *p-value* *95% Confidence Interval*	*Coefficient* *p-value* *95% Confidence Interval*	*Coefficient* *p-value* *95% Confidence Interval*
Monthly rate of increase in beneficiaries filling a benzodiazepine prescription prior to PDMP	0.03 <0.01 0.02, 0.04	0.04 <0.01 0.03, 0.05	0.02 <0.01 0.01, 0.03
Monthly rate of increase in beneficiaries filling a benzodiazepine prescription after PDMP implementation	0.03 <0.01 0.02, 0.04	0.02 <0.01 0.01, 0.03	0.02 <0.01 0.02, 0.03
Change in the rate of increase of beneficiaries filling a benzodiazepine prescription pre/post PDMP	0.00 0.65 -0.02, 0.01	-0.02 0.01 -0.03, -0.01	0.00 0.70 -0.01, 0.01
Change in the level one month after PDMP implementation	-0.15 0.04 -0.30, 0.01	-0.03 0.72 -0.16, 0.11	0.01 0.82 -0.11, 0.14

Table 6.3c. Interrupted time series analysis examining the percentage of beneficiaries filling a benzodiazepine prescription by month (Illinois).

	Illinois	States with no PDMP throughout the study period	States with a PDMP throughout the study period
	Coefficient *p-value* *95% Confidence Interval*	*Coefficient* *p-value* *95% Confidence Interval*	*Coefficient* *p-value* *95% Confidence Interval*
Monthly rate of increase in beneficiaries filling a benzodiazepine prescription prior to PDMP	0.03 <0.01 0.02, 0.04	0.03 <0.01 0.02, 0.03	0.02 <0.01 0.01, 0.04
Monthly rate of increase in beneficiaries filling a benzodiazepine prescription after PDMP implementation	0.02 <0.01 0.01, 0.03	0.02 <0.01 0.02, 0.03	0.02 <0.01 0.02, 0.03
Change in the rate of increase of beneficiaries filling a benzodiazepine prescription pre/post PDMP	-0.01 0.26 -0.02, 0.01	0.00 0.59 -0.02, 0.01	0.00 0.91 -0.01, 0.01
Change in the level one month after PDMP implementation	-0.08 0.30 -0.22, 0.07	0.20 <0.01 0.09, 0.31	-0.03 0.65 -0.15, 0.10

Table 6.3d. Interrupted time series analysis examining the percentage of beneficiaries filling a benzodiazepine prescription by month (Iowa).

	Iowa	States with no PDMP throughout the study period	States with a PDMP throughout the study period
	Coefficient *p-value* *95% Confidence Interval*	*Coefficient* *p-value* *95% Confidence Interval*	*Coefficient* *p-value* *95% Confidence Interval*
Monthly rate of increase in beneficiaries filling a benzodiazepine prescription prior to PDMP	0.03 <0.01 0.02, 0.04	0.04 <0.01 0.03, 0.04	0.02 <0.01 0.02, 0.02
Monthly rate of increase in beneficiaries filling a benzodiazepine prescription after PDMP implementation	0.06 <0.01 0.04, 0.08	0.03 <0.01 0.02, 0.04	0.03 <0.01 0.02, 0.03
Change in the rate of increase of beneficiaries filling a benzodiazepine prescription pre/post PDMP	0.03 <0.01 0.01, 0.05	-0.01 0.18 -0.02, 0.01	0.00 0.38 -0.01, 0.01
Change in the level one month after PDMP implementation	-0.28 0.01 -0.48, -0.08	-0.11 0.06 -0.22, 0.01	0.00 0.95 -0.08, 0.08

Table 6.3e. Interrupted time series analysis examining the percentage of beneficiaries filling a benzodiazepine prescription by month (Louisiana).

	Louisiana	States with no PDMP throughout the study period	States with a PDMP throughout the study period
	Coefficient *p-value* *95% Confidence Interval*	*Coefficient* *p-value* *95% Confidence Interval*	*Coefficient* *p-value* *95% Confidence Interval*
Monthly rate of increase in beneficiaries filling a benzodiazepine prescription prior to PDMP	0.03 <0.01 0.02, 0.04	0.04 <0.01 0.03, 0.05	0.02 <0.01 0.01, 0.03
Monthly rate of increase in beneficiaries filling a benzodiazepine prescription after PDMP implementation	0.04 <0.01 0.04, 0.05	0.03 <0.01 0.02, 0.04	0.02 <0.01 0.02, 0.03
Change in the rate of increase of beneficiaries filling a benzodiazepine prescription pre/post PDMP	0.01 0.45 -0.01, 0.03	-0.01 0.04 -0.03, 0.00[a]	0.00 0.51 -0.01, 0.01
Change in the level one month after PDMP implementation	-0.13 0.14 -0.31, 0.04	-0.11 0.02 -0.22, -0.02	-0.03 0.57 -0.13, 0.07

[a] Confidence interval contains 0.00 due to rounding

Table 6.3g. Interrupted time series analysis examining the percentage of beneficiaries filling a benzodiazepine prescription by month (South Carolina).

	South Carolina	States with no PDMP throughout the study period	States with a PDMP throughout the study period
	Coefficient *p-value* *95% Confidence Interval*	*Coefficient* *p-value* *95% Confidence Interval*	*Coefficient* *p-value* *95% Confidence Interval*
Monthly rate of increase in beneficiaries filling a benzodiazepine prescription prior to PDMP	0.05 <0.01 0.03, 0.07	0.03 <0.01 0.02, 0.03	0.02 <0.01 0.01, 0.04
Monthly rate of increase in beneficiaries filling a benzodiazepine prescription after PDMP implementation	0.04 <0.01 0.02, 0.05	0.02 <0.01 0.02, 0.03	0.02 <0.01 0.02, 0.03
Change in the rate of increase of beneficiaries filling a benzodiazepine prescription pre/post PDMP	-0.01 0.43 -0.03, 0.01	0.00 0.59 -0.02, 0.01	0.00 0.91 -0.01, 0.01
Change in the level one month after PDMP implementation	-0.10 0.38 -0.33, 0.13	0.20 <0.01 0.09, 0.31	-0.03 0.65 -0.15, 0.10

Table 6.4. Odds of filling a benzodiazepine prescription between January 2007 and December 2009 among continuously enrolled adult beneficiaries in the United States.

Variable	*Odds Ratio*	*p-value*	*95% Confidence Interval*
PDMP			
No operational PDMP monitoring Schedule IV CS	Ref.		
PDMP operational and monitoring Schedule IV CS	0.92	<0.01	0.92 – 0.93
Sex			
Male	Ref.		
Female	2.07	<0.01	2.04 – 2.10
Race			
White	Ref.		
Black	0.49	<0.01	0.48 – 0.51
Hispanic	0.63	<0.01	0.61 – 0.64
Other	0.64	<0.01	0.63 – 0.65
Age			
Age 44 and under	Ref.		
Age 45 and over	2.52	<0.01	2.49 – 2.55
Diagnosis of a Psychiatric Disorder			
No psychiatric disorder diagnosis	Ref.		
Anxiety	47.92	<0.01	46.84 – 49.02
Depression	9.91	<0.01	9.70 – 10.13
Insomnia	10.23	<0.01	10.00 – 10.46
Multiple psychiatric diagnoses	0.22	<0.01	0.21 – 0.22
Economic Climate			
Unemployment rate[a]	1.00	0.03	1.00 – 1.00[b]
Time Trend			
Additional month[c]	1.02	<0.01	1.02 – 1.02

[a] Unemployment rate interpretation is the effect of a one percentage point increase in the unemployment rate

[b] Confidence interval includes 1.00 due to rounding

[c] Month interpretation is the effect of time progressing forward one additional month

Table 6.5. Odds of filling a benzodiazepine prescription among subgroups within a population of continuously enrolled adult beneficiaries in the United States between January 2007 and December 2009.

Variable	*Odds Ratio*	*p-value*	*95% Confidence Interval*
PDMP			
No operational PDMP monitoring Schedule IV CS	Ref.		
PDMP operational and monitoring Schedule IV CS	0.97	<0.01	0.95 – 0.98
Sex			
Male	Ref.		
Female	2.11	<0.01	2.08 – 2.14
Race			
White	Ref.		
Black	0.50	<0.01	0.49 – 0.52
Hispanic	0.64	<0.01	0.63 – 0.66
Other	0.66	<0.01	0.65 – 0.68
Age			
Age 44 and under	Ref.		
Age 45 and over	2.62	<0.01	2.59 – 2.66
Diagnosis of a Psychiatric Disorder			
No psychiatric disorder diagnosis	Ref.		
Anxiety	45.99	<0.01	44.90 – 47.10
Depression	9.83	<0.01	9.60 – 10.05
Insomnia	9.85	<0.01	9.61 – 10.09
Multiple psychiatric diagnoses	0.22	<0.01	0.21 – 0.23
Economic Climate			
Unemployment rate	1.00	0.05	1.00 – 1.00[a]
Time Trend			
Additional month	1.02	<0.01	1.02 – 1.02
Interaction variables			
PDMP * Female	0.96	<0.01	0.94 – 0.97
PDMP * Black	0.93	<0.01	0.90 – 0.97
PDMP * Hispanic	0.91	<0.01	0.88 – 0.94
PDMP * Other	0.92	<0.01	0.89 – 0.94
PDMP * Age over 45	0.90	<0.01	0.88 – 0.91
PDMP * Anxiety	1.12	<0.01	1.10 – 1.14
PDMP * Depression	1.02	0.03	1.00[a] – 1.05
PDMP * Insomnia	1.11	<0.01	1.08 – 1.13
PDMP * Multiple psychiatric diagnoses	0.98	<0.01	0.94 – 1.01

[b] Confidence interval includes 1.00 due to rounding

Table 6.6. Linear combinations of effect estimates comparing odds of subgroups within a population of continuously enrolled adult beneficiaries in the United States filling a benzodiazepine prescription with and without the presence of a PDMP monitoring Schedule IV controlled substances.

Variable	Odds of filling a benzodiazepine prescription when no PDMP monitoring Schedule IV CS is present (p-value) (95% CI)	Odds of filling a benzodiazepine prescription when a PDMP monitoring Schedule IV CS is present (p-value) (95% CI)	Comparison of odds of filling a benzodiazepine prescription when a PDMP monitoring Schedule IV CS is present to without (p-value) (95% CI)
Female	2.11 <0.01 (2.18 – 2.14)	1.94 <0.01 (1.90 – 1.98)	0.92 <0.01 (0.90 – 0.94)
Black	0.50 <0.01 (0.49 – 0.52)	0.45 <0.01 (0.43 – 0.47)	0.90 <0.01 (0.86 – 0.94)
Hispanic	0.64 <0.01 (0.63 – 0.66)	0.57 <0.01 (0.55 – 0.59)	0.88 <0.01 (0.85 – 0.91)
Other	0.66 <0.01 (0.65 – 0.68)	0.59 <0.01 (0.57 – 0.60)	0.89 <0.01 (0.86 – 0.91)
Age 45 and over	2.62 <0.01 (2.59 – 2.66)	2.27 <0.01 (2.22 – 2.31)	0.87 <0.01 (0.85 – 0.88)
Anxiety	45.99 <0.01 (44.90 – 47.10)	49.74 <0.01 (48.31 – 51.22)	1.08 <0.01 (1.06 – 1.11)
Depression	9.83 <0.01 (9.60 – 10.05)	9.72 <0.01 (9.44 – 10.01)	0.99 0.15 (0.96 – 1.01)
Insomnia	5.78 <0.01 (5.67 – 5.89)	10.55 <0.01 (10.23 – 10.88)	1.07 <0.01 (1.04 – 1.10)
Multiple psychiatric disorder diagnoses	0.22 <0.01 (0.21 – 0.23)	0.21 <0.01 (0.20 – 0.22)	0.94 <0.01 (0.91 – 0.98)

Table 6.7. Characteristics of prescription drug monitoring programs 2007-2009.[31,32]

State	*Housing Agency*	*Authorized Users*	*Schedules Monitored*	*Reporting Frequency*
Alabama	Health Focused	Prescribers Pharmacists	II-V	Weekly
Arizona	Licensing Board	Prescribers Pharmacists	II-IV	Weekly
California	Safety Focused	Prescribers Pharmacists Law Enforcement	II-IV	Monthly
Colorado	Licensing Board	Prescribers Pharmacists	II-V	Bi-monthly
Connecticut	Safety Focused	Prescribers Pharmacists	II-V	Weekly
Hawaii	Safety Focused	Prescribers Pharmacists	II-IV	Monthly
Idaho	Licensing Board	Prescribers Pharmacists Law Enforcement	II-IV Non-controlled substances	Monthly
Illinois	Health Focused	Prescribers Pharmacists Law Enforcement	II-III (until Dec 31, 2007) II-V (starting Jan 1, 2008)	Bi-monthly
Indiana	Licensing Board	Prescribers Law Enforcement	II-IV	Bi-monthly
Iowa	Licensing Board	Prescribers Pharmacists	II-IV	Bi-monthly
Kentucky	Health Focused	Prescribers Pharmacists Law Enforcement	II-V	Weekly
Louisiana	Licensing Board	Prescribers Pharmacists	II-IV	Bi-monthly
Maine	Health Focused	Prescribers Pharmacist	II-IV	Bi-monthly
Massachusetts	Health Focused	Prescribers Pharmacists	II	Monthly
Michigan	Licensing Board	Prescribers Pharmacists Law Enforcement	II-V	Monthly
Mississippi	Licensing Board	Prescribers Pharmacists	II-IV Non-controlled substances	Monthly
Nevada	Licensing Board	Prescribers Pharmacists	II-V Non-controlled substances	Monthly
New Mexico	Licensing Board	Prescribers Pharmacists Law Enforcement	II-IV	Monthly

Table 6.7. Characteristics of prescription drug monitoring programs 2007-2009 (cont'd).

New York	Health Focused	Prescribers	II-V	Monthly
North Carolina	Health Focused	Prescribers Pharmacists	II-V	Monthly
North Dakota	Licensing Board	Prescribers Pharmacists Law Enforcement	II-V Non-controlled substances	Daily
Ohio	Licensing Board	Prescribers Pharmacists	II-V Non-controlled substances	Bi-monthly
Oklahoma	Safety Focused	Prescribers Pharmacists	II-V	Monthly
Tennessee	Licensing Board	Prescribers Pharmacists Licensing Boards	II-V	Weekly
Pennsylvania	Safety Focused	Prescribers Pharmacists	II	Monthly
Rhode Island	Licensing Board	Law Enforcement	II-III	Monthly
South Carolina	Health Focused	Prescribers Pharmacists Law Enforcement	II-IV	Monthly
Texas	Safety Focused	Prescribers Pharmacists Law Enforcement	II	Monthly
Utah	Licensing Board	Prescribers Pharmacists	II-V	Monthly
Vermont	Health Focused	Prescribers Pharmacists	II-IV	Weekly
Virginia	Licensing Board	Prescribers Pharmacists	II-IV	Bi-monthly
West Virginia	Licensing Board	Prescribers Pharmacists	II-V	Weekly
Wyoming	Licensing Board	Prescribers Pharmacists	II-V Non-controlled substances	Monthly

Table 6.8. Characteristics of PDMPs that impact the dispensing of benzodiazepines.

Variable	*Odds Ratio*	*p-value*	*95% Confidence Interval*
PDMP			
No operational PDMP	Ref.		
Operational PDMP	0.96	0.21	0.91 – 1.02
Housing Agency			
Licensing agency	1.00	0.83	0.97 – 1.04
Health focused agency	0.97	0.06	0.93 – 1.01
Safety focused agency	0.70	<0.01	0.68 – 0.73
Groups Authorized to Access			
No pharmacist access	Ref.		
Pharmacists	1.24	<0.01	1.21 – 1.27
No law enforcement access	Ref.		
Law Enforcement Officials	1.03	<0.01	1.01 – 1.05
Schedules Monitored			
Schedule II only	Ref.		
Schedule II & III	1.03	0.13	0.99 – 1.06
Schedules II-IV	1.01	0.80	0.95 – 1.07
Schedule II-V	1.17	<0.01	1.12 – 1.24
Reporting Frequency			
Monthly	Ref.		
Bi-monthly	0.87	<0.01	0.85 – 0.88
Weekly	1.10	<0.01	1.07 – 1.13
Daily	0.74	<0.01	0.66 – 0.83
Authority to monitor non-controlled substances			
Non-controlled substance monitoring not authorized	Ref.		
Authority to monitory non-controlled substances	0.91	<0.01	0.89 – 0.93

Figure 6.1. Percentage of study population who filled a benzodiazepine prescription in each month between January 2007 and December 2009.

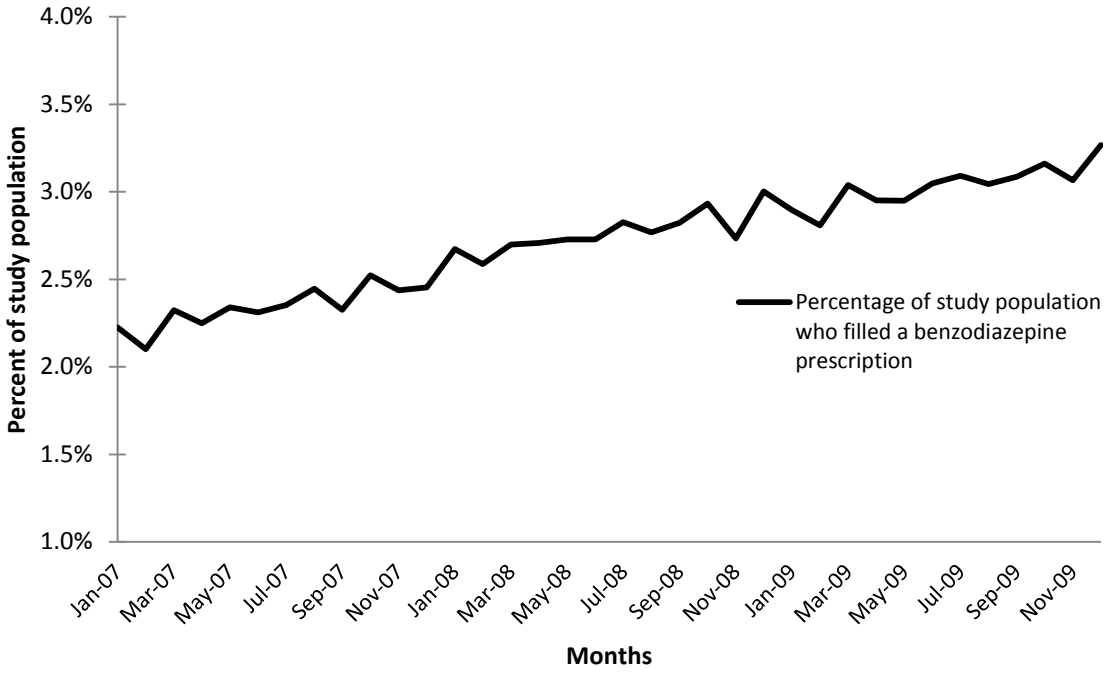


Figure 6.2a. Relative effect of PDMP implementation on the proportion of beneficiaries filling a benzodiazepine prescription (Arizona).

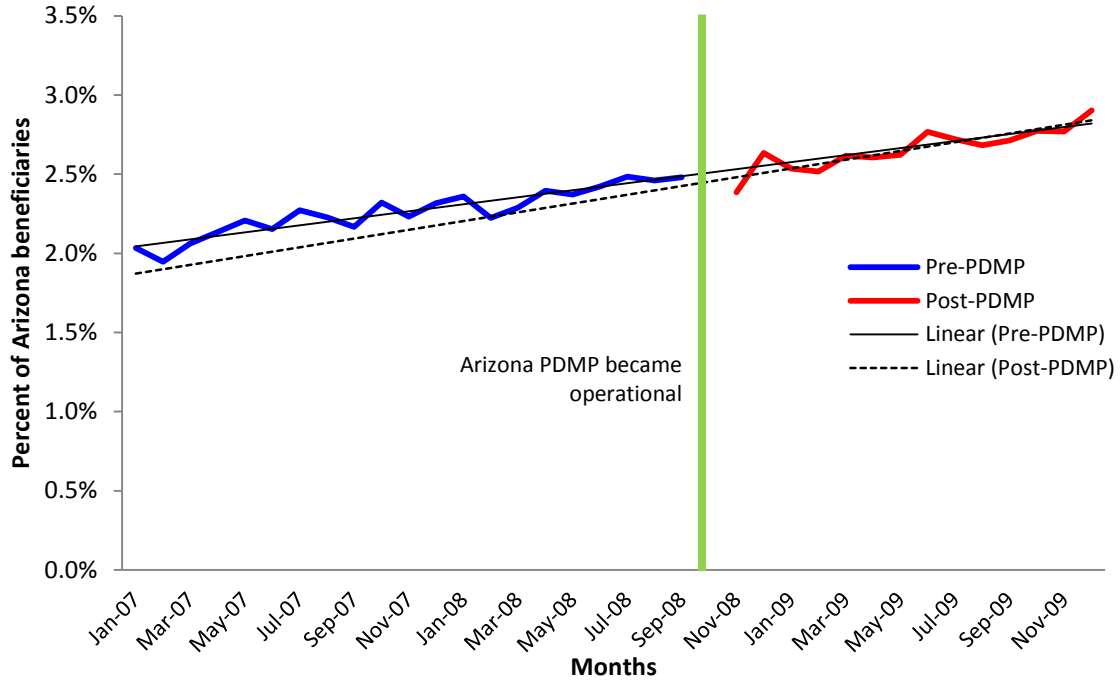


Figure 6.2b. Relative effect of PDMP implementation on the proportion of beneficiaries filling a benzodiazepine prescription (Connecticut).

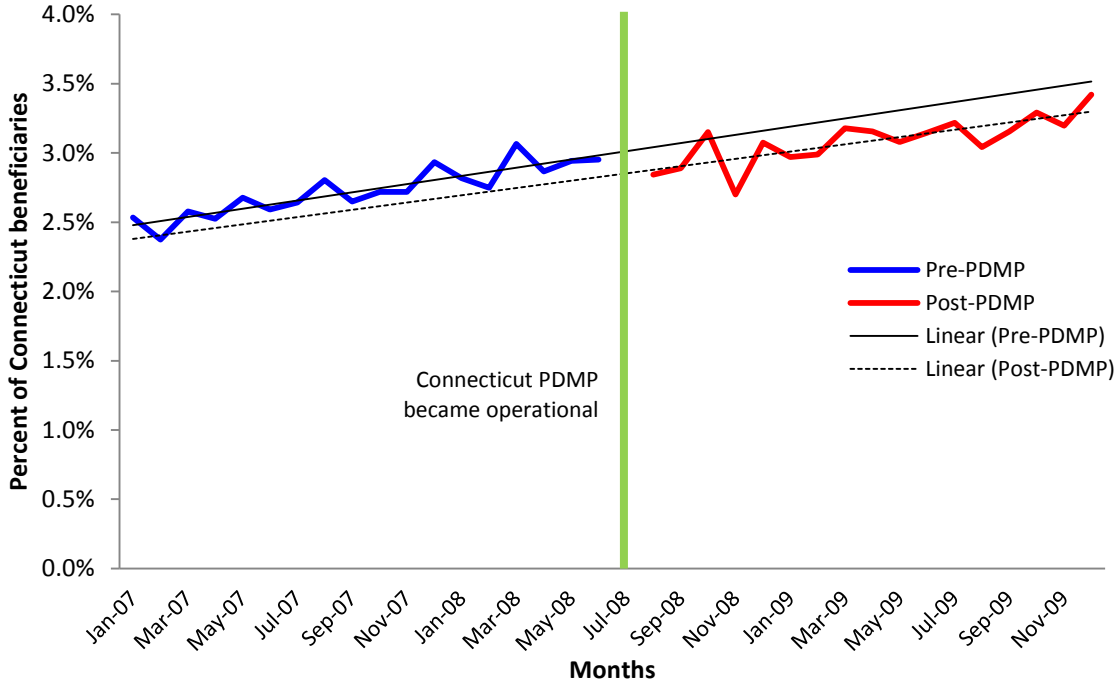


Figure 6.2c. Relative effect of PDMP implementation on the proportion of beneficiaries filling a benzodiazepine prescription (Illinois).

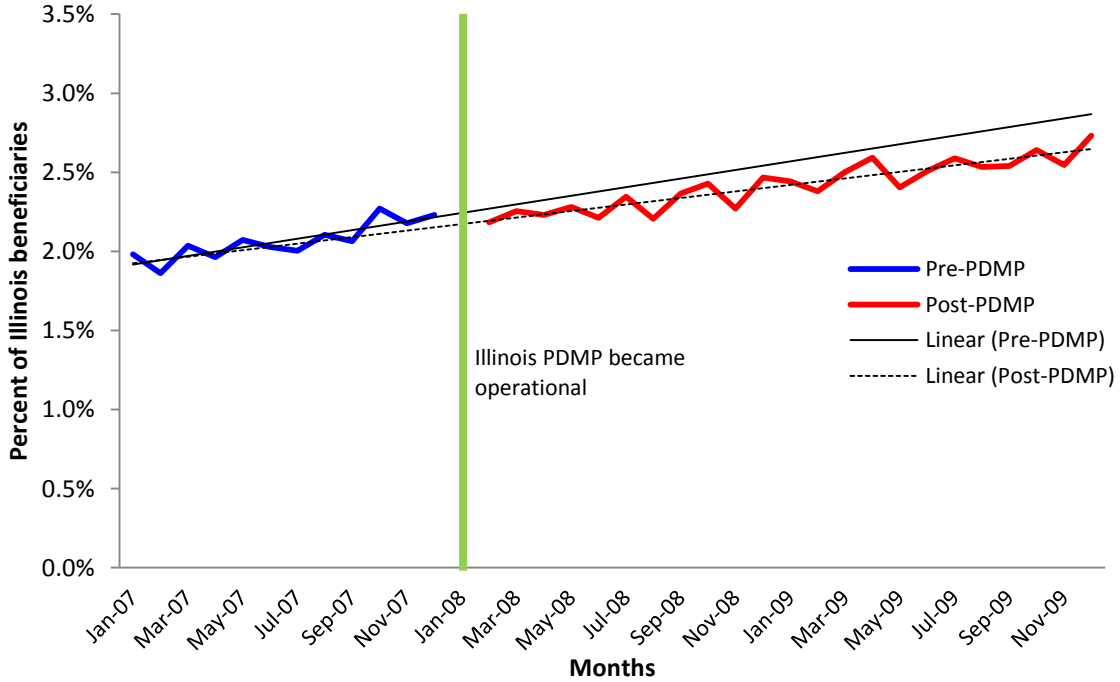


Figure 6.2d. Relative effect of PDMP implementation on the proportion of beneficiaries filling a benzodiazepine prescription (Iowa).

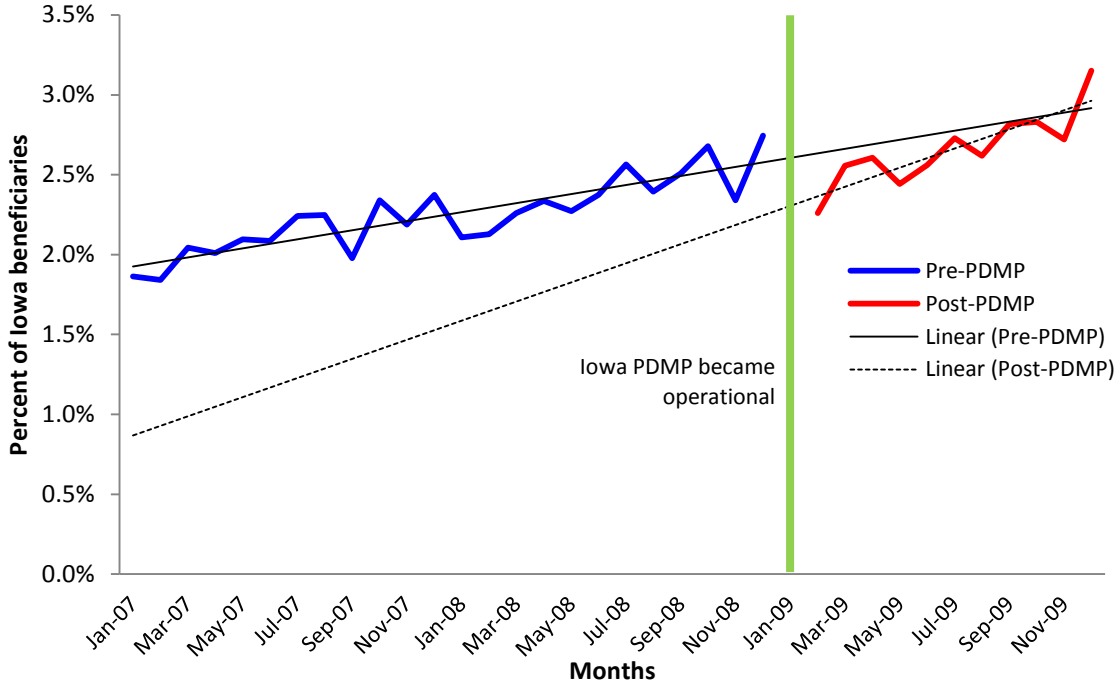


Figure 6.2e. Relative effect of PDMP implementation on the proportion of beneficiaries filling a benzodiazepine prescription (Louisiana).

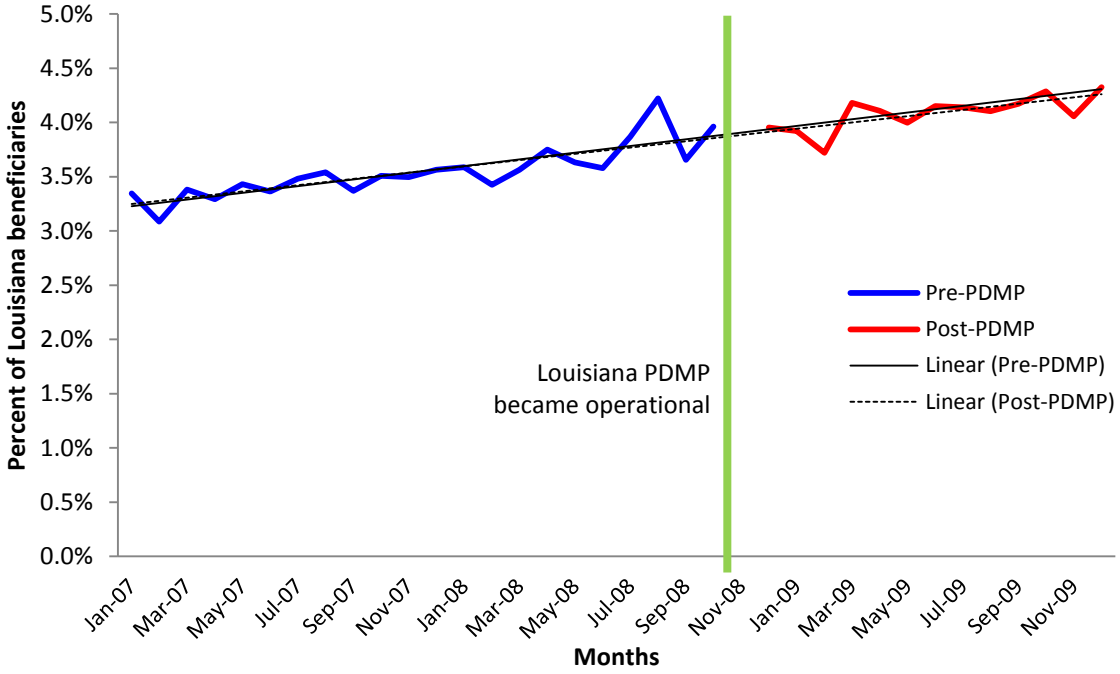
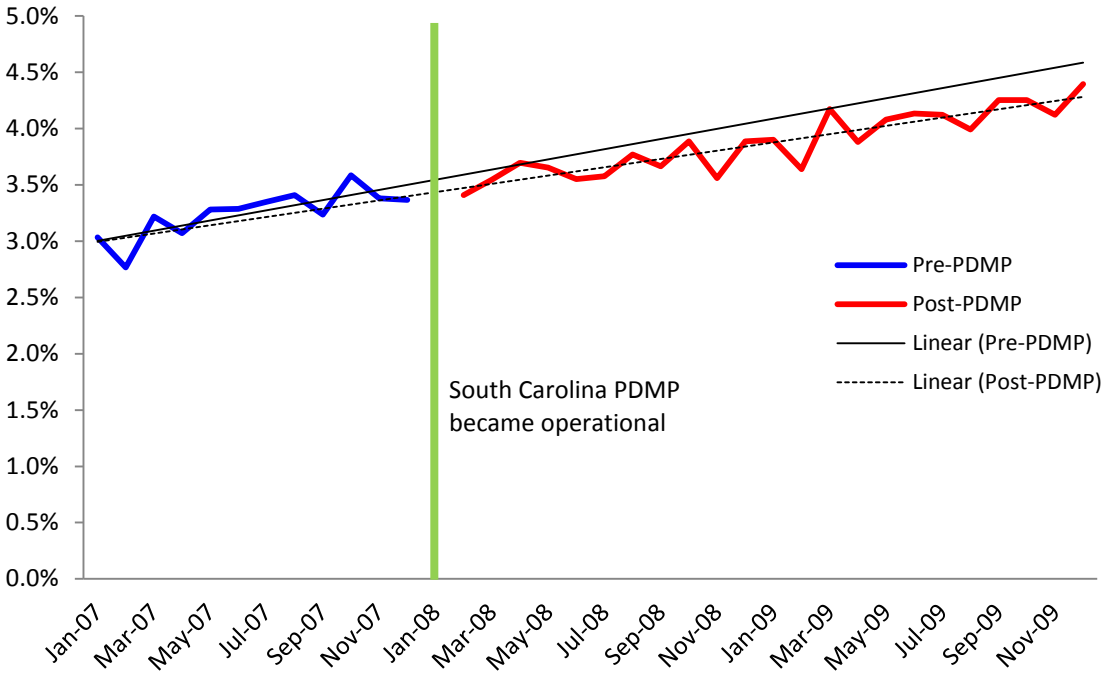


Figure 6.2g. Relative effect of PDMP implementation on the proportion of beneficiaries filling a benzodiazepine prescription (South Carolina).



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Curriculum Vitae

SARAH E. WIXSON

Education

Lexington, KY — **University of Kentucky, College of Pharmacy** — **2011 - 2015**
Doctor of Philosophy
Pharmaceutical Sciences
Track: Pharmaceutical Outcomes and Policy
Dissertation Title: "Medication misadventures: the case of benzodiazepines"

Lexington, KY — **University of Kentucky, Graduate School** — **2012 - 2013**
Graduate Certificate
Informatics

Lexington, KY — **University of Kentucky, College of Agriculture** — **2009 – 2011**
Master of Science
Agricultural Economics
Thesis Title: "Price asymmetric relationships in the commodity and energy markets"

Lexington, KY — **University of Kentucky, College of Agriculture** — **2004 – 2008**
Bachelor of Science
Agricultural Economics

Research and Academic Positions

2011 – Present	Graduate Research Assistant, Institute for Pharmaceutical Outcomes and Policy, University of Kentucky
2011 – 2014	Teaching Assistant, Pharmacy Practice and Science, University of Kentucky
2010 – 2011	Teaching Assistant, Agricultural Economics, University of Kentucky
2008	Laboratory Assistant, Agricultural Economics, University of Kentucky

Academic Honors and Awards

2014	International Society for Pharmacoepidemiology (ISPE) Scholarship to attend annual meeting
2014	Best Student Poster Presentation, International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 19th Annual International Meeting, Montreal, Canada
2013	International Society for Pharmacoepidemiology (ISPE) Scholarship to attend annual meeting
2013	University of Kentucky Student Support Funding, awarded for travel to professional meetings to present research (twice)
2012	University of Kentucky Student Support Funding, awarded for travel to professional meetings to present research
2011	University of Kentucky Student Support Funding, awarded for travel to professional meetings to present research

Affiliations

2013 – Present	International Society for Pharmacoepidemiology
2011 – Present	International Society for Pharmacoeconomics and Outcomes Research
2011 – 2015	Department of Pharmacy and Science Graduate Education Research Committee, University of Kentucky, Graduate Student Representative
2011 – 2012	Agricultural and Applied Economics Association
2010 – 2011	Southern Agricultural Economics Association

Bibliography

Peer Reviewed Publications

Wixson SE, Blumenschein K, Goodin AJ, Talbert J, Freeman PR. Prescription drug monitoring program utilization in Kentucky community pharmacies. *Pharm Pract.* 2015;13(2):540.

Wixson SE, Blumenschein K, Goodin AJ, Higgins GE, Vito GF, Talbert J, Freeman PR. Law enforcement perceptions of a prescription drug monitoring program. *International Journal of Police Science & Management.* 2014;16(4)288-296.

Wixson SE, Brouwer ES. Sex differences in benzodiazepine use in the HIV-infected population. *AIDS Care.* 2014;26(10):1218-22.

Published Abstracts

Wixson SE, Brouwer ES. Benzodiazepine use in the HIV-infected population. *Pharmacoepidemiology and Drug Safety*. 2013 October;22(s1): 499.

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Wixson SE, Katchova AL, Woods TA, Hu W. The role of specialty food stores and farmer's markets in the procurement of local foods. *Journal of Agricultural and Applied Economics*. 2011 Aug;43(3): 471.

Non-Peer Reviewed Contributions

Wixson SE, Katchova AL. Does price asymmetry exist in commodity and energy markets? Prepared for the Agricultural and Applied Economics Association (AAEA) Annual Meeting, July 2011. Available at: http://ageconsearch.umn.edu/bitstream/103735/2/AAEA%20Poster%20Presentation%20ID13476.pdf.

Wixson SE, Katchova AL, Woods TA, Hu W. The Role of Specialty Food Stores and Farmer's Markets in the Procurement of Local Foods. Prepared for the Southern Agricultural Economics Association (SAEA) Annual Meeting, February 2011. Available at: http://ageconsearch.umn.edu/bitstream/97969/2/The%20Role%20of%20Specialty%20Food%20Stores%20and%20Farmers%20Markets.pdf.

Scholarly Presentations

Podium

Optimizing prescription drug monitoring programs to support law enforcement activity. Hal Rogers Prescription Drug Monitoring Program National Meeting, Washington DC, September 2014.

The role of specialty food stores and farmer's markets in the procurement of local foods. Southern Agricultural Economics Association (SAEA) Annual Meeting, Corpus Christi, TX, February 2011.

Posters

Wixson SE, Brouwer ES. Increased benzodiazepine abuse among HIV-infected individuals in the United States. International Conference on Pharmacoepidemiology & Therapeutic Risk Management. Taipei, Taiwan, October 2014.

Wixson SE, Blumenschein K, Goodin AJ, Freeman PR, Talbert J. Community pharmacist characteristics associated with use of a prescription drug monitoring program. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual Meeting, Montreal, Canada, June 2014.

Wixson SE, Brouwer ES. Benzodiazepine use in the HIV-infected population. 29th International Conference on Pharmacoepidemiology & Therapeutic Risk Management. Montreal, Canada, August 2013.

Wixson SE, Blumenschein K, Brouwer ES, Freeman PR, Talbert J. Impact of South Carolina's prescription drug monitoring program on the use of benzodiazepines in a commercially insured population. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual Meeting, New Orleans, LA, May 2013.

Wixson SE, Talbert J, Blumenschein K, Freeman PR. Impact of prescription monitoring programs on pharmacists' controlled substance dispensing behavior. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual Meeting, Washington DC, June 2012.

Wixson SE, Katchova AL. Price asymmetric relationships in commodity and energy markets. European Association of Agricultural Economists (EAAE) 123rd Seminar, Dublin, Ireland, February 2012.

Wixson SE, Katchova AL. Does price asymmetry exist in commodity and energy markets? Agricultural and Applied Economics Association (AAEA) Annual Meeting, Pittsburgh, PA, July 2011.

Scientific Journal Peer Review

Journal of the American Pharmacists Association

Research Experience

Benzodiazepine use in the COPD population and the risk of mortality. Faculty Advisor: Dr. Emily S. Brouwer, 2014-2015.

Optimizing prescription drug monitoring programs to enhance law enforcement activity. Faculty Advisor: Dr. Patricia R. Freeman, 2012-2015.

Benzodiazepine use in the HIV-infected population. Faculty Advisor: Dr. Emily S. Brouwer, 2012-2015.

Impact of South Carolina's prescription drug monitoring program on the use of benzodiazepines in a commercially insured population. Faculty Advisor: Dr. Karen Blumenschein, 2012-2015.

Prescription drug monitoring programs: the consumer's perspective on the "chilling effect". Faculty Advisor: Dr. Karen Blumenschein, 2012-2013.

Teaching Experience

Summer 2014	PPS 760 – Techniques in Secondary Data Research: Prepared and presented a workshop on how to use Stata for outcomes research. Topics included understanding Stata interface, importing data into Stata, data analysis commands, data manipulation, and descriptive statistics; 8 students; 1 lecture
Fall 2013	PPS 910 Introduction to Pharmacy Practice and Science: Assisted with course development; prepared and presented lecture on research in pharmaceutical outcomes and policy; graded student assignments, presentations, and term papers; maintained course records; 140 students; 1 lecture
Spring 2013 & 2014	PPS 920 Communication and Behavior in Pharmacy Practice: Prepared and presented lecture on introductory health economics; maintained course records; graded student assignments; 140 students; 1 lecture
Fall 2012	PPS 910 Introduction to Pharmacy Practice and Science: Assisted with lecture and development of laboratory exercise for conducting literature reviews in an academic setting; maintained course records; graded student assignments; 140 students; 4 lectures
Spring 2011	AEC 321 Agricultural Futures Markets: Assisted with course development; provided lectures on hedging agricultural commodities; coordinated a guest lecturer; graded student assignments; 40 students
Fall 2010	AEC 320 Agriculture Product Marketing and Sales: Assisted with course development; provided guest lectures on inventory management; updated course website on a weekly basis; graded student presentations and written assignments; 30 students

Spring 2008	AEC 302 Agricultural Management Principles: Provided assistance to students on the creation of financial worksheets for an agricultural management setting; 45 students