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Dated: August 13, 2015

EPIDEMIOLOGY OF CONTROLLED SUBSTANCE PRESCRIPTION DRUG UTILIZATION IN TEXAS: AN ANALYSIS OF PRESCRIPTION DRUG MONITORING PROGRAM DATA

by

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SIGNATURE PAGE

Signatures are on file with the department of Pharmaceutical Health Outcomes and Policy

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PROJECT SUMMARY

Prescription drug abuse is an escalading problem in the U.S. The mortality rate associated with prescription drug abuse is estimated at 46 deaths per day, with the majority of cases attributed specifically to prescription opioids (Centers for Disease Control and Prevention, 2014c; LJ Paulozzi, Jones, Mack, & Rudd, 2011; Substance Abuse and Mental Health Services Administration, 2014a). In addition to the vast mortality rates, the morbidity associated with abuse has left a extensive impact on public health in the U.S. While national prescription drug abuse rates have been extensively studied, the prevalence of prescription drug abuse is not well known in the State of Texas. The main purpose of this study was to identify the current state of controlled substance prescription (CSP) utilization and aberrant CSP use in the State of Texas. This was achieved through the objectives of this study, which included: 1) conducting descriptive statistics of patients utilizing CSPs and the frequencies of all classes of CSPs dispensed in Texas during 2013-2014; 2) identifying CSP utilization behaviors that are considered aberrant and highly associated with prescription drug abuse (e.g., use of multiple providers to obtain CSPs, overlapping CSPs, high daily dose of opioids); 3) utilizing patient-level, prescription utilization and county-level factors to identify the predictors of patient's utilizing overlapping CSPs and also of having multiple provider episodes. This study utilized the Texas Prescription Drug Monitoring Program Database (PDMP) for all analysis. The PDMP database provided for a unique epidemiological approach to analyzing CSP use within a state, as all outpatient CSPs dispensed within the state are collected within this database. The findings of this exploratory study will be

used to help build a foundation for identifying CSP prescribing practices and patient utilization of CSPs. This study will also assist in informing both clinical care and policy decisions regarding CSP prescribing and identifying patients with aberrant CSP utilization behaviors.

Objectives

Objective 1

The first objective aims to highlight aberrant CSP behavior which can be identifiable through PDMP data. Three aberrant behaviors discussed in this paper include: receiving inappropriate and/or overlapping combinations of CSPs; utilizing multiple providers (i.e., doctor shopping) to obtain opioids and CSPs; and consuming a high daily morphine equivalents dose (MED).

Objective 2

The second objective of this research was to identify the prevalence and factors associated with patients receiving potentially inappropriate overlapping CSPs in the State of Texas. Logistic regression was used to identify the patient-level and prescription utilization factors associated with the use of potentially inappropriate combination of CSPs.

Objective 3

The third objective of this study used the indicators of prescription drug abuse to identify the current state and burden of controlled substance prescription drug use and abuse in Texas. Multilevel logistic modeling was employed to examine the prevalence and individual-level and regional-level factors associated with patients having an MPE in the State of Texas.

LITERATURE REVIEW

1.1 EPIDEMIOLOGY OF CHRONIC PAIN

Chronic pain has been recognized as a significant public health problem and burden due to its prevalence, economic cost, biological and sociological impact (Institute of Medicine, 2011). In the United States, it is believed that every year over 100 million Americans suffer from chronic pain conditions (Table 1.1), reaching epidemic proportions (The American Academy of Pain Medicine, 2012). It is estimated that economic burden of chronic pain in the U.S. is around $635 billion annually, as a result of the associated health care costs, such as disability, lost wages, readmission and lost productivity (Institute of Medicine, 2011). Pain currently affects more Americans than diabetes, heart disease and cancer combined (The American Academy of Pain Medicine, 2012). According to the American Chronic Pain Association, "chronic pain can be defined as ongoing or recurrent pain, lasting beyond the usual course of acute illness or injury, and which adversely affects the individual's well-being" (American Chronic Pain Association, 2014). The International Association for the Study of Pain (IASP) defines chronic pain as pain without apparent biological value that has persisted beyond the normal tissue healing time (usually taken to be three months). However, chronic pain has proven to be a complex, subjective condition that a precise definition is unknown and varies across studies (Andersson, Ejlertsson, Leden, & Rosenberg, 1993; Peters et al., 2013; Schopflocher, Taenzer, & Jovey, 2011; Smith et al., 2001).

Table 1.1. Incidence of Pain, as Compared to Major Medical Conditions		
Condition	Number of Sufferers	Source
Chronic Pain	100 million Americans	Institute of Medicine of The National Academies
Diabetes	25.8 million Americans (diagnosed and estimated undiagnosed)	American Diabetes Association
Coronary Heart Disease	16.3 million Americans	American Heart Association
Stroke	7.0 million Americans	American Heart Association
Cancer	11.9 million Americans	American Cancer Society

Source: The American Academy of Pain Medicine, 2012

Barriers to adequate pain treatment and care are one of the greatest contributors to the prevalence of chronic pain in the United States. These barriers are the result of a multitude of factors, including limited physician education and training in pain management, provider attitudes, insurance coverage, cultural attitudes of patients, geographic barriers, and regulatory barriers (Institute of Medicine, 2011).

One consequence of the escalating rates of chronic pain is the increasing rates of prescription drug use, such as pain medications. The effectiveness of treating chronic pain solely through the use of prescription medications, especially as a long-term treatment plan, is a highly debated topic (Institute of Medicine, 2011; Martell et al., 2007; Wu, Lang, Hasson, Linder, & Clark, 2010). Research in this area including both clinical trials and observational studies have found limited evidence supporting the long-term use of prescription pain medications in treating chronic pain conditions. Many feel that the risks associated with using these medications outweigh the benefits (Chou, Ballantyne, Fanciullo, Fine, & Miaskowski, 2009; Kuijpers et al., 2011; Manchikanti et al., 2011; Trescot et al., 2008). Therefore, managing chronic pain and providing appropriate medication therapy is a challenging facet for both primary care providers and specialists. Healthcare practitioners are conflicted in their efforts to appropriately treat non-cancer chronic pain and face a delicate balance between the under treatment of pain and the overprescribing of pain medications (Agency Medical Directors Group, 2010).

1.2 CONTROLLED SUBSTANCE PRESCRIPTIONS

Controlled substance prescriptions are drugs that have some potential for abuse or dependence (AWARxE Prescription Drug Safety). According to the U.S. Department of

Justice Drug Enforcement Administration Office of Diversion Control, drugs and other substances that are considered controlled substances under the Controlled Substances Act (CSA) are divided into five schedules. Controlled substances are scheduled based on whether they have a currently accepted medical use for treatment in the United States, their potential for abuse, and their likelihood of causing dependence when abused (U.S. Department of Justice Drug Enforcement Administration Office of Diversion Control, 2014). Definitions of how controlled substances (Schedule I-V) are classified, along with common examples for each, are provided in Table 1.2.

Table 1.2. Definition of Controlled Substance Schedule		
Controlled Substance Schedule	Definition	Examples
Schedule I	This schedule has no currently accepted medical use in the United States, a lack of accepted safety for use under medical supervision, and a high potential for abuse	Heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), 3,4-methylenedioxymethamphetamine ("Ecstasy")
Schedule II	This schedule has a high potential for abuse which may lead to severe psychological or physical dependence	Narcotics: combination products containing hydrocodone (Vicodin®), hydromorphone (Dilaudid®), methadon (Dolophine®), meperidine (Demerol®), oxycodone (OxyContin®, Percocet®), fentanyl (Sublimaze®, Duragesic®), morphine, opium, and codeine Stimulants: amphetamine (Dexedrine®, Adderall®), methylphenidate (Ritalin®)
Schedule III	This schedule has potential for abuse less than substances in Schedules I or II and abuse may lead to moderate or low physical dependence or high psychological dependence	Narcotics: products containing not more than 90 milligrams of codeine per dosage unit (Tylenol with Codeine®), buprenorphine (Suboxone®) Non-narcotics: anabolic steroids, benzphetamine, phendimetrazine, ketamine
Schedule IV	This schedule has a low potential for abuse relative to substances in Schedule III	alprazolam (Xanax®), carisoprodol (Soma®), clonazepam (Klonopin®), diazepam (Valium®), lorazepam (Ativan®)
Schedule V	This schedule has a low potential for abuse relative to substances listed in Schedule IV and consist primarily of preparations containing limited quantities of certain narcotics.	Cough preparations containing not more than 200 milligrams of codeine per 100 milliliters or per 100 grams (Robitussin AC®, Phenergan with Codeine®)

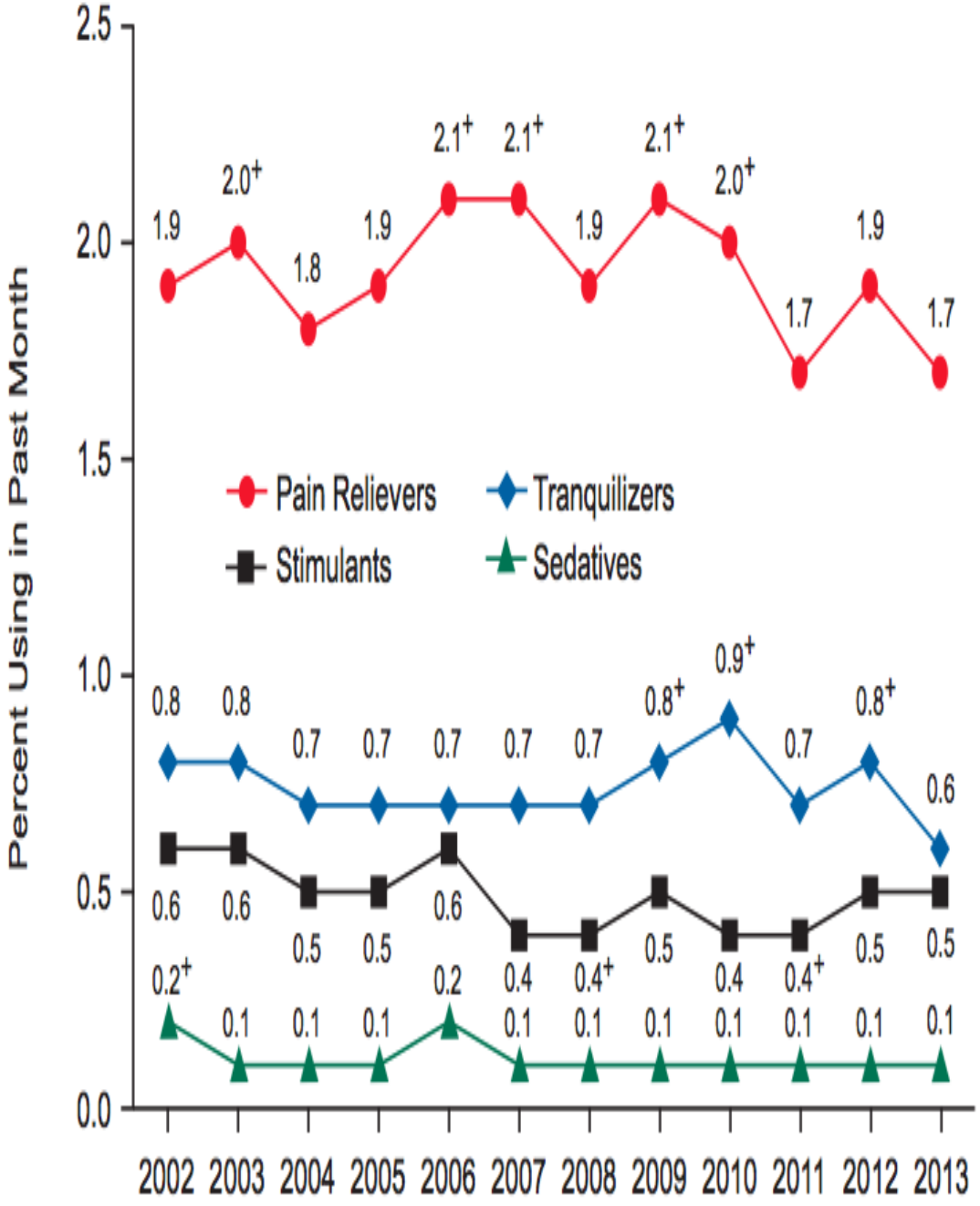
Source: U.S. Department of Justice Drug Enforcement Administration Office of Diversion Control, 2014

1.3 PRESCRIPTION DRUG ABUSE: A NATIONAL EPIDEMIC

The nonmedical use of prescription drugs has been drastically rising in the United States, reaching what are now considered by the Centers for Disease Control and Prevention (CDC) as epidemic proportions (Centers for Disease Control and Prevention, 2013b; S. E. McCabe, Cranford, & West, 2008). Prescription drug abuse is a perilous public health problem that has resulted in an excess of deaths, emergency room visits and millions of healthcare dollars consumed.

Reported estimates of nonmedical use of prescription drugs are 20% of U.S. individuals aged 12 or older have reported abusing prescription drugs for nonmedical reasons at least once in their lifetime (Substance Abuse and Mental Health Services Administration, 2006). The Substance Abuse and Mental Health Services Administration (SAMHSA) 2013 National Survey on Drug Use and Health (NSDUH) findings indicated that 15.7 million persons aged 12 or older reported using prescription-type drugs non-medically within the past year (Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality, 2013a). This report from 2002 to 2012 indicates an over 75% increase in non-medical use of opioids (Jones, 2012). Additionally, 1.7% of the U.S. population (4.5 million) reported nonmedical use of pain relievers within the past month in 2013 (Figure 1.1) (Substance Abuse and Mental Health Services Administration, 2014a).

Figure 1.1. Past Month Nonmedical Use of Drugs among Persons Aged 12 or Older: 2002-2013



Source: SAMHSA, 2013

SAMHSA defines the nonmedical use of prescription drugs as use of drugs without a prescription or use that occurs simply for the experience or feeling the drug causes (Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality, 2013a). The terms abuse, dependence and misuse have separate definitions, however they are commonly used interchangeably in the literature and will be used interchangeably for the purpose of this research.

1.3.1 MOST FREQUENTLY ABUSED CONTROLLED SUBSTANCES

Controlled substance medications can be effective when they are used appropriately, but can be addictive and potentially dangerous when abused. There are three classes of prescription drugs that have been found to be the most frequently abused: opioid analgesics (e.g., morphine), central nervous system depressants (e.g., benzodiazepines) and central nervous system stimulants (e.g., methylphenidate) (U.S. Department of Health and Human Services National Institutes of Health, 2011).

1.3.2 OPIOID ANALGESICS

Opioid analgesics (i.e., opioids) are prescription medications that reduce the intensity of pain signals reaching the brain by binding to opioid receptors in the brain and affecting the areas of the brain which control emotion, often diminishing the effects of a painful stimulus (U.S. Department of Health and Human Services National Institutes of Health, 2011). Some examples of medications that fall into this category are codeine, morphine, hydrocodone, oxycodone, and fentanyl (National Institute on Drug Abuse, 2011b). There are several side affects and complications associated with both short-term

and long-term use, including constipation, nausea, dizziness, drowsiness (Furlan, Sandoval, Mailis-Gagnon, & Tunks, 2006), respiratory depression, and vomiting (Benyamin et al., 2008). Opioid use for treating acute pain and terminal illness pain is generally well accepted in practice (Ballantyne & Shin, 2008; Noble et al., 2010). However, their use in the long-term treatment of chronic non-cancer pain is debated for many reasons, including their high risk for both physical and psychological dependence, as well as a lack of evidence for their efficacy in the long-term treatment of chronic non-cancer pain (Benyamin et al., 2008; Manchikanti et al., 2011).

Research and associated statistics have also revealed devastating consequences related to overuse and abuse of opioids. This includes increases in accidental overdose, abuse, addiction, diversion, and accidents involving injuries associated with opioid use (Agency for Healthcare Research and Quality, 2013; Substance Abuse and Mental Health Services Administration, 2011b, 2012a). In 2009 opioids were found to be present in 50% of cases seen in emergency departments related to nonmedical-use of pharmaceuticals (National Institute on Drug Abuse, 2011d). According to the CDC, almost three out of four prescription drug overdoses are associated with prescription pain relievers, including opioids (Centers for Disease Control and Prevention, 2013b). Overdose deaths involving opioids exceed deaths involving all illicit drugs (e.g., heroin, cocaine) combined (Centers for Disease Control and Prevention, 2013c; LJ Paulozzi et al., 2011). Based on 2014 estimates, the CDC reported that 46 individuals die each day from an overdose of opioid or narcotic pain relievers in the U.S. (Centers for Disease Control and Prevention, 2014c). The CDC has also reported that in 2012, 72% of deaths related to pharmaceutical misuse were attributed to opioids (Centers for Disease Control

and Prevention, 2014d). Peirce et al. (2012) reported that exposure to opioids was associated with a greater odds of drug-related death (odds ratio [OR]=3.39, 95% confidence interval [CI]=1.60-7.21) (Peirce, Smith, Abate, & Halverson, 2012). Many opioid overdose deaths have been associated with chronic pain, with studies estimating that 50-80% of individuals dying from an opioid overdose had a history of chronic pain (E. Johnson et al., 2013; LJ Paulozzi et al., 2009).

1.3.3 CENTRAL NERVOUS SYSTEM DEPRESSANTS

Central nervous system (CNS) depressants, also referred to as sedatives and tranquilizers, are substances that work by slowing brain activity by depressing the central nervous system, causing a drowsy or calming effect (National Institute on Drug Abuse, 2011a). CNS depressant medications are often prescribed for conditions such as anxiety, seizure disorders and sleep disorders and include medications such as benzodiazepines (e.g., Xanax®, Valium®), non-benzodiazepine sleep medications (e.g., Ambien®, Lunesta®), and barbiturates (e.g., phenobarbitals) (National Institute on Drug Abuse, 2011a). As with opioids, CNS depressants have a high potential for dependence and abuse (Hanson, Venturelli, & Fleckenstein, 2015). In 2009 and 2010 over 42,000 emergency room visits were attributed to overmedication of zolpidem (Ambien®), of which two-thirds of cases were females (Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality, 2014).

1.3.4 CENTRAL NERVOUS SYSTEM STIMULANTS

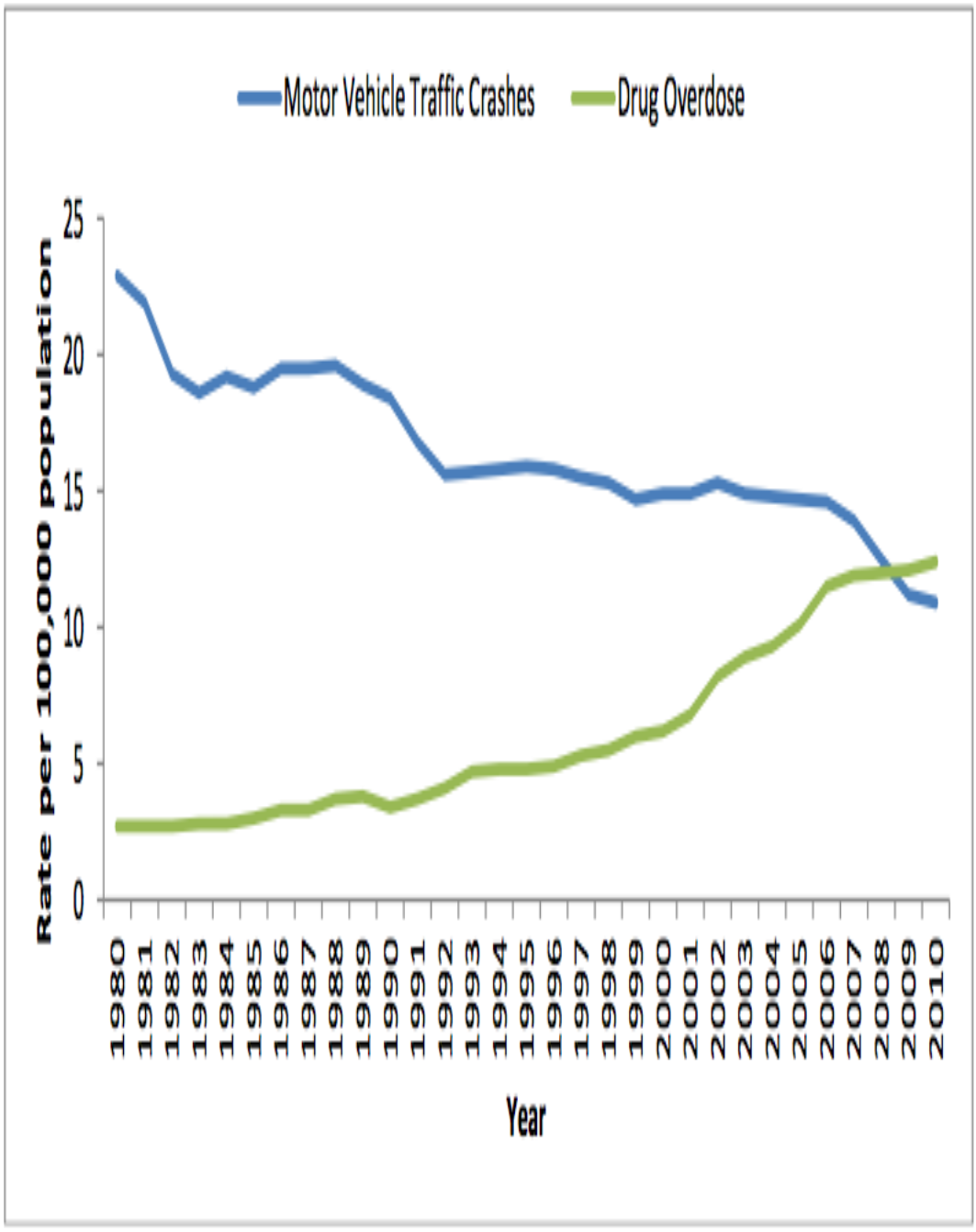
Central nervous system stimulants (i.e., stimulants) increase alertness, attention, and energy by enhancing the effects of norepinephrine and dopamine chemicals in the brain (National Institute on Drug Abuse, 2011e). Stimulants are often prescribed for attention deficit hyperactivity disorder (ADHD), narcolepsy and depression and include methylphenidate (e.g., Ritalin®) and amphetamines (e.g., Adderall®) (National Institute on Drug Abuse, 2011e). The CDC currently estimates that 11% of children between the ages of 4-17 having been diagnosed with ADHD, and 6.1% of all children in this age category are taking a medication for ADHD (Centers for Disease Control and Prevention, 2014a). Nonmedical use and abuse of prescription stimulants, especially ADHD medications, is a rising problem across the country, especially among adolescents and college students (Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD), 2015). Prevalence rates of nonmedical use of stimulants among college students are between 4.1% and 10.8% (Arria, O'Grady, Caldeira, Vincent, & Wish, 2008; S. McCabe, Knight, Teter, & Wechsler, 2005; Teter, McCabe, LaGrange, Cranford, & Boyd, 2006).

1.4 HEALTH OUTCOMES AND CONSEQUENCES ASSOCIATED WITH PRESCRIPTION DRUG ABUSE

The health consequences associated with misuse and abuse of prescription medications have been devastating to this country in recent years. Drug overdose deaths were found to be the leading cause of injury death in the United States in 2012, outnumbering the number of deaths due to motor vehicle crashes (Figure 1.2) (Centers

for Disease Control and Prevention, 2014d). The majority these cases were attributed specifically to opioids (LJ Paulozzi et al., 2011).

Figure 1.2. Rates of Motor Vehicle Traffic Crashes and Drug Overdose (1980-2010)



Source: U.S. Department of Health and Human Services, 2013.

In addition to overwhelming mortality rates, the morbidity associated with abuse has increased to unprecedented levels, creating a drastic impact on public health in the U.S. For every overdose death there is a multiplicity of relative negative health outcomes (Table 1.3). Emergency department visits involving nonmedical use of pharmaceuticals increased 98.4% over a five-year period from 2004 to 2009, with oxycodone incidents increasing 242.2% and hydrocodone incidents increasing 124.5% (National Institute on Drug Abuse, 2011d). An additional consequence not frequently well known are the adverse health consequences associated with long-term use of pain medication combination products containing acetaminophen (i.e., Vicodin®). Acetaminophen overdose is the leading cause of acute liver failure in the U.S. and long-term use can lead to hepatotoxicity and even acute liver failure (Kurtovic, Riordan, & Williams, 2005; Larson et al., 2005; Michna, Duh, Korves, & Dahl, 2010).

Table 1.3. Health Outcomes Associated with Opioid Use

For Every 1 Painkiller Death There Are…

Abuse treatment admissions[a]	9
Emergency department visits for misuse abuse[b]	35
People with abuse and/or dependence[c]	161
Nonmedical users[c]	461

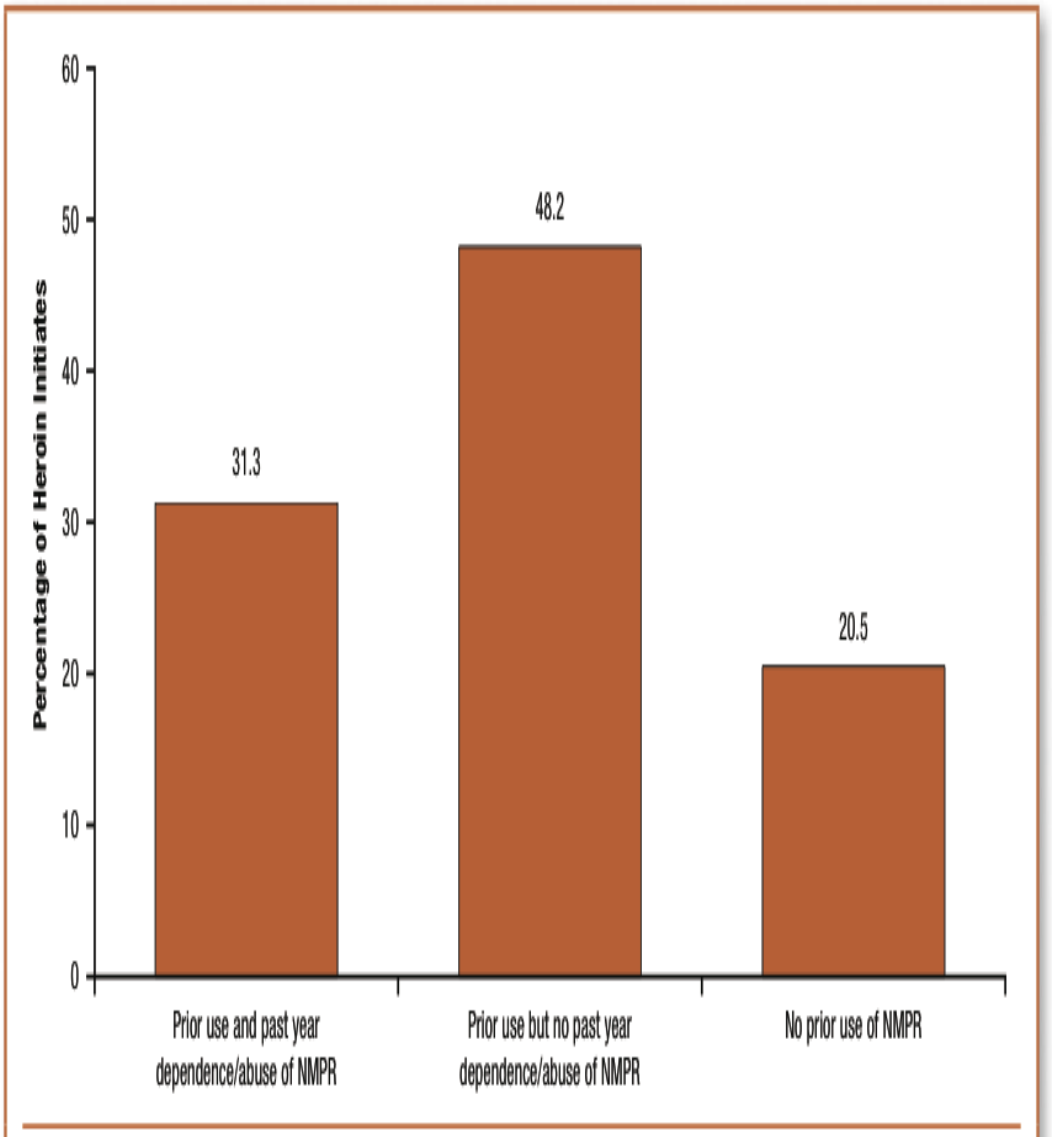
Source:
a. Treatment admissions for primary use of opioids Treatment Exposure Data set;
b. Emergency department (ED) visits are from Drug Abuse Warning Network;
c. Abuse/dependence and nonmedical use in the past month are from the National Survey on Drug Use and Health

Individuals abusing prescription medications often regress to other forms of substance abuse (National Institute on Drug Abuse, 2014a). The use of prescription drugs for non-medical reasons is highly associated with other drug use behaviors, including cigarette smoking, heavy drinking, marijuana use and other illicit drug use (Boyd, McCabe, & Teter, 2006).

1.4.1 ASSOCIATED HEROIN USE

Paralleling increasing opioids abuse rates, rates of heroin abuse, also an opiate, are on the rise. Recent increases in the annual number of persons in the U.S. who used heroin for the first time have raised concerns that prior nonmedical use of prescription pain relievers may have led to heroin use in many individuals (Figure 1.3) (Substance Abuse and Mental Health Services Administration, 2012b). A recent survey reported that the incidence rate of heroin was 19 times higher among those who reported prior nonmedical pain reliever use than among those who did not (Muhuri, Gfroerer, & Davies, 2013). Data from the National Survey on Drug Use and Health (NSDUH) has indicated that the number of individuals aged 12 or older with heroin dependence or abuse has more than doubled since 2002 (Muhuri et al., 2013). A study by Martyres et al. (2004) also found that among young adults aged 14-24 who died from a heroin overdose, 80% had other prescription drugs in their system, of which most were either benzodiazepines or opioids (Martyres, Clode, & Burns, 2004).

FIGURE 1.3 Percentage of Heroin Initiates among Persons Aged 12 to 49, by Prior and Past Year Dependence/Abuse of Nonmedical Pain Relievers (NMPR): 2002-2011



Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2002-2004, 2005-2010 (2012).

1.4.2 ECONOMIC CONSEQUENCES

In addition to the devastating health-related consequences of prescription drug abuse, the economic burden due to the vast resource utilization and monetary costs of abuse are substantial. It is estimated that abuse of opioids alone result in between $53-$72 billion in medical costs each year (Birnbaum et al., 2011; Coalition Against Insurance Fraud, 2007; Hansen, Oster, Edelsberg, Woody, & Sullivan, 2011). The economic figures associated with abuse account for medical and drug abuse treatment costs, lost productivity, medical complications and criminal justice costs (Birnbaum et al., 2011; Hansen et al., 2011; Strassels, 2009). As a result of the extensive healthcare resource utilization among abusers, a case-control study found that as compared to non-abusing citizens, the mean annual direct healthcare costs estimated for opioid abusers were more than 8.7 times higher than for nonabusers (White et al., 2005). Similarly to the adverse health consequences of abuse, much of the economic burden of abuse can be attributed to opioids. Hansen et al (2011) found that five controlled substance drugs, OxyContin®, oxycodone, hydrocodone, propoxyphene, and methadone, accounted for two-thirds of the total economic cost associated with abuse (Hansen et al., 2011). With increasing rates and prevalence of abuse, the societal burden associated with prescription drug abuse costs may reach astronomical levels in the coming years.

1.5 CONTRIBUTING FACTORS TO PRESCRIPTION DRUG ABUSE AND DIVERSION

Prescription drug misuse, abuse, and diversion is a complex and multi-faceted problem, occurring as the result of both legitimate and illegitimate means. There are multiple contributors to the problem, such as a belief by many individuals that

prescription drugs are not dangerous (National Institute on Drug Abuse, 2014a); an increase in the availability of controlled substances on the market (Kaye, Vadivelu, & Urman, 2014); inappropriate prescribing (U.S. Department of Health and Human Services, 2013); and the use of multiple providers to obtain prescriptions (Centers for Medicare & Medicaid Services, 2014).

1.5.1 PERCEPTIONS ABOUT SAFETY

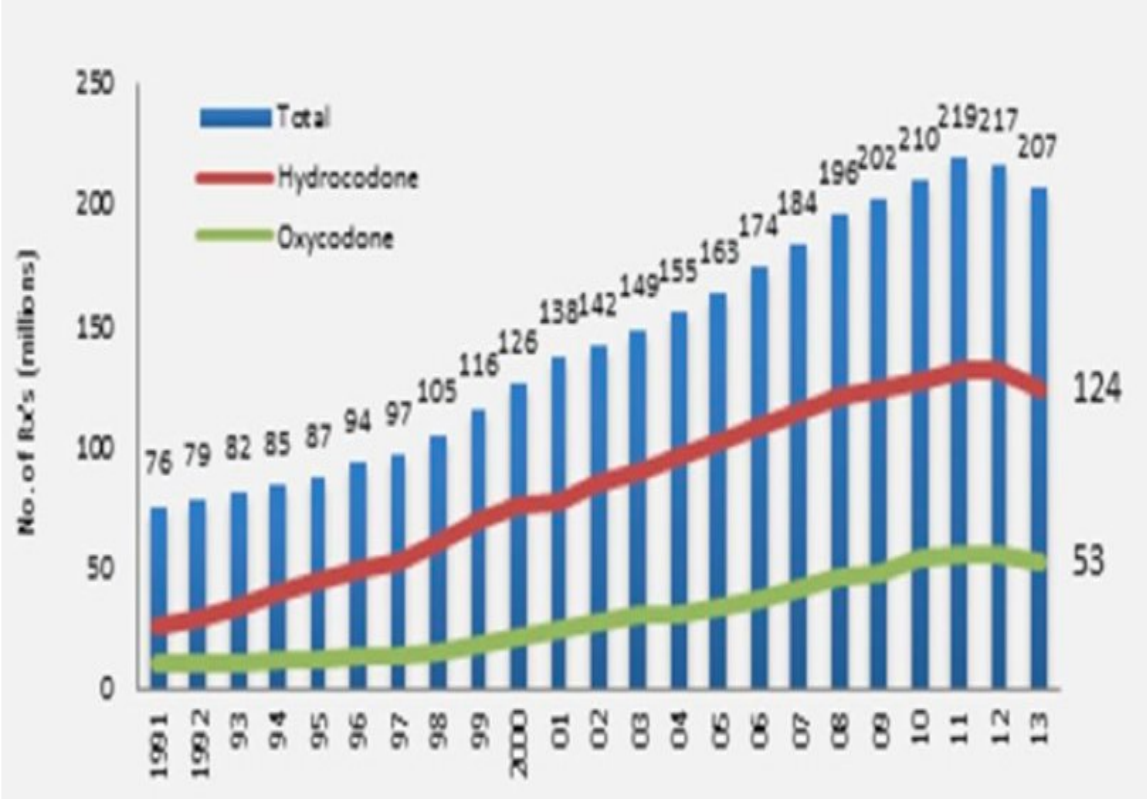
One major factor that is believed to contribute to prescription drug and opioid abuse are patient perceptions that opioids are safer than illicit drugs because they are prescribed by doctors (Condon, 2012). Many individuals do not understand or are not educated by their healthcare providers that certain prescription medications (i.e., opioids) may affect the brain in ways very similar to that of illicit drugs. For example opioid pain relievers attach to the same cell receptors targeted by illegal opioids, such as heroin, and achieve their medicinal effects by acting on the same neurotransmitter systems as cocaine (National Institute on Drug Abuse, 2014a). Individuals may also misuse prescription medications inadvertently by concurrently using them with alcohol or other contraindicating medications or taking them at too high of a dose for too long. All of which can lead to an increased risk of dependence and negative health consequences, including death (Agency for Healthcare Research and Quality, 2013; Gudin, Mogali, Jones, & Comer, 2013).

1.5.2 OVER PRESCRIBING AND AVAILABILITY

The U.S. has seen a dramatic increase in in the number of prescriptions written and dispensed for opioids in the past quarter century (Figure 1.4) (IMS Institute for

Healthcare Informatics, 2014). Alarmingly, The International Narcotics Control Board has reported that the U.S. is actually the largest consumer of opioids worldwide, accounting for almost all hydrocodone consumption (99%) and the vast majority of oxycodone consumption (83%) (International Narcotics Control Board, 2013).

Figure 1.4. National Utilization and Trends of Opioid Prescriptions Dispensed by U.S. Retail, Years 1991-2013



Source: IMS Health, Vector One 2014

Healthcare providers wrote 259 million prescriptions for opioid painkillers in 2012, an amount estimated to be enough for every American adult to have their own bottle of painkillers (Centers for Disease Control and Prevention). This equivocates to medicating every American adult with a dose of 5 mg of hydrocodone every 4 hours for one month (LJ Paulozzi et al., 2011). Hydrocodone-combination painkillers were the most commonly prescribed drugs in the U.S. in 2013, accounting for 130 million prescriptions, and have been for the past five years (Table 1.4) (IMS Institute for Healthcare Informatics, 2014).

Table 1.4. Top Medications Dispensed in the U.S. by Number of Prescriptions					
Medication	**2009**	**2010**	**2011**	**2012**	**2013**
acetaminophen/hydrocodone	129.4	132.1	136.7	136.4	129.2
levothyroxine	100.2	103.2	104.7	112.2	115.2
lisinopril	83.0	87.6	88.8	99.1	101.5
metoprolol	76.9	76.6	76.3	82.6	83.9
simvastatin	84.1	94.4	96.8	89.3	79.1

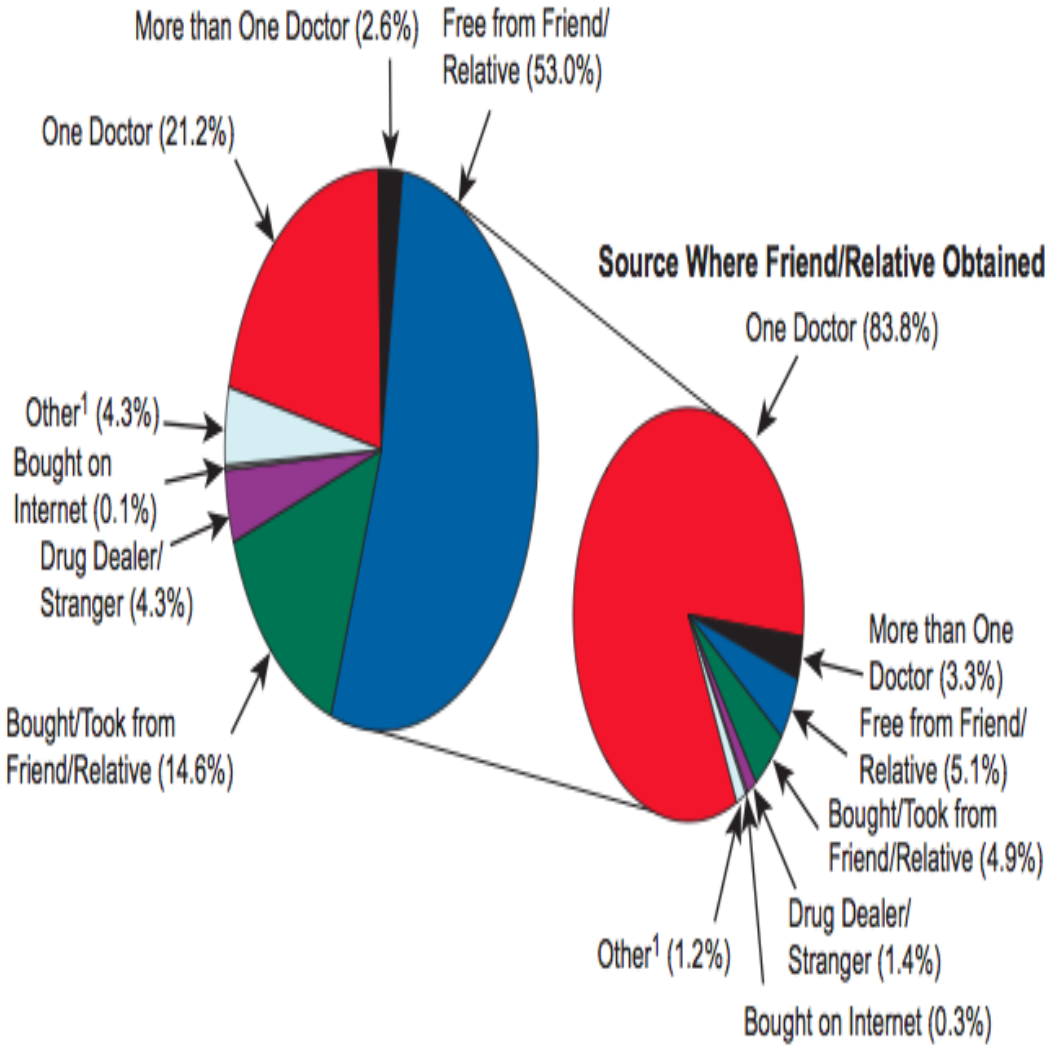
Source: IMS Health, National Prescription Audit, 2013

Higher prescribing and availability of opioid painkillers has been found to be positively associated with higher rates of overdose deaths (Centers for Disease Control and Prevention, 2014c; Manchikanti, Fellows, Ailinani, & Pampati, 2010). A strong correlation ($p<0.001$) between increasing daily opioid dose, admission rates (Reisman, Shenoy, Atherly, & Flowers, 2009), and overdose risk has been revealed by several studies (Bohnert et al., 2011; Dunn et al., 2010; Gomes, Mamdani, Dhalla, Paterson, & Juurlink, 2011). Dunn et al. (2010) found that as compared to patients receiving 1-20 mg of opioids per day, patients receiving 100 mg or greater had an 8.9 fold increase in the odds of overdose risk (95% CI=4.0-19.7). Current clinical practice guidelines generally recommend prescribers to first consider alternatives to opioids, both pharmaceutical and nonpharmaceutical, for their chronic non-cancer pain patients, and then to start with lower dose, short-acting opioids (Centers for Disease Control and Prevention, 2014b). However, recent trends in prescribing have shifted towards prescribing long-acting opioid formulations as well as increased average daily dose (Boudreau et al., 2009; Franklin et al., 2011; T Gomes et al., 2011).

Almost all prescription drugs involved in overdoses come from prescriptions originally prescribed by doctors and obtained from pharmacies, and not from illegitimate reasons such as being purchased online or stolen from pharmacies (Centers for Disease Control and Prevention, 2013b; Substance Abuse and Mental Health Services Administration, 2014a). Given that 21.2% of individuals who reported abusing opioid pain relievers nonmedically cited having received them from one doctor and 53% cited that a friend/relative was their source (of which 83.8% of those individuals reported obtaining from one doctor) (Figure 1.5), individual doctors appear to be a main

contributing source of prescription pain relievers for abusers (Substance Abuse and Mental Health Services Administration, 2014a).

Figure 1.5. Source Where Opioid Pain Relievers Were Obtained for Most Recent Nonmedical Use Among Past Year Users Aged 12 or Older: 2012-2013



Source: SAMHSA, 2014

The majority of pain relievers used for non-medical reasons originated from one or more doctors, however several studies that found that only a small percentage of

prescribers are responsible for prescribing the majority of opioids (K Blumenschein et al., 2010; Iyengar & Henderson, 2014; Oregon Health Authority, 2013; Swedlow, Ireland, & Johnson, 2011). Data from the Oregon Prescription Drug Monitoring Program found that 59% of the controlled substance prescriptions written in the state in 2012 were by the top 2,000 prescribers, representing only 4.1% of the state's prescribers (Oregon Health Authority, 2013). Swedlow et al. (2011) also found that 3% of physicians accounted for 55% of all Schedule II prescriptions prescribed in their study. Nationwide a recent study from Express Scripts® found that 40% of U.S. narcotic prescriptions between 2011-2012 were written by only 5% of opioid prescribers (Iyengar & Henderson, 2014). Therefore a small percentage of high-volume prescribers can have a large impact on opioid use, abuse and overdose death rates.

1.5.3 LACK OF PRESCRIBER EDUCATION

Concerns have been raised that only a small percentage of high volume prescribers are registered as pain specialists, who are ideally most suited to manage pain conditions and prescribe controlled pain medications. However as of July 2014 there were currently only 2,300 board certified physicians in pain medicine (American Board of Pain Medicine, 2014). It should be dually and especially noted that overprescribing and failure to adequately address chronic pain and explore alternative therapies is not completely at the fault of primary care physicians. Primary care is often the main treatment modality for patients with pain, however primary care is often organized in a way that rarely allows clinicians time to perform comprehensive patient pain assessments and develop individualized treatment plans for each patient (Upshur, Luckmann, &

Savageau, 2006). Moreover, many health professionals lack training and education in a pain management role and appropriate opioid prescribing, not to mention that there is little reimbursement for their additional efforts (Institute of Medicine, 2011). Given that chronic pain is one of the most prevalent conditions in the U.S., additional healthcare provider training in this area is warranted.

However, what is of concern is a lack of action on behalf of healthcare providers when aberrant behavior is suspected or detected among their patients. A cohort study from 2011 found that when aberrant behavior was detected through urine drug testing (UDT) among individual patients, 55% of providers actually continued to prescribe opioids, with only 20% of prescribers discontinuing the therapy (Gupta, Patton, Diskina, & Cheatle, 2011). Findings such as this may force the reexamination of where to target abuse prevention efforts and/or narrow efforts to educate the small percentage of prescribers contributing to the problem.

1.5.4 ABBERANT CSP UTILIZATION BEHAVIORS

There are several aberrant behaviors that suggest CSP misuse or abuse that are readily identifiable by reviewing PDMP data. Aberrant behavior can be defined as patient behaviors that may indicate prescription medication abuse or behaviors that are more likely to be associated with misuse/abuse (National Institute on Drug Abuse). Three aberrant behaviors discussed in this research include: receiving inappropriate and/or overlapping combinations of CSPs; utilizing multiple providers (i.e., doctor shopping) to obtain opioids and CSPs; and consuming a high daily morphine equivalents dose (MED).

1.5.4.1 SIMULTANEOUS OR OVERLAPPING CONTROLLED SUBSTANCE PRESCRIPTIONS

Utilization of opioids alone and in combination with benzodiazepines accounted for for almost half of the drug overdose deaths and three-fourths of drug-related ER visits in 2009 (Substance Abuse and Mental Health Services Administration, 2010b). Additionally, Wilsey et al. reported that individuals who had received stimulants and benzodiazepines simultaneously had a 20 times increase in odds ratio of utilizing multiple providers to obtain their prescriptions. The same study reported that individuals who were prescribed a stimulant/anorectic, a benzodiazepine, and an opioid within the same month were 13 times more likely to utilize multiple providers to obtain CSPs (OR=13.12, 95% CI=12.01-14.33), and 25.1 times increase (OR= 25.10, 95% CI=22.73-27.72) if the individual had simultaneous prescriptions for stimulants/anorectics, benzodiazepines and opioids (Wilsey et al., 2010).

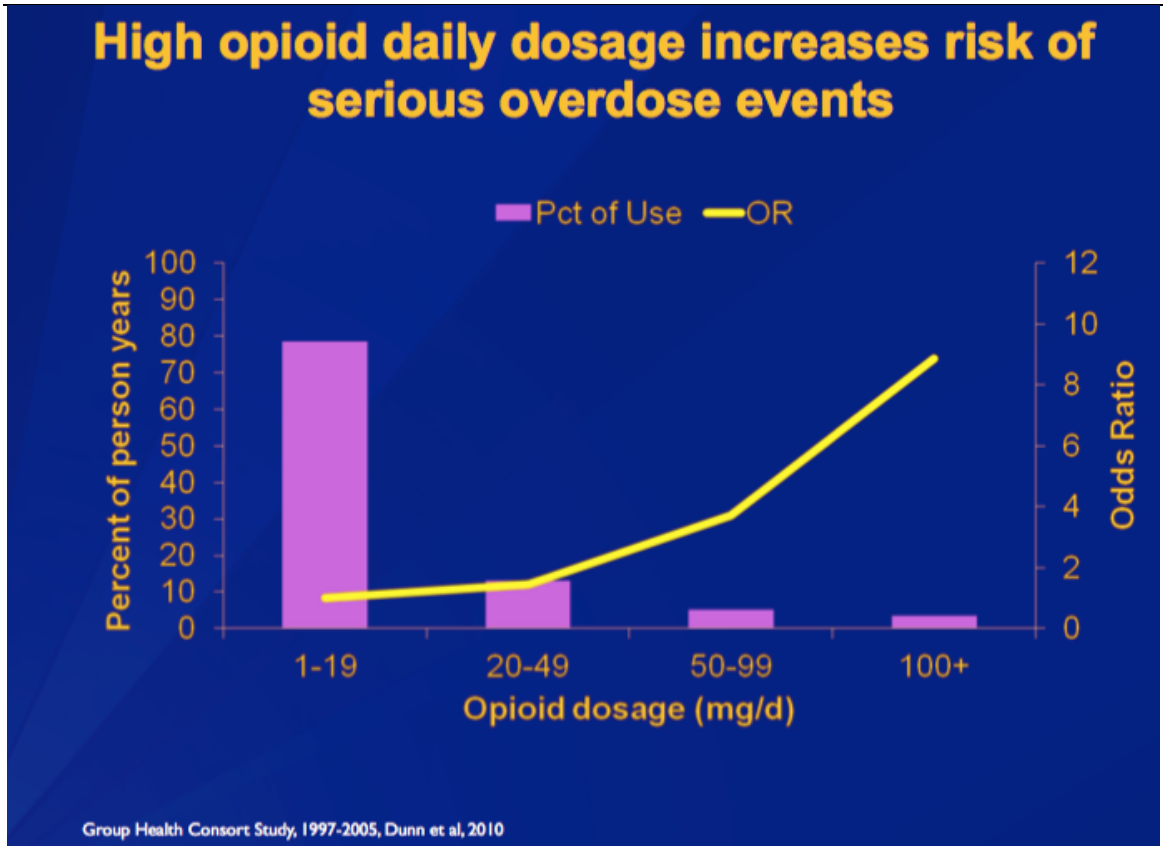
1.5.4.2 HIGH DAILY MORPHINE EQUIVALENT DOSE

Overdose deaths have been found to be highly correlated with a high average daily morphine equivalent dose (MED). Measuring daily MED is a method of comparing doses across different opioids regardless of their formulation.(Boudreau et al., 2009; AM Gilson, Maurer, Ryan, Rathouz, & Cleary, 2013; Manchikanti, Abdi, et al., 2012; Prescription Drug Monitoring Program Training and Technical Assistance Center, 2013) The average MED morphine equivalent can be calculated using the following formula:

$$\text{MME Conversion Formula: } \frac{(\text{Drug Strength})(\text{Drug Quantity})(\text{MME Conversion Factor})}{\text{Days Supply}}$$

Current opioid dosing guidelines recommending that the daily dose of opioids for patients with chronic non-cancer pain should not exceed 120 mg of oral morphine (Agency Medical Directors Group, 2010). However, Dunn et al. reported that as compared to patients receiving 1-20mg of opioids per day, those receiving 100mg or more per day had an 8.9 fold increase in overdose risk and a 1.8% annual overdose rate (Figure 1.6) (Dunn et al., 2010).

Figure 1.6. National Utilization and Trends of Opioid Prescriptions Dispensed by U.S. Retail, Years 1991-2013



Data Source: Dunn et al, 2010; Image Source: Paulozzi, 2010

1.5.4.3 MULTIPLE PROVIDER EPISODES/DOCTOR SHOPPING

The CDC has recommended that prescription drug abuse prevention efforts focus resources on patients at highest risk in terms of prescription opioid painkiller dosage, numbers of controlled substance prescriptions, and numbers of prescribers (Centers for Disease Control and Prevention, 2013b). This includes individuals who obtain prescriptions for the same drugs and/or controlled substances from multiple healthcare practitioners without the prescribers' knowledge of the other prescriptions (Centers for Disease Control and Prevention National Center for Injury Prevention and Control Division of Unintentional Injury Prevention, 2012; McDonald & Carlson, 2013; Sansone & Sansone, 2012). Patients in this category of prescription drug abuse are often classified as "doctor shoppers" or "pharmacy shoppers" and represent a significant contribution to diversion rates. The author of this dissertation prefers the term 'multiple provider episodes' (MPE), given that shopping behavior occurs across healthcare providers (i.e., physicians and pharmacists). However, the current literature utilizes both terms, therefore both terms will be used interchangeably throughout. Additionally, the terms 'doctor shopping' and 'pharmacy shopping' have been found to be correlated and often interchangeable, given that the as the number of providers that a patient uses increases the number of pharmacies has been found to increase as well. The term "doctor shopping" varies based on different definitions and indicators of questionable activity, such as: the numbers of pharmacies visited; numbers of prescribers used; prescriptions that are overlapping; using more than one class of controlled substance prescription from different providers; early refills of prescriptions; and excess of 'standard' doses over different periods of time. These individuals often receive additional prescriptions for

medication than intended by their provider(s). Some doctor shoppers may be obtaining multiple prescriptions to divert the medications to other individuals. As documented from SAMHSA's 2010 survey, over 75% of individuals who abuse prescription medications obtained them from someone else's prescription (Substance Abuse and Mental Health Services Administration, 2011a).

As shown in Table 1.5, several studies have been conducted characterizing patients doctor and pharmacy shopping for controlled substances. A variety of thresholds and different criteria were used to identify aberrant utilization in these studies. Hall et al. characterized doctor shopping as obtaining prescriptions for controlled substances from five or more clinicians during the preceding year (Hall et al., 2008). Whereas other studies used less specific standards and define doctor shopping as 'patient consultation with multiple physicians in a short time frame with the explicit intent to deceive them in order to obtain controlled substances' (Shaffer & Moss, 2010). Therefore there is currently no "gold standard" definition for identifying aberrant behavior.

Table 1.5. Definitions and Operationalization of Doctor and Pharmacy Shopping in the Literature		
Study	Operational Definition	Findings
Prevalence and determinants of pharmacy shopping behavior (Buurma et al., 2008)	Non-shopper: 1 pharmacy Light: >1 pharmacy Moderate: 3-4 pharmacies and proportion of prescriptions elsewhere >10% and number of prescriptions elsewhere >10 Heavy: >5 pharmacies, proportion of prescriptions elsewhere >10% and number of prescriptions elsewhere >10	Even light shopping behavior may put the patient at risk for unintentional drug-related problems
Usefulness of prescription monitoring programs for surveillance--analysis of Schedule II opioid prescription data in Massachusetts, 1996-2006 (Katz et al., 2010)	>4 pharmacies and >4 prescribers for any Schedule II drug or >2 pharmacies and >2 prescribers for the opioid product in question	The greater number of providers used, the greater the number of pharmacies used
Time Series Analysis of California's Prescription Monitoring Program: Impact on Prescribing and Multiple Provider Episodes (Gilson et al., 2012)	Receiving prescriptions for the same medication from 2 or more practitioners within a 30-day period	Multiple provider episodes represented almost 10% of all Schedule II opioid prescriptions issued during the 7-year study period
Doctor and Pharmacyf Shopping for Controlled Substances. (Peirce et al., 2012)	≥4 doctors in 6 months-doctor shopping ≥4 pharmacies in 6 months-pharmacy shopping	25.21% of individuals who had died from a drug-related death were identified as doctor shoppers; 20.23% of doctor shoppers were also pharmacy shoppers, and 55.60% of pharmacy shoppers were doctor shoppers
Patterns of abuse among unintentional pharmaceutical overdose fatalities (Hall et al., 2008)	>5 clinicians in year before death	Most overdose deaths involved opioid analgesics; 21.4% deaths involved doctor shopping
Distance Traveled and Frequency of Interstate Opioid Dispensing in Opioid Shoppers and Nonshoppers (Cepeda et al., 2013)	Shopper: filled overlapping opioid prescriptions written by >1 prescriber at ≥3 pharmacies. Heavy shopper: ≥5 shopping episodes	Opioid shoppers travel greater distances and more often cross state borders to fill opioid prescriptions than nonshoppers, and their dispensings accounted for a disproportionate number of opioid dispensings
Profiling multiple provider prescribing of opioids, benzodiazepines, stimulants, and anorectics (Wilsey et al., 2010)	Receiving a prescription for the same medication from ≥2 practitioners filled by ≥2 pharmacies within a 30-day period.	Opioid prescriptions (12.8%) were most frequently involved in multiple provider episodes and patients with simultaneous categories of controlled substances

Consequently, the lack of a standard definition for doctor shopping, and the wide variation across studies, may result in the unintended consequence of a high risk for both false positives and negatives. Using criteria that is not stringent enough in its criteria (e.g., ≥ 3 doctors and/or ≥ 3 pharmacies) may lead to the misclassification of patients who may actually be using opioids appropriately, resulting in false positives for doctor shopping. However, increasing this criteria to be too lenient (e.g., ≥ 5 doctors and/or ≥ 5 pharmacies) may result in excess false negatives and missed opportunities to identify individuals with apparent behavior (Katz et al., 2010). The uncertainty with identifying doctor shopping individuals may also be elevated due to the fact that most PDMPs are not linked with patient medical records, which may verify that a patient has a diagnosis warranting excessive controlled substance use. Consequently, in settings such as community pharmacies where pharmacists may not have access to patient records, identifying doctor shoppers may be challenging and problematic. Therefore, clinical expertise should be consulted before setting specific doctor shopping thresholds, as well as conducting sensitivity analysis based on the specific objectives of the study. Katz et al. (2010) also recommends the use of both multiple providers and multiple pharmacies for defining 'doctor shopping' (Katz et al., 2010), hence the term 'multiple provider episodes'.

While defining doctor shopping is problematic, healthcare providers are also faced with the issue of what to do if a patient is suspected of doctor shopping. In West Virginia, where prescription drug overdose rates are the highest in the nation, a physician survey reported that while 40% of responding physicians suspected a patient of doctor

shopping at least once a week, only 22% were presently reporting doctor shopping. However, 85% of physicians responded that they would be likely to report doctor shopping if there was a law granting immunity to physicians for reporting doctor shoppers in good faith to law (Shaffer & Moss, 2010).

1.6 PREVALENCE OF DOCTOR SHOPPING

Prevalence estimates of doctor shopping vary by state and depend on the definition of doctor shopping. Based on prescription drug monitoring data in Kentucky, doctor shopping estimates were 18% between 2001-2002 (Manchikanti et al., 2003) and 9% in 2005 (Manchikanti et al., 2006). A 2012 follow up study found that doctor shopping rates had fallen to 2.1% (Manchikanti, Pampati, et al., 2012). While exact prevalence rates were not reported, an Ohio study of 179 participants in an emergency department setting found that among the patients involved in the study the number of opioid prescriptions that individuals had ranged from 0 to 128 within a 12-month period, with prescriptions in some cases being obtained from up to 40 different physicians (D Baehren et al., 2010). Within the California Controlled Substance Utilization Review and Evaluation System (CURES) PDMP database, two different studies found incidence rates of doctor shopping to be 8.4% (Wilsey et al., 2010) and 9.5% of all prescriptions involving opioids (AM Gilson, Fishman, Wilsey, Casamalhuapa, & Baxi, 2012). While only a small percentage of individuals meet the criteria for doctor shopping, these individuals account for a disproportionately large number of opioid prescriptions dispensed. A recent retrospective cohort study found that while doctor shoppers only accounted for 0.7% of the subjects in the study, they consumed 8.6% of all opioids

dispensed (Cepeda, Fife, Yuan, & Mastrogiovanni, 2013). McDonald and Carlson (2013) also reported that extreme doctor shoppers only account for 0.7% of the patient population in a national study, however they bought 1.9% of all opioid prescriptions (4% weighted to national population).

1.7 CHARACTERISTICS ASSOCIATED WITH DIVERSION AND DOCTOR SHOPPING

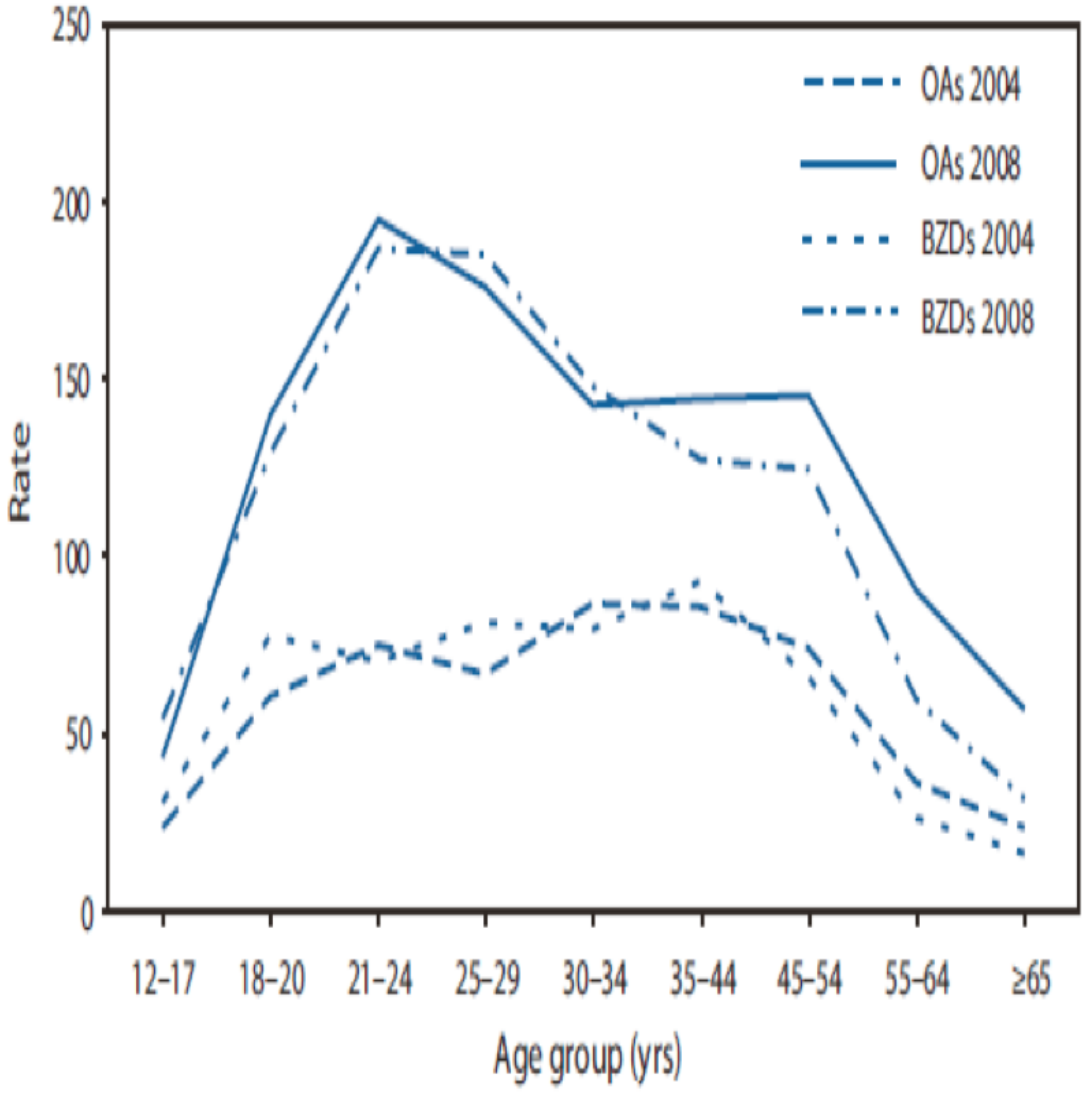
Research has shown that certain factors may make individuals or groups particularly vulnerable to prescription drug abuse and misuse, including underlying demographic, socioeconomic, geographic, and clinical factors. Understanding the factors associated with abuse and diversion is important in identifying the individuals and populations at highest risk for abuse and doctor shopping activities, as well as for the creation of interventions targeting these individuals.

1.7.1 INDIVIDUAL LEVEL CHARACTERISTICS ASSOCIATED WITH DIVERSION AND DOCTOR SHOPPING

Individual characteristics have been found to be strong predictors of nonmedical use of prescription medications, particularly opioids, as well as doctor shopping behavior (Buurma et al., 2008; Fishman, 2010; Han, Kass, Wilsey, & Li, 2012; Jones, 2012; Wilsey et al., 2010). As was found with chronic nonmedical use of opioids (Jones, 2012) and emergency room admissions for nonmedical use of opioids (Figure 1.7) (Substance Abuse and Mental Health Services Administration, 2010a), several studies have found that using multiple pharmacies and prescribers is associated with younger age (i.e., 18-25 years of age) (Buurma et al., 2008; Fishman, 2010; Han et al., 2012; Peirce et al., 2012;

Wilsey et al., 2010). However, the probability of being admitted for treatment involving opioid pain reliever abuse has been found to increase with age (Simeone, Holland, & Simeone Associates, 2006). Additionally, the rate of drug overdose deaths was found to be highest among individuals between the ages of 45-54 (Centers for Disease Control and Prevention, 2012).

Figure 1.7. Age-specific Rates of Emergency Department Visits for Nonmedical Use of Opioid Analgesics (OAs) and Benzodiazepines (BZDs) — United States, 2004 and 2008

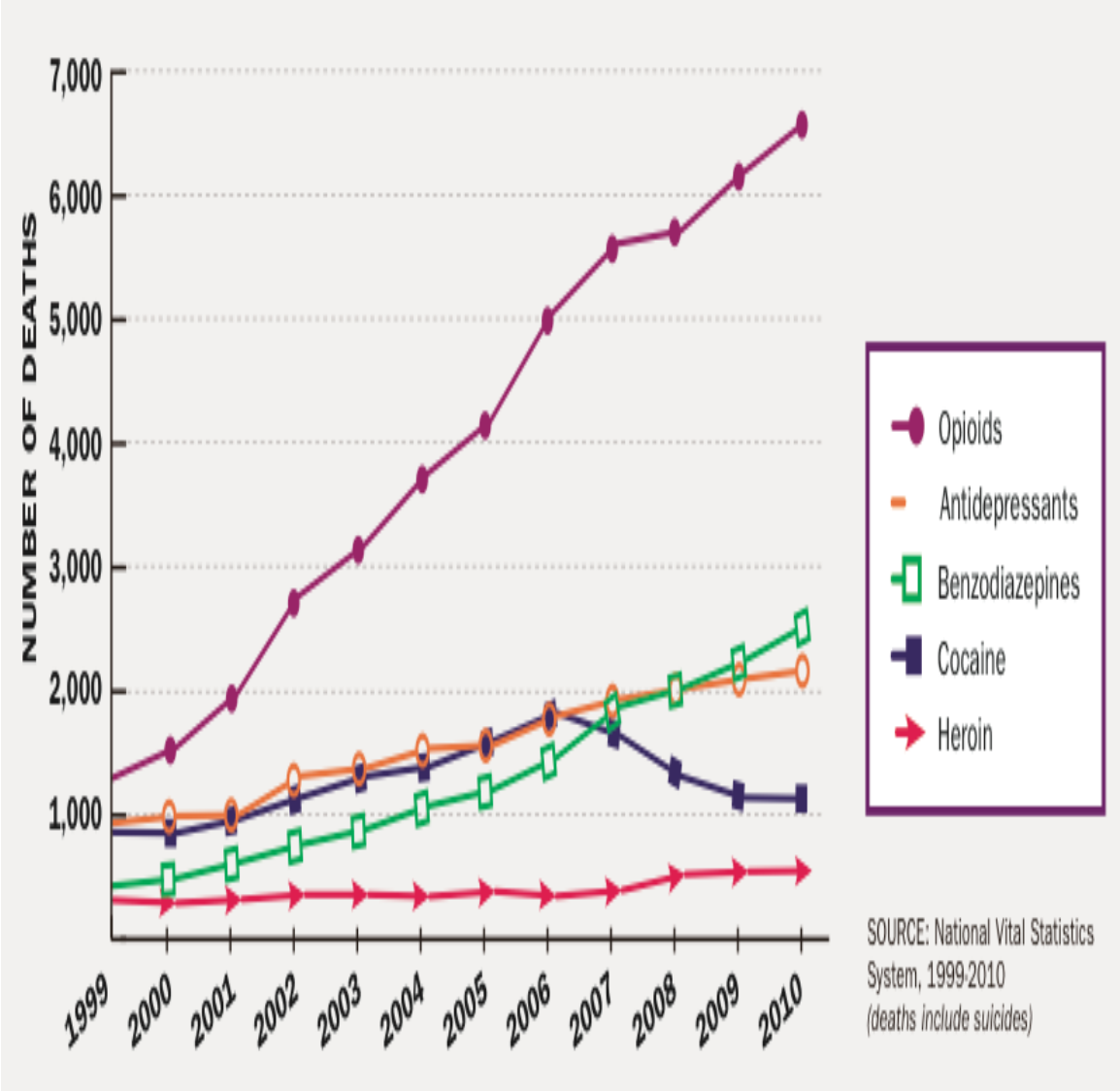


Source: SAMHSA, 2010

Gender has also been found to play a role in both abuse of controlled substance prescriptions and doctor shopping behaviors. While the literature has revealed conflicting reports of the association between gender and opioid abuse, it is believed that males are more likely to abuse prescription drugs and develop substances disorders (Eaton et al., 2011; National Institute on Drug Abuse, 2014b). However, as shown in Figure 1.8 the rate at which females are abusing prescription medications, particularly opioids, is growing exponentially, and the use of multiple provider episodes is more frequent among females (Han et al., 2012). The rate at which women are dying from prescription painkiller overdoses has increased 400% since 1999 for women and 265% for males, or about 18 women per day (Centers for Disease Control and Prevention, 2013a). The Drug Abuse Warning Network (DAWN) has also reported that approximately every three minutes a woman goes to the emergency department for prescription opioid misuse or abuse (Substance Abuse and Mental Health Services Administration, 2013). A survey using the National Household Survey on Drug Abuse (NHSDA) revealed that females have a 43% increased odds of any past-year prescription drug nonmedical use as compared to males (OR=1.43, 95% CI=1.19–1.69) (Simoni-Wastila, Ritter, & Strickler, 2004). Rosenblum et al. found that women were more likely than men to abuse prescription opioids in the past 30 days (Rosenblum et al., 2007). Females have also been found to have the greatest number of claims for opioid analgesics (Curtis et al., 2006). Studies from Buurma et al. and Hall et al. have found a greater risk of doctor shopping behaviors among females (OR=1.2, 95% CI=1.1-1.2; OR=2.2, 95% CI=1.2-4.1), respectively (Buurma et al., 2008; Hall et al., 2008). The literature has also

reviled that females also have higher probabilities of admission involving abuse (Simeone et al., 2006).

Figure 1.8. Prescription Painkiller Overdose Deaths Among Women



Source: National Vital Statistics System, 1999-2010

Certain socio-economic factors, such as full-time employment status, have been found to reduce the probability of admission involving abuse (Simeone et al., 2006). An individual's insurance status may also increase the likelihood of developing opioid abuse, as insurance status is often an indicator of both an individual's socioeconomic and health status (Bonito, Bann, Eicheldinger, & Carpenter, 2008). An analysis of chronic opioid use among commercially insured individuals and Medicaid patients, found that chronic use was more prevalent among Medicaid patients (Edlund et al., 2010). In Kentucky 28.6% of individuals identified as doctor shoppers had Medicaid as their form of insurance coverage, as compared to 14.3% insured by a third party (Manchikanti, Pampati, et al., 2012).

The number and type of prescriptions for controlled substances that a patient has is found to be positively associated with doctor shopping behavior (Fishman, 2010; Hall et al., 2008; Han et al., 2012; Katz et al., 2010; Kim, Small, Hwang, & Muldrew, 2014; Rosenblum et al., 2007; White et al., 2005; Wilsey et al., 2010). A case-control study conducted by Wilsey et al. (2010) using the California CURES database found that among the 8.5% of the study population that were identified as 'doctor shoppers', opioid prescriptions were the most frequently involved prescription (12.8%). Additionally, odds ratios for multiple provider prescribing increased exponentially when more than one controlled substance class was prescribed. The study reported that individuals who were prescribed stimulant/anorectic and benzodiazepines along with an opioid during the same 30 days had a 13 times increase in probability of multiple provider prescribing (OR=13.12, 95% CI=12.01-14.33), and 25.1 times increase (OR= 25.10, 95% CI=22.73-27.72) if the individual had simultaneous prescriptions for stimulants/anorectics,

benzodiazepines and opioids (Wilsey et al., 2010). Han et al. (2012) found that as compared to using just Schedule II controlled substance prescriptions, individual's who used both Schedule II and III opioids utilized more prescribers and pharmacies (OR=3.02, 95% CI=2.98-3.06). When analyzing a cohort of only Schedule II drugs, Katz et al. (2010) found that oxycodone was the opioid most highly associated with questionable activity. Also in analyzing prescription opioid abuse among enrollees in a methadone maintenance treatment, Rosenblum et al (2007) reported that the most frequently abused prescription opioids among the abusers in their lifetime were oxycodone (89%), hydrodocone (88%) and morphine (59%). An increased risk has also been found for individuals with ≥ 3 prescriptions (Buurma et al., 2008), use of long-acting opioids, use higher total daily drug doses, and use oxycodone, morphine, and fentanyl (Kim et al., 2014). In West Virginia 21.4% of individuals who had died of an overdose had received prescriptions for controlled substances from 5 or more clinicians during the year prior to their death (Hall et al., 2008). In Maine using prescription claims data, White et al found that having 12 or more opioid prescriptions in three months resulted in an over twofold (OR=2.12, 95% CI=1.73-2.61) increase of risk of overdose (White, Birnbaum , Schiller, Tang, & Katz, 2009). Using data collected from the California CURES database, a preliminary, unpublished analysis from Fishman (2010) found that the likelihood of an individual receiving opioids from more than one provider doubled if they also had a prescription for an additional controlled substance prescription. Additionally, the likelihood of doctor shopping increased by 13 times if the individual received three or more prescriptions for different schedules of medications.

1.7.2 REGIONAL LEVEL AND SOCIODEMOGRAPHIC CHARACTERISTICS ASSOCIATED WITH DIVERSION AND DOCTOR SHOPPING

While it is individuals who abuse controlled substances, regional-level characteristics and population-specific demographics that vary by communities, counties and states, are believed to influence individual behavior and potential for an increased risk of abuse (Fishman, 2010; Han et al., 2012; PDMP Center of Excellence, 2012; Simeone et al., 2006). Local public health authorities can better understand and efficiently serve populations through resource allocation, prevention and treatment efforts if they know the distribution and prevalence of nonmedical use of prescription drugs in certain regions (e.g., metropolitan, urbanized non-metropolitan, and rural).

Geographical location may play an important role in aberrant prescription drug use. Previous research has indicated that variances in regulations, policies and even diverse populations by geographic location affect not only opioid and CSP use, but also abuse (Curtis et al., 2006). Wilsey et al found that smaller populated counties were associated with a decreased likelihood of having multiple prescriber episodes, as compared to metropolitan areas with greater than one million people (Wilsey et al., 2010). A study from Fishman also reported a positive association between doctor shopping behavior and residence in metropolitan areas (Fishman, 2010). The findings from these studies are supported by the results of the National Surveys on Drug Use and Health (NSDUH) from 2005-2011 (Table 1.6), which found that individuals located in metropolitan and urbanized counties reported higher rates of nonmedical use within the past year, as compared to rural citizens. Certain CSP are also more frequently involved in multiple provider episodes by geographical location. Wilsey et al. found that

benzodiazipines were more prevalent in MPE cases in larger urban areas (Wilsey et al., 2010). However, rates were similar across all three county types for past month use (Substance Abuse and Mental Health Services Administration, 2014a). Nonetheless, nonmedical use of prescription medications remains a concern across all county types.

Table 1.6. Past Year and Past Month Nonmedical Use of Prescription-Type Drugs among Persons Aged 12 or Older, by County Type: 2005 to 2011

County Type	Past Year	Past Month
Metropolitan	6.4%	2.7%
Urbanized Non-metropolitan	6.6%	2.8%
Rural	5.4%	2.4%

Source: SAMHSA, National Surveys on Drug Use and Health (NSDUHs), 2014

A multi-level modeling approach to defining abuse by state-level factors found that the probability of prescription stimulant abuse is a function of the per capita supply of prescription stimulants. This study also found that increasing the supply of opioid pain relievers in a state increases the probability of admission to treatment involving pain reliever abuse; and increasing the supply of stimulants increases the probability of admission to treatment involving stimulant abuse (Simeone et al., 2006).

A nationwide study of counties also found a positive association between the number of surgical specialists in and area the and the number of claims for opioid prescriptions (Curtis et al., 2006). Analyzing individual-level and county-level factors associated with multiple provider episodes in California, Han et al found that the total number of licensed physicians and surgeons in a county was linearly associated with multiple provider episodes (Han et al., 2012). Other factors that have been found to be positively correlated with prescription opioid drug rates are both poverty and unemployment rates (Spiller, Lorenz, Bailey, & Dart, 2009).

1.8 CONSEQUENCES OF DOCTOR SHOPPING

Recent research has found an association between shopping behavior and an increased risk for drug-related death (T Gomes et al., 2011; Hall et al., 2008; Peirce et al., 2012). One such factor associated with doctor shopping is the lack of continuity of care within and across providers. Discontinuity of care increases the risk of medication errors and poor clinical outcomes, inhibits appropriate patient medication surveillance (Buurma et al., 2008; Moore, Wisnivesky, & McGinn, 2003; Van Walraven, Mamdani, & Austin,

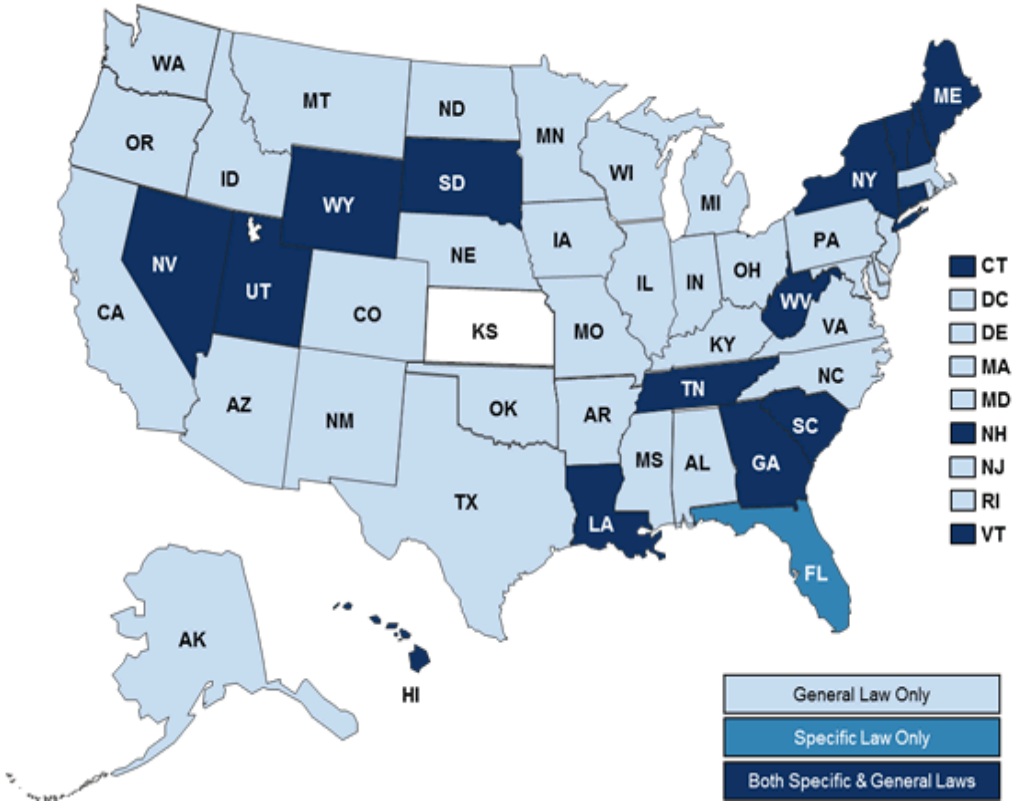
2004) and increases the risk for drug–drug interactions (Buurma et al., 2008). The risk of a potentially inappropriate drug combination has been found to increase with the number of prescribing physicians (Tamblyn, McLeod, Abrahamowicz, & Laprise, 1996; Vingerhoets, Wieringa, Egberts, Jansen, & Jansen, 2014). As discussed by Vingerhoets et al. (2014) most doctors do not have a complete overview of all the medicines prescribed or used by patients and often do not have sufficient time or knowledge to evaluate polypharmacy, therefore the increasing number of doctors utilized contributes to inappropriate prescribing. However, use of a single primary care physician and a single dispensing pharmacy may offer "protective" effects by lowering the risk of potentially inappropriate drug combination (Tamblyn et al., 1996). A study conducted in the Netherlands concluded that even light shopping behavior (>1 pharmacy) may impede appropriate medication surveillance and put patients at risk for unintentional drug therapy-related problems, such as duplicate medications, drug–disease interactions and drug–drug interactions (Buurma et al., 2008).

1.9 DOCTOR SHOPPING LAWS

As of 2012 only 16 states have ‘specific’ fraud statutes pertaining to doctor shopping (Figure 1.9). Specific doctor shopping laws prohibit patients from not disclosing to their healthcare practitioners that they have received: a controlled substance or prescription order from another practitioner; the same controlled substance or of similar therapeutic use within a specified time interval or at any time previously (Centers for Disease Control and Prevention National Center for Injury Prevention and Control Division of Unintentional Injury Prevention, 2012). The other 34 states have ‘general’

statutes, derived from the Uniform Narcotic Drug Act of 1932 or the Uniform Controlled Substances Act of 1970. The majority of general statutes refer to doctor shopping as obtaining drugs through fraud, deceit, misrepresentation, subterfuge, or concealment of material fact and non-disclosure (Centers for Disease Control and Prevention National Center for Injury Prevention and Control Division of Unintentional Injury Prevention, 2012) (The National Alliance for Model State Drug Laws (NAMSDL), 2010).

Figure 1.9. States with Doctor Shopping Laws



Source: CDC, 2012

1.10 APPROACHES TO ADDRESSING DIVERSION AND DOCTOR SHOPPING

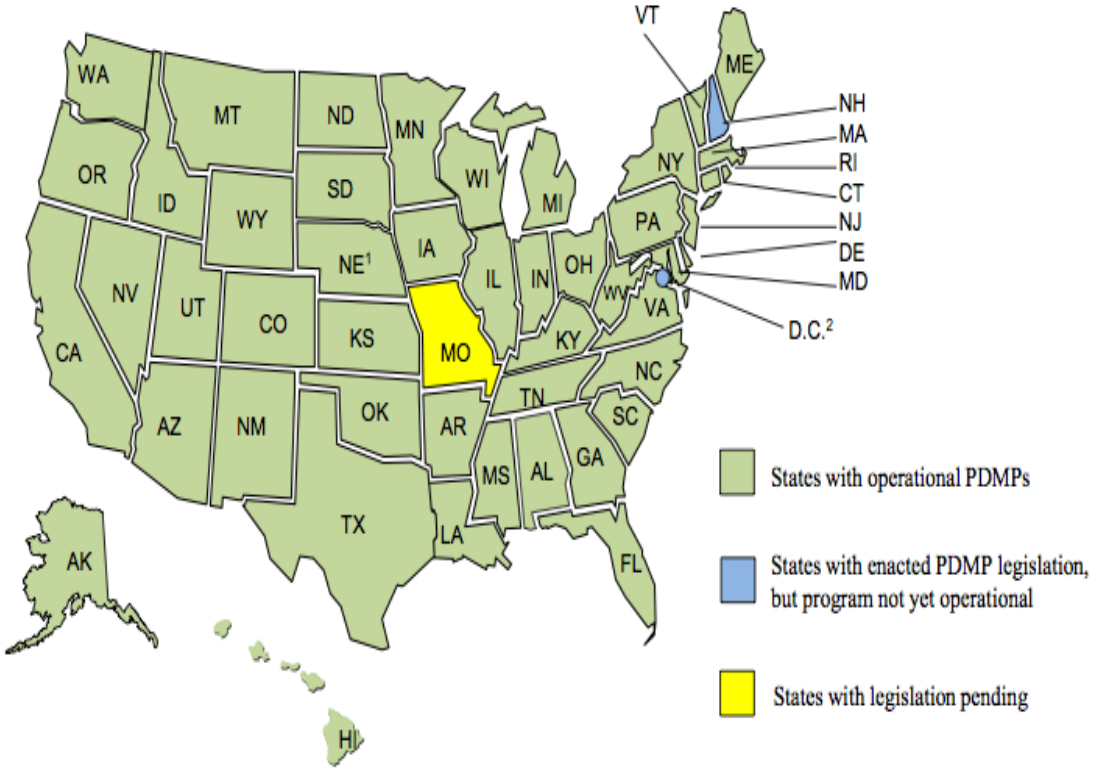
In response to the escalating problem of prescription drug abuse, in recent years states across the U.S. have began implementing programs and policies to reduce prescription drug abuse. However, few tools or programs encompass more than one of the components of the Department of Health and Human Services (HHS) eight domains for addressing drug abuse activities: 1) surveillance, 2) drug abuse prevention, 3) patient and public education, 4) provider education, 5) clinical practice tools, 6) regulatory and oversight activities, 7) drug abuse treatment, and 8) overdose prevention initiatives. However, one program has utility in each of these domains and the Department of Health and Human Services has referred to it as "one of the most promising clinical tools to address prescription drug abuse" (U.S. Department of Health and Human Services, 2013). This tool is state prescription drug monitoring programs.

1.10.1 PRESCRIPTION DRUG MONITORING PROGRAMS (PDMPS)

Prescription drug monitoring programs (PDMPs) are statewide electronic databases which collect designated data on controlled substances prescriptions and certain noncontrolled substances (e.g., tramadol) dispensed within the state (U.S. Department of Justice Drug Enforcement Administration Office of Diversion Control, 2011). Currently, 49 states, the District of Columbia and one U.S. territory (Guam) have authorized legislation for the creation and operation of a state PDMP (Figure 1.10). Forty-eight states and Guam currently have a PDMP that is operational. Operational status means that the program is currently collecting data from dispensers and reporting

information from the database to authorized users (The PDMP Training and Technical Assistance Center, 2014).

Figure 1.10. Status of State Prescription Drug Monitoring Programs



Source: The National Alliance for Model State Drug Laws, 2014

Prescription drug monitoring programs were first established in 1939 in the State of California. Based in the Department of Justice, the program was designed to monitor prescriptions for Schedule II controlled substances for law enforcement purposes. During this time state-issued paper triplicate and serialized prescription forms were used, lasting up until the late 1990s. Starting in the 1990s PDMPs starting incorporating advances in the technology and functionality of PDMPs, with electronic submission of prescription data increasing the accuracy and timeliness of submissions.(PDMP Training and

Technical Assistance Center, 2012) Most state PDMPs now have secure online portals for authorized providers to access patient PDMP data. In 1995, Nevada became the first state to require collecting prescription data for Schedule II-IV drugs. The introduction of the Harold Rogers Prescription Drug Monitoring Programs Grant in 2003 provided funding and support for the creation of 33 new state PDMPs (Clark, Eadie, Kreiner, & Strickler, 2012; PDMP Training and Technical Assistance Center, 2012).

1.10.2 CHARACTERISTICS OF PDMPS

Individual states vary in how the monitoring programs are operated. This includes their objectives, design, which schedules of controlled substances they monitor, who can access the data, the frequency of reporting data and which state agency houses the PDMP (Finklea, Sacco, & Bagalman, 2014). PDMPs serve a variety of functions across different states, but all are ultimately intended to promote legitimate access to controlled substances and reduce the abuse of controlled substance pharmaceutical drugs (Finklea et al., 2014; A Gilson, Husain, Payne, & Twillman, 2013; Simeone et al., 2006). PDMPs can function to address prescription drug abuse by improving patient care through the quick identification of high-risk patients, providing complete prescription history information to emergency department providers, and conveying current and accurate information to guide appropriate clinical decision making for both physicians and pharmacists (U.S. Department of Health and Human Services, 2013).

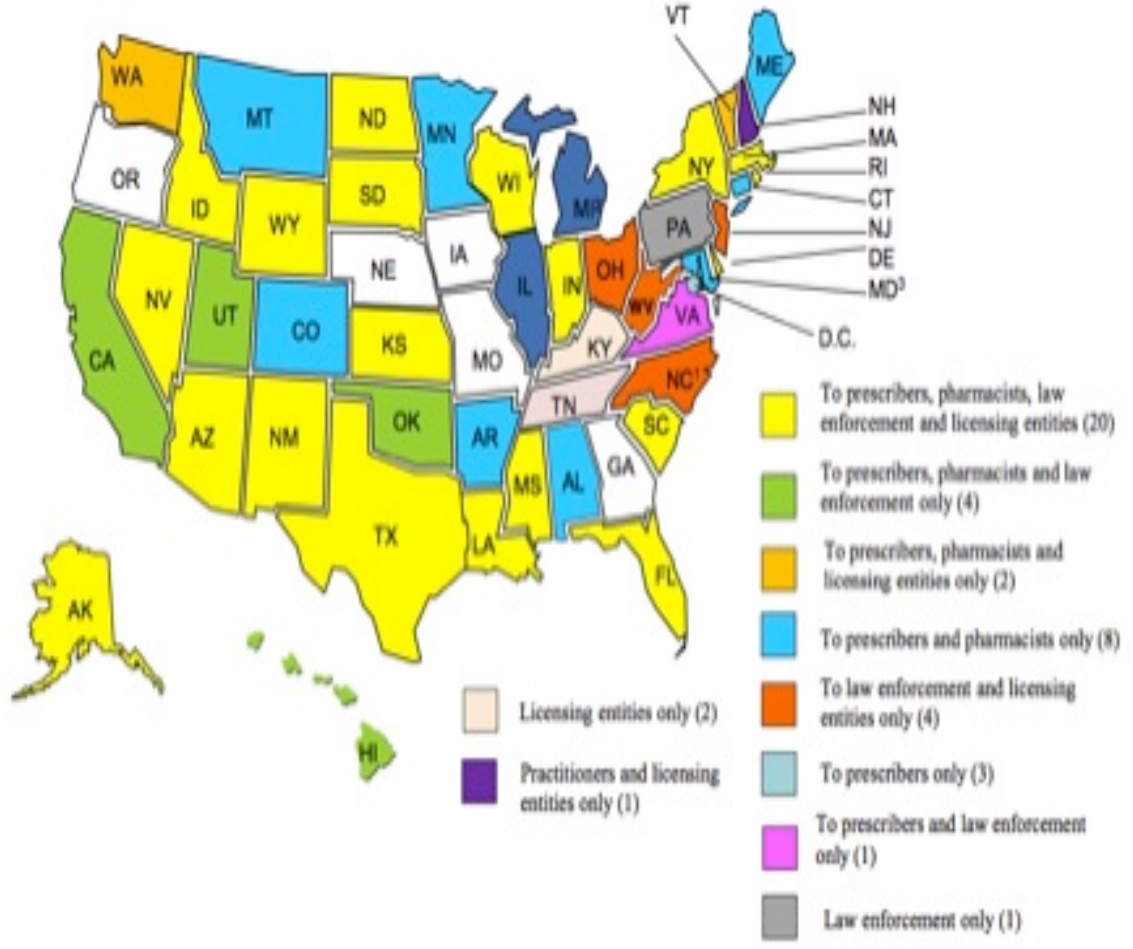
1.10.3 SOLICITED AND UNSOLICITED REPORTING

State PDMPs can also be classified as a *reactive* or *proactive* system based on how the state generates reports based on PDMP data to authorized users (K Blumenschein et al., 2010; Simeone et al., 2006). Solicited reports, also known as reactive reporting, are provided to authorized users upon on their request for more information (e.g., pharmacists). Authorized users vary by state, but include prescribers, dispensers, law enforcement, and regulatory boards. Unsolicited reporting, also referred to as proactive reporting, produces reports to authorized individuals based on pre-established thresholds established by the individual PDMP (PDMP Training and Technical Assistance Center, 2013a). Unsolicited reporting may be triggered if analysis of PDMP data indicates potential questionable activity either by a patient or a prescriber. This includes sending reports to prescribers and pharmacists to notify them that a patient may potentially be doctor shopping or diverting controlled substances or to notify investigative agencies and professional licensing boards that a prescriber may be prescribing inappropriately or excessively (Astho, 2014; Centers for Disease Control, 2013). The Prescription Drug Monitoring Program Center of Excellence cites the unsolicited reporting of PDMP data to prescribers, dispensers, licensing boards, and law enforcement agencies as a PDMP best practice for states, as it helps to promote safe prescribing and limit diversion of controlled substances (PDMP Center of Excellence, 2014c). Unsolicited reporting of PDMP data has shown potential to improve clinical practice by alerting providers about patients with multiple prescribers and potentially medically unnecessary prescriptions (Thomas et al., 2014). Simeone and Associates found that states which have PDMPs, particularly proactive PDMPs, have a reduced

supply of opioids and in so doing have an indirect effect on abuse rates (Simeone et al., 2006).

Several components of reporting vary across state programs, including whether the program produces both solicited and unsolicited reports, the timeliness of generating reports to end users and the users who are authorized to receive these reports (Figure 1.11) (National Council for Prescription Drug Programs, 2013).

Figure 1.11. Status of Unsolicited Reporting



Source: National Alliance for Model State Drug Laws, 2014

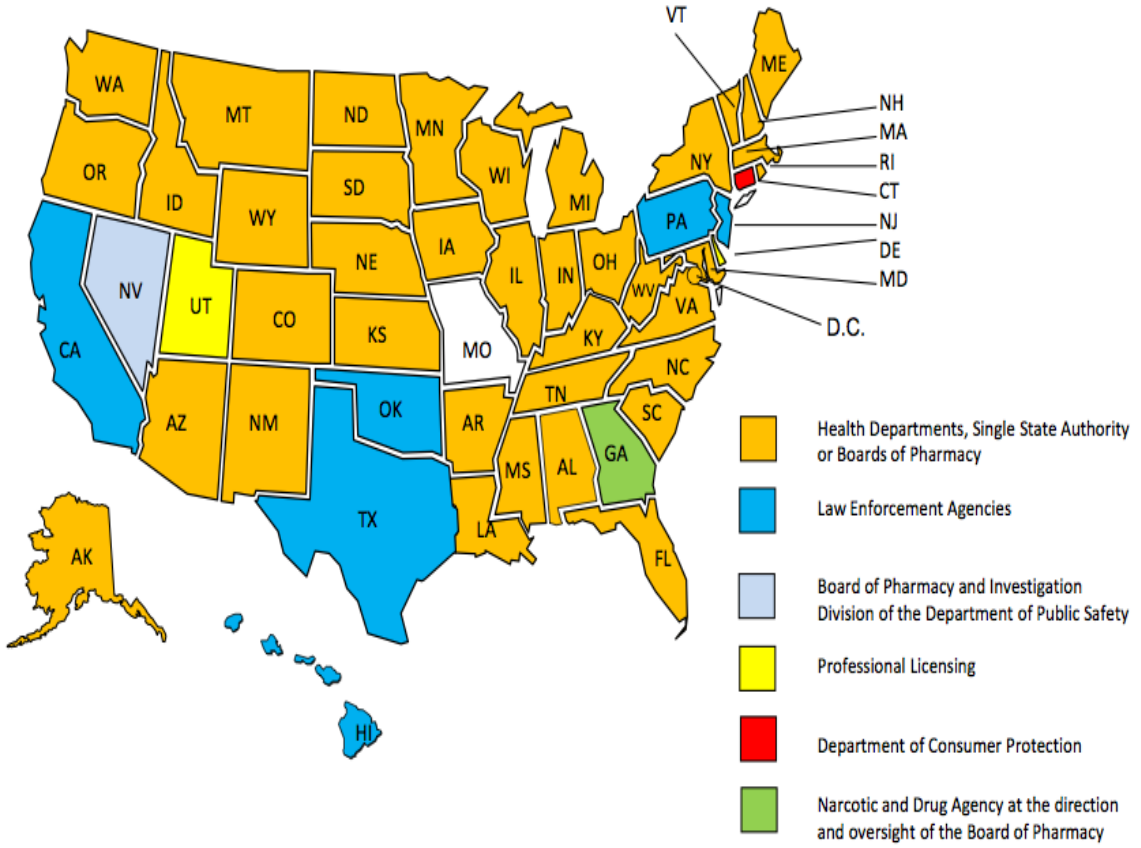
1.10.4 ADMINISTRATION OF PDMPS

PDMPs are housed in and operated by different governmental agencies, including health or human services departments, single state authority on drugs and alcohol, boards of pharmacy, law enforcement agencies, professional licensing agencies and consumer protection agencies (National Alliance for Model State Drug Laws, 2009). However, the majority of PDMPs are operated by state boards of pharmacy (Figure 1.12) (K Blumenschein et al., 2010). The housing of PDMPs has been a debated topic among stakeholders, with some organizations raising concerns about healthcare versus law enforcement uses of PDMP data (Finklea et al., 2014). Both the American Medical Association (AMA) and the American Society of Addiction Medicine (ASAM) have recommended that PDMPs should be housed in health-related agencies, citing that PDMP data should be used for the purpose of educating providers, not for civil action against physicians. Both organizations have also expressed concerns over agencies outside of the healthcare system accessing private personal identifiable information contained in the PDMP (AMA Advocacy Resource Center, 2012; American Society of Addiction Medicine, 2012). Additionally, Fleming et al. reported that among law enforcement–governed PDMPs, healthcare provider utilization was lower compared with PDMPs under health or pharmacy boards (ML Fleming, Chandwani, Barner, Weber, & Okoro, 2013).

Other components of PDMPs that vary based on their administration and state laws are: the schedules of controlled substances that are monitored under each program; the extent of data that is collected by the program; the timeliness of submitting prescription information; and who is authorized to access the database (e.g., doctors,

pharmacists, law enforcement, state medical examiners, researchers) (Finklea et al., 2014).

Figure 1.12. PDMP Housing Entities



Resource: National Alliance for Model State Drug Laws, 2014

1.11 STRENGTHS OF PDMPS AND UTILIITY IN COMBATTING PRESCRIPTION DRUG ABUSE

Prescription Drug Monitoring Programs are currently being recognized as one of the key components to combatting prescription drug abuse (Kerlikowske, Jones, Labelle, & Condon, 2011; Office of National Drug Control Policy, 2013). Data collected from PDMPs can be utilized as a public health surveillance tool given its utility in the ongoing,

systematic collection. This public health tool can be used to reduce morbidity and mortality and to improve health outcomes (Centers for Disease Control and Prevention, 2001). Evidence is beginning to accumulate which illustrates that PDMPs are effective for law enforcement, improving clinical decision-making, reducing excessive controlled substance prescription prescribing, and reducing prescription drug abuse and doctor shopping. (Haffajee, Jena, & Weiner, 2015; PDMP Center of Excellence, 2014a; Simeone et al., 2006; U.S. General Accounting Office, 2002)

1.11.1 UTILITY FOR EVALUATION PURPOSES

The inherent structure of data collected from state PDMPs is strong in its usefulness for evaluation and research. Most state PDMP databases include a high level of drug detail, including the drug name, formulation, prescriber, and dispenser identifications. PDMP data also have high statistical power, given that there are observations for millions of patients. Patients, provider and pharmacy data can also be linked longitudinally across time (L Paulozzi, 2010). PDMPs have also assisted law enforcement agencies and regulatory investigators by reducing the amount of time and effort required to explore leads in possible drug diversion cases. In Nevada the state's PDMP was found to reduce the investigation time of alleged doctor shoppers from approximately 120 days to 20 days. State drug control investigators in Kentucky reported taking an average of 156 days to complete the investigation of alleged doctor shoppers before the state's PDMP (KASPER) implementation, dropping down to 16 hours on average after its implementation (United States General Accounting Office, 2002).

1.11.2 REDUCE PRESCRIBING AND DISPENSING OF CONTROLLED SUBSTANCES

The presence of an active PDMP has been found to reduce the per capita supply of prescription pain relievers and stimulants, while also indirectly reducing the probability of abuse for such drugs (Reisman et al., 2009; Simeone et al., 2006). Several states have reported success in using their state PDMPs as a tool in improving controlled substance prescribing practices. Curtis et al found that while claims rates for opioids varies greatly across states, states with long-standing prescription monitoring programs had the lowest rates of claims for opioid analgesics and controlled-release oxycodone (Curtis et al., 2006). In New York State, mandatory utilization requirement of the state's PMDP (I-STOP) for prescribers resulted in and 9.51% decrease in the number of individuals with prescriptions for opioids (PDMP Center of Excellence, 2014b). Following the inception Florida's PDMP program (E-FORCSE®**:** Electronic-Florida Online Reporting of Controlled Substance Evaluation Program), prescribing of oxycodone and methadone fell by 24% and 8%, respectively, between 2011-2012 (Florida Health, 2013). Other states reporting a decline in dispensing of opioids in the year following prescriber mandates to use their respective PDMPs were Tennessee (7% decline in opioids) and Kentucky (8.5% decrease in opioid prescriptions (PDMP Center of Excellence, 2014b).

1.11.3 IMPROVING PATIENT CARE

One important element of PDMPs is their function as a clinical-decision making tool for healthcare providers. Most PDMPs provide of a complete record of a patient's controlled substance prescribing history for a designated amount of time, enhancing

patient safety by enabling a provider to avoid potentially deadly combinations of medications (A Gilson et al., 2013). An example of what a patient profile might look like is provided in Figure 1.13.

PDMP data can help inform appropriate clinical decision-making and give healthcare providers confidence to ensure that prescriptions are medically necessary (PDMP Center of Excellence, 2014a). Several studies have recently been conducted analyzing provider use of state PDMPs, showing the clinically appropriate action that was taken by providers after reviewing PDMP data. In Ohio Baehren et al. reported that in an emergency department setting, the use of Ohio's PDMP (OARRS) data influenced the provider's opioid prescribing pattern. After reviewing PMDP data, providers changed their clinical management plan in 41% of the cases. Within those cases 61% of the study patients were prescribed fewer or no opioid medications than had been originally planned, and 39% of patients received more opioid medication than originally planned (D Baehren et al., 2010). Also in Ohio 89% of attending physicians and residents cited utilizing the OARRS database when they had concerns about prescription drug abuse (Feldman, Skeel Williams, Knox, & Coates, 2012). In a second study of emergency providers, physician exposure to PDMP data resulted in changed plans to prescribe opioids at discharge in 9.5% of cases, some of which receiving opioids not previously planned (Weiner et al., 2013). In an Indiana survey, 50.1% of prescribers reported changing their treatment plan for a patient based on PDMP data and over 90% stated that as a result they had prescribed fewer controlled substances (Kooreman, Carnes, & Wright, 2014). In Oregon providers who were active users of the Oregon Prescription Drug Monitoring Program (PDMP) reported haven spoken with a patient about controlled

substance use (78%), confirmed patient not misusing prescriptions (68%), confirmed patient was doctor shopping (59%) and/or reduced or eliminated prescriptions for a patient (59%) (Multnomah County Health Department and Oregon Health Authority, 2013).

Figure 1.13. Example of Patient PDMP Profile

Number of Hits: 9 **Start Date: 01/01/2012 End Date: 01/01/2013**

Date Filled	First Name	Last Name	DOB	Address	Drug Name	Form	Str.	Qty	PHY. Name	PHY #	Dr. DEA #	Dr. Name	Rx #	Refill #
1/1/12	JOHN	DOE	6/6/58	123 Red St. Houston, TX 77054	Vicodin	TAB	100 mg	10	Walgreens #120	1234	TX243	Smith, John	123	1
1/23/12	JOHN	DOE	6/6/58	123 Red St. Houston, TX 77054	Xanax	TAB	10 mg	30	CVS #59	5678	TX675	Olson, Jane	574	1
3/2/12	JOHN	DOE	6/6/58	123 Red St. Houston, TX 77054	Hydrocodone - APAP	TAB	5-325 mg	30	Walgreens #120	1234	TX675	Olson, Jane	342	1
6/9/12	JOHN	DOE	6/6/58	123 Red St. Houston, TX 77054	Vicodin	TAB	100 mg	10	CVS #59	5678	TX675	Olson, Jane	765	1
11/2/12	JOHN	DOE	6/6/58	123 Red St. Houston, TX 77054	Xanax	TAB	40 mg	30	CVS #59	5678	TX243	Smith, John	578	1
1/20/13	JOHN	DOE	6/6/58	123 Red St. Houston, TX 77054	Hydrocodone - APAP	TAB	5- 325 mg	30	Walgreens #120	1234	TX243	Smith, John	245	1
3/16/13	JOHN	DOE	6/6/58	123 Red St. Houston, TX 77054	Vicodin	TAB	100 mg	10	CVS #59	5678	TX243	Smith, John	764	1
6/4/13	JOHN	DOE	6/6/58	123 Red St. Houston, TX 77054	Vicodin	TAB	100 mg	10	CVS #59	5678	TX243	Smith, John	891	1
8/7/13	JOHN	DOE	6/6/58	123 Red St. Houston, TX 77054	Xanax	TAB	40 mg	30	Walgreens #120	1234	TX675	Olson, Jane	345	1

1.11.4 REDUCE PRESCRIPTION DRUG ABUSE AND DOCTOR SHOPPING

As data from 'modern' state PDMPs begins to be collected, studies are beginning to analyze PDMPs and their utility in identify potential doctor and pharmacy shoppers,

both retrospectively and at the point of care (Manchikanti, Pampati, et al., 2012; Peirce et al., 2012). A prescriber survey in Massachusetts found that when prescribers received unsolicited reports from the Massachusetts Prescription Monitoring Program (MA PMP) only 28 respondents (8.4%, of which most were oncology/hematology specialists) reported being aware of most, nearly all, or all prescribers listed in the report. The survey reported that emergency department providers were the least aware of other prescribers (Thomas et al., 2014). This study highlights the importance of using PMDPs as a tool for identifying potential doctor shopping behavior and assuring for the clinical appropriateness of controlled substances.

Several states have released recent reports of their state's doctor shopping status as the result of PDMP utilization. In Kentucky Manchikanti et al concluded that with the assistance of the state PDMP KASPER's enhanced monitoring (Kentucky All Schedule Prescription Electronic Reporting) doctor shopping was reduced from 18% to 2.1% over a period of 10 years (Manchikanti, Pampati, et al., 2012). Following a 2013 mandate requiring New York prescribers to use the state's prescription drug monitoring program (I-STOP), the state saw a 75% decline in the number of patients obtaining painkillers from multiple prescribers (5 prescribers/5 pharmacies over 3 months) (PDMP Center of Excellence, 2014b). In 2011 in Florida as the result of years of extensive overprescribing, dispensing, and prescription drug misuse, several initiatives were set forth to address the problem, including dispenser mandatory reporting to the state's new PDMP (E-FORCSE®) (H. Johnson, Paulozzi, Porucznik, Mack, & Herter, 2014). As a result Florida saw a 51% reduction in doctor shopping behavior (5 or more doctors or five or more pharmacies in 90 days) (Florida Health, 2013). Other states reporting a

decline in doctor shopping rates post-PDMP implementation are Virginia (73% reduction) (Virginia Department of Health Professions, 2014) and Tennessee (36% reduction) (PDMP Center of Excellence, 2014b).

A study from the Bouches-du-Rhoˆ ne region of France found a reduction of doctor shopping rates for buprenorphine, a medication generally used for opioid maintenance treatment, from 21.7% to 16.9% after the inception of its prescription monitoring program (Pradel et al., 2009).

1.11.5 REDUCTION IN OVERDOSES AND RELATED DEATHS

While directly linking implementation of a state PMDP with a reduction in opioid overdoses and deaths has not been wholly established, states are reporting reductions in overdose rates post-PDMP implementation alongside other state prevention initiatives to reduce abuse rates. In the year following a state overhaul of pain clinics and a mandate that prescribers use the KASPER system before prescribing many controlled substances, Kentucky saw a decline in prescription overdoses for the first time in over a decade (Governor's Communication Office press release, 2013). Following Florida's implementation of E-FORCSE® in 2011, the state saw a oxycodone-related overdose deaths fall by 41% (Florida Health, 2013). Alongside new pain management rules for healthcare providers, the Department of Health in Washington implemented its PDMP at the end of 2011 and saw overdose death rates drop by 27% (WA Department of Public Health press release, 2014).

1.12 PROBLEMS AND LIMITATIONS ASSOCIATED WITH PDMPS

As with the benefits associated with PDMP use, there is potential for unintended consequences of PDMPs, which have created debate among the program's advocates and critics.

1.12.1 UNDERUTILIZATION

While PDMPs may be an effective tool in identifying and deterring shopping behavior and aberrant use of prescription medications, they are widely underutilized in most states where use is not considered 'mandatory'. This type of program must be fully utilized to reach its full potential in controlling prescription drug abuse and diversion (Kerlikowske et al., 2011). A 2012 study of Ohio resident physicians found that only 51% of residents reporting utilizing the Ohio OARRS system (Feldman et al., 2012). A 2013 survey in Indiana reported that 23.1% of medical doctor (M.D.) respondents still hadn't heard of the state's PDMP 'Indiana Scheduled Prescription Electronic Collection and Tracking Program' (INSPECT), even though the modern system had been launched almost 10 years earlier in 2004 (Kooreman et al., 2014). In Indiana 28.2% of physician respondents in a survey reported reviewing PDMP data for only 1-10% of their patients receiving prescribed controlled substances (Kooreman et al., 2014). As of June 2014, only 20 states had laws mandating that prescribers and in some cases dispensers enroll with the PDMP, and 22 states had laws mandating that prescribers and in some cases dispensers use the PDMP in certain circumstances (PDMP Center of Excellence, 2014b).

1.12.2 LIMITING ACCESS TO MEDICATIONS USED FOR LEGITIMATE USE

The discussion of PDMP's ability to reduce supply of certain controlled substances is debated as both a positive and negative aspect of the program. Concerns have been raised that PDMPs may have a "chilling effect", deterring physicians from prescribing opioids to successfully treat a patient's pain, due to the potentially negative influence of drug enforcement agents monitoring their prescribing behaviors (Finklea et al., 2014). However, several studies have dispelled these claims, implying that data from prescription monitoring programs can be used to reduce the frequency of diversion, without threatening legitimate access to prescription drugs (D Baehren et al., 2010; Pradel et al., 2009; Reisman et al., 2009).

Additionally, given that PDMP data does not include diagnosis information it cannot be initially determined without further investigation or availability of the patient's medical records if the individual is or isn't diverting prescriptions for nonmedical purposes. However, even excessive prescriptions for an individual with a medically warranted condition may indicate inappropriate treatment or medical care.

Discrepancies in the evaluation of the effectiveness of PDMPs in reducing prescription drug abuse may be the result of differences and objectives of different state programs. However, as with any drug abuse policy, the overall goal of PDMPs is to achieve a balance between the mitigation of inappropriate use and providing care for those individuals with legitimate need for controlled substance prescriptions.

1.13 TEXAS-PRESCRIPTION DRUG ABUSE

Since 1982 Texas prescribers have been required to use single or multiple (triplicate) copy forms, issued by the Department of Public Safety, when writing

prescriptions for Schedule II controlled substances.(Texas Department of Public Safety, 2011) Believed to be a result of this program, the prescribing of long-acting and high-dose opioids falls in Texas is below the national average.(Lakey & Lewis, 2014)

Drug overdose rates in Texas also fall on the lower spectrum of drug overdose rates, as compared to the rest of the United States, with 9.6 deaths per 100,00 people, however the number of drug overdose deaths have increased by 78% since 1999 (Trust for America's Health, 2013). Data from Texas poison centers in 2010 has shown a 160% increase in opioid analgesic abuse between the years 2000-2010. The most frequently reported opioid drug was hydrocodone followed by tramadol, propoxyphene, codeine, and oxycodone. Hydrocodone was involved in 60% of the opioid analgesic abuse cases reported to Texas poison centers (Table 1.7).

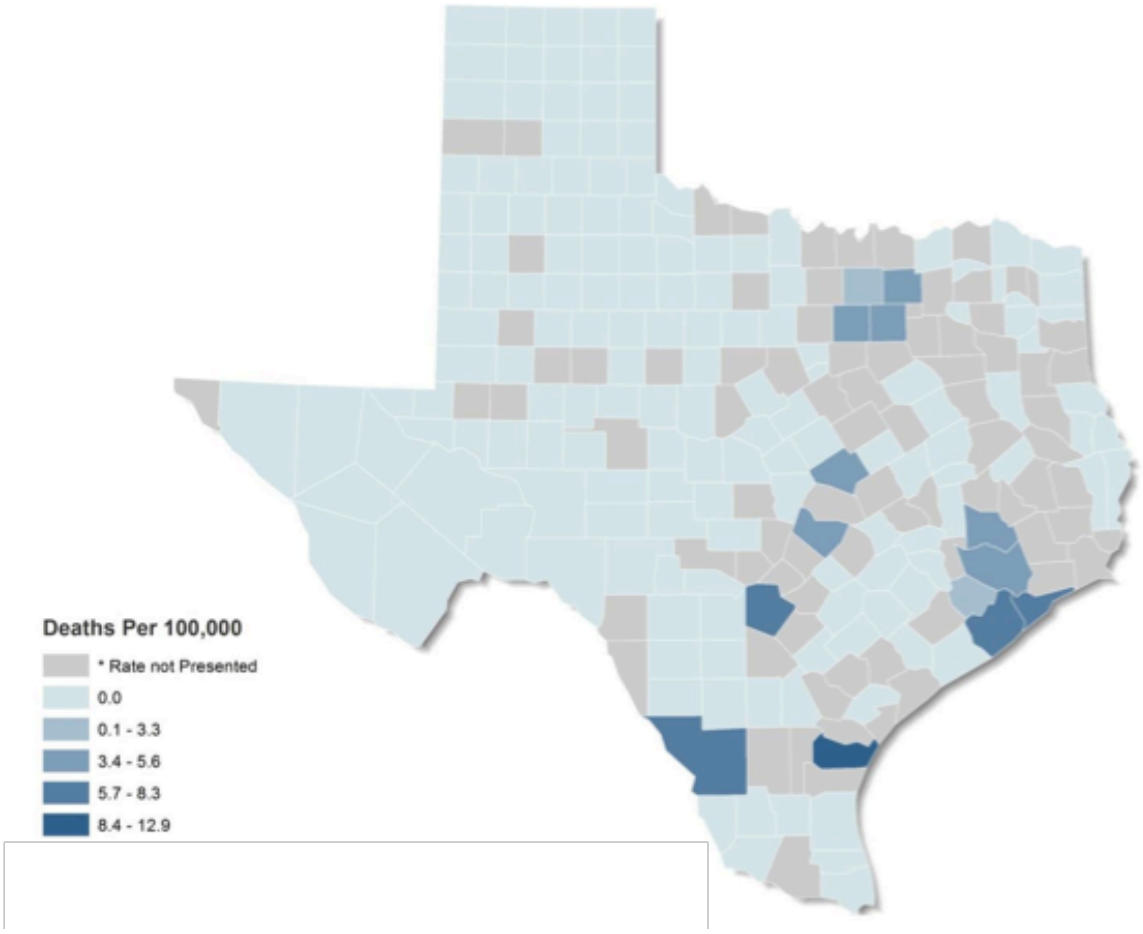
Table 1.7. Specific Drugs Involved in Opioid Analgesic Abuse Cases Reported to the Texas Poison Center Network During 2000–2010

Drug	Number	%
Hydrocodone	5,063	59.2
Tramadol	744	8.8
Propoxyphene	679	8.0
Codeine	640	7.5
Oxycodone	586	6.9
Methadone	555	6.6
Morphine	299	3.5
Fentanyl	160	1.9
Buprenorphine	87	1.0
Hydromorphone	85	1.0
Meperidine	41	0.5
Butorphanol	29	0.3
Pentazocine	27	0.3
Dihydrocodeine	12	0.1
Nalbuphine	10	0.1
Tapentadol	4	0.0
Oxymorphone	3	0.0
Levorphanol	1	0.0
Total	8,555	

Source: Forrester, 2012

Using the Texas poison data, Forrester also revealed variation in abuse rates by geographical regions in the state (Figure 1.14) (M. B. Forrester, 2012).

Figure 1.14. Opioid-Related Deaths by County 2012

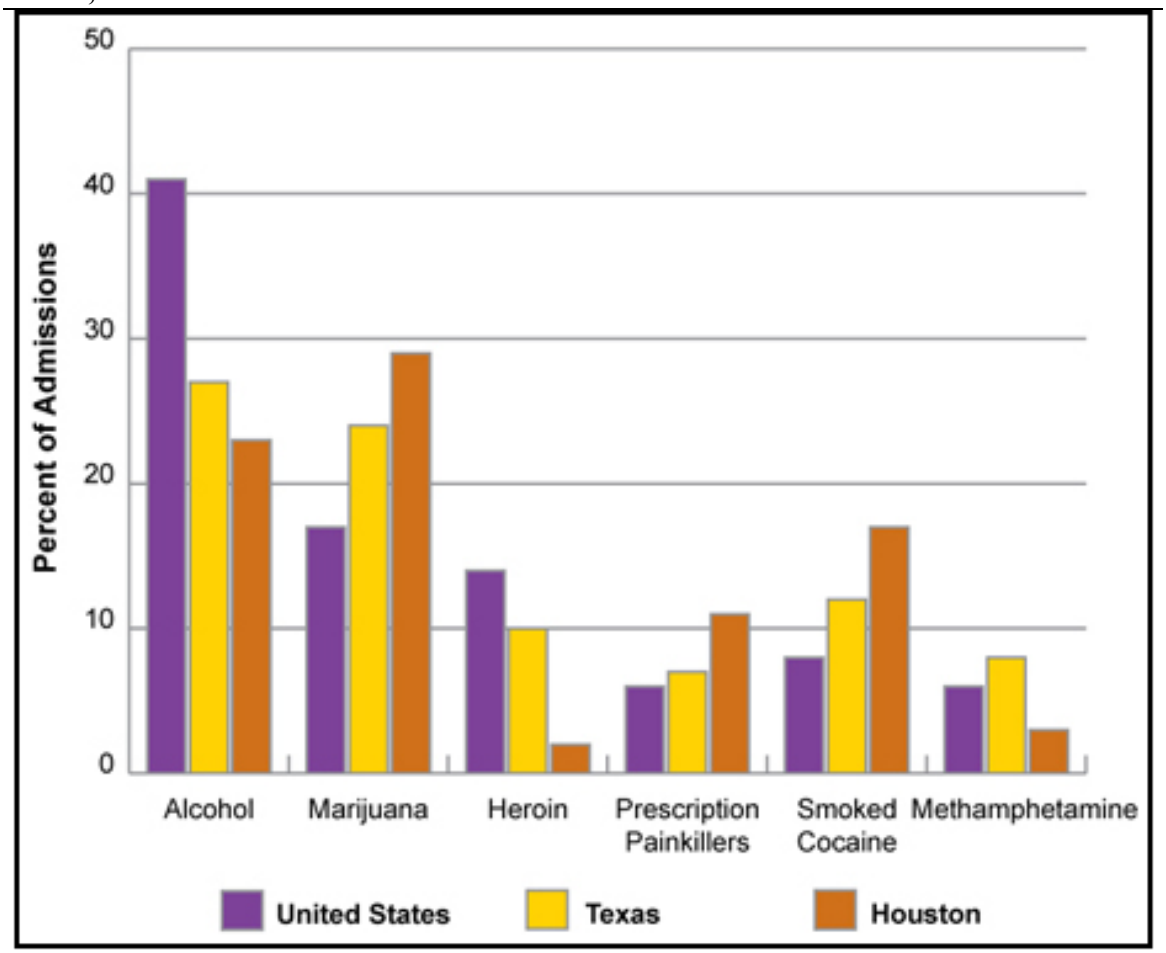


Data Source: Texas Vital Events Death Data Files, Texas Residents
Prepared by: Texas Department of State Health Services, Center for Health Statistics

Abuse rates and substance abuse treatment admissions for prescription painkillers are a problem for both the state of Texas and particularly around the metropolitan area of Houston (Figure 1.15). National averages for treatment admission for prescription pain killer abuse are 6%, however in Texas they are 7% and 11% in Houston. Females were also more likely (14% vs. 8%) to be admitted for painkiller abuse than males and those

identifying as non-hispanic white (18%) (Substance Abuse and Mental Health Services Administration, 2010c).

Figure 1.15. Treatment Admissions: Primary Substance of Abuse: United States, Texas, and Houston: TEDS 2008

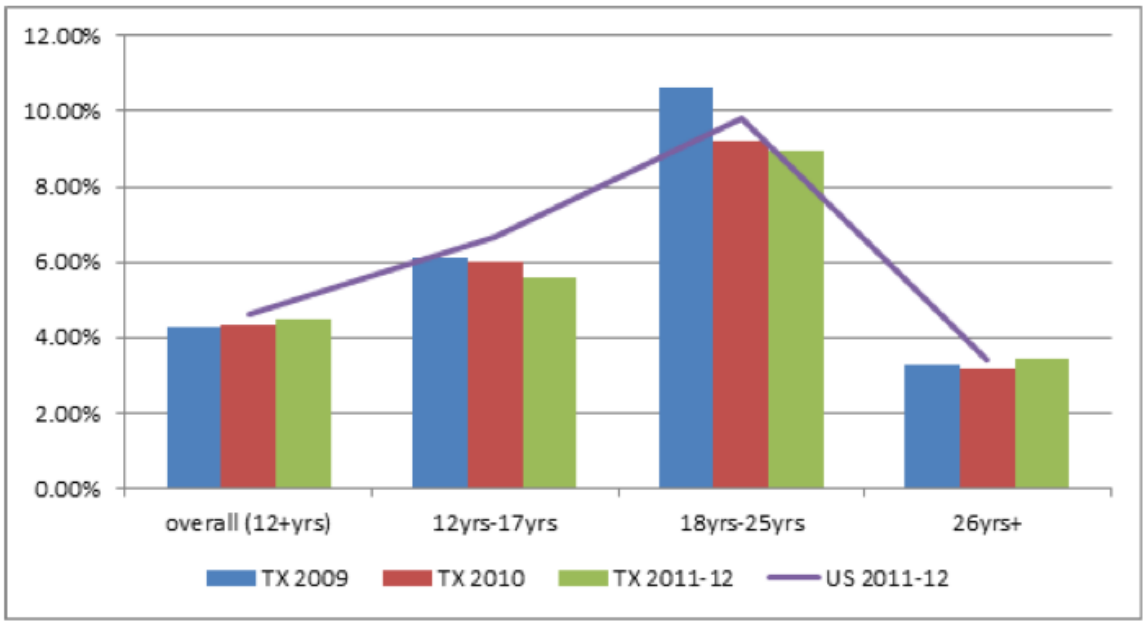


Source: Treatment Episode Data Set (TEDS) 2008

The use of opioids nonmedically is most prevalent among 18-25 year olds in Texas, which is consistent with national findings (Figure 1.16). A 2012 survey of Texas students in grades 7-12 found that 10.8% reported using codeine cough syrup nonmedically at some point in their lives, and 4.0% did so in the past month (Texas

Department of State Health Services, 2012. Prevalence rates for using oxycodone and hydrocodone products nonmedically anytime in their lifetime were higher in 2012 (3.6% and 7.5%, respectively) than the rates reported in 2008 and 2010 (Texas Department of State Health Services, 2012). In 2013 almost 20% of high school students in Texas have ever taken prescription pills without a doctor's prescription

Figure 1.16. Nonmedical Use of Prescription Pain Relievers



Source: Substance Abuse and Mental Health Services Administration, National Survey on Drug Use and Health 2013

1.13.1 DOCTOR SHOPPING IN TEXAS

Currently there is very limited research analyzing the prevalence of and factors associated with doctor shopping in Texas. As demonstrated in Figure H, the State of Texas falls under the "General Law" of the Uniform Controlled Substances Act of 1970 pertaining to doctor shopping. Texas does not currently have specific laws pertaining to

doctor shopping, however Section 481.129 discussing the offense of fraud states that if "A person commits an offense if the person knowingly: possesses, obtains, or attempts to possess or obtain a controlled substance or an increased quantity of a controlled substance: by misrepresentation, fraud, forgery, deception, or subterfuge.(Centers for Disease Control and Prevention National Center for Injury Prevention and Control Division of Unintentional Injury Prevention, 2012; Texas Department of State Health Services, 1989; The National Alliance for Model State Drug Laws (NAMSDL), 2010)

1.14 PRESCRIPTION ACCESS IN TEXAS

In 1982 the 67th Texas Legislature created the state's original prescription drug monitoring program, Texas Prescription Program (TPP), under the Department of Public Safety, to monitor all Schedule II prescriptions. The Department of Public Safety is a law enforcement agency in Texas. Texas is one of six states whose PDMP is administered by a law enforcement agency (The National Alliance for Model State Drug Laws (NAMSDL), 2014). In 2008 the Texas Legislature expanded the program to monitor Schedule II-V controlled substances (National Alliance for Model State Drug Laws, 2014a; Texas Department of Public Safety Regulatory Services Division).

In 2012 the Regulatory Services Division of the Texas Department of Public Safety launched a secure online prescription monitoring program called Prescription Access in Texas (PAT) (Texas Department of Public Safety, 2012). PAT monitors all controlled substances Schedule II-IV dispensed in the past 12 months in the state by a pharmacy in Texas (Texas Department of Public Safety Regulatory Services Division). Dispensing pharmacists are required to report dispensing information to PAT within seven days of dispensing. The users authorized to receive information from PAT are

prescribers, pharmacists, physician assistants, law enforcement and judicial/prosecutorial officials, and licensing/regulatory boards (National Alliance for Model State Drug Laws, 2014c). All registrants are still required by statue to have a current State (DPS) and Federal (Green et al.) registration in order to possess, administer, prescribe or dispense controlled substances (Texas Department of Public Safety Regulatory Services Division). In 2013 PAT collected information on over 49 million prescriptions in the year 2013 (Texas Department of Public Safety Regulatory Services Division). To put this into perspective, the 2013 Texas Census population was over 26.5 million (Texas Department of State Health Services, 2014).

Currently there are no training requirements for authorized users before utilizing the system and prescribers/dispensers are not mandated to access or enroll in the system. PAT utilizes both solicited and unsolicited reporting methods and reports are generated for prescribers, pharmacists, law enforcement agencies and licensing agencies (National Alliance for Model State Drug Laws, 2014b). Unsolicited reports are currently provided to prescribers, pharmacists, law enforcement, and licensing boards. PAT allows for interstate sharing with authorized users in other states (National Alliance for Model State Drug Laws, 2014c)

1.15 SUMMARY

After extensive review of the current literature, it can be concluded that prescription drug abuse is a vast problem affecting not only the State of Texas but individuals across the U.S.. Further research is currently needed to examine the current state of controlled substance prescription utilization and the prevalence of indicators of abuse, particularly in Texas.

MANUSCRIPT 1

Using Prescription Drug Monitoring Program Data to Identify Aberrant Prescription Drug Use Behaviors

Background

Challenges in Defining Abuse

Prescription drug abuse is a perilous public health problem that has resulted in an excess of deaths, emergency room visits and millions of healthcare dollars consumed (Birnbaum et al., 2011; Centers for Disease Control and Prevention, 2014d; Hansen et al., 2011; National Institute on Drug Abuse, 2011d). According to the Centers for Disease Control and Prevention (CDC), each day nearly 7,000 people are treated in emergency departments (ED) for the nonmedical use of prescription opioids (Centers for Disease Control and Prevention, 2015). Overdose deaths involving opioids have exceeded deaths involving all illicit drugs (e.g., heroin, cocaine) combined (Centers for Disease Control and Prevention, 2013c; LJ Paulozzi et al., 2011). Prescription drug abuse is a complex and multi-faceted problem, occurring as the result of both legitimate (e.g., originating from prescribers, dispensed by pharmacies) and illegitimate means (e.g., illegitimate internet pharmacies, theft) (American College of Preventive Medicine, 2011). While controlled substance prescriptions (CSPs) obtained by illicit use is a huge problem, in the US it has been found that most prescriptions used for nonmedical means originate from prescribers (Manchikanti, Abdi, et al., 2012; Substance Abuse and Mental Health Services Administration, 2011a). Research attributing the recent rise in incident heroin abuse cases to individuals with previous opioid dependence has escaladed the necessity of addressing this problem. Studies have reported that almost 80% of new heroin users had previous utilized opioids for nonmedical purposes (Muhuri et al., 2013).

Consequently, efforts to identify and address prescription drug abuse are needed now more than ever.

There are numerous factors which contribute to prescription drug abuse. One major challenge to addressing this epidemic is interpreting the enigmatic definition of abuse. Both the National Institute on Drug Abuse (NIDA) and the Substance Abuse and Mental Health Services Administration (SAMHSA) define prescription drug abuse as using a medication without a prescription, in a way other than as prescribed, or for the experience or feelings elicited (National Institute on Drug Abuse, 2014c; Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality, 2013a). However, translating this definition into daily clinical practice can be confusing and often difficult for healthcare providers to interpret.

The discord of identifying prescription drug abuse in individual patients has conceivably manifested out of the epidemic proportions of heterogeneous individuals abusing or misusing prescription medications (Ohio Prescription Drug Abuse Task Force, 2010; Substance Abuse and Mental Health Services Administration, 2014b). Drug abuse is no longer limited solely to individuals who have a *stereotypical* drug abuser profile. Prescription drug abuse spans across age groups, gender, and socioeconomic status (Buurma et al., 2008; Centers for Disease Control and Prevention, 2013a; Hall et al., 2008; Han et al., 2012; Substance Abuse and Mental Health Services Administration, 2014a; White et al., 2009). In the past, abuse of illicit drugs had been highly associated with males (Substance Abuse and Mental Health Services Administration, 2014a). However, among prescription opioid abusers, the propensity for abuse between genders has varied greatly across studies and is no longer specific to males (Buurma et al., 2008;

Hall et al., 2008; Han et al., 2012; White et al., 2009). In fact, the rate at which women have died as a result of opioid overdoses increased 400% from 1999 to 2010 for women compared to 265% for males during the same time period (Centers for Disease Control and Prevention, 2013a; Substance Abuse and Mental Health Services Administration, 2014a). While illicit drug abuse is most common among young adults (e.g., 18-35 years old), studies on prescription drug abuse have reported indicators spanning across all different age categories and patient characteristics (Buurma et al., 2008; Centers for Disease Control and Prevention, 2012; Fishman, 2010; Simeone et al., 2006; Substance Abuse and Mental Health Services Administration, 2010b; Wilsey et al., 2010). Moreover, the relatively vast indicators for prescription drug abuse are often difficult to conceptualize and quantify in research and practice. Therefore, epidemiological studies focused on issues of pain management and opioid use would benefit from establishing consistent criteria for indicators of abuse (Astho, 2014).

Use of Databases to Identify Abuse

A large number of prior studies which examined prescription drug abuse trends, have utilized insurance prescription and medical claims databases. However, study limitations may underestimate the prevalence of prescription drug abuse. For example, claims databases often have limited generalizability given they only capture patients covered by insurance (Crystal, Akincigil, Bilder, & Walkup, 2007). Cash payment (i.e., no third party payment) of CSPs, especially opioids, has been shown to be significantly correlated with prescription drug abuse and misuse (M. S. Cepeda, D. Fife, W. Chow, G. Mastrogiovanni, & S. C. Henderson, 2013; McDonald & Carlson, 2013). Given this

limitation, claims data often produces biased estimates of both the prevalence and risk factors for prescription drug abuse. Not to mention claims databases are not utilized or available in daily clinical practice for prescribers and pharmacists. Additionally, claims databases can be very costly to obtain for research purposes.

Conversely, one tool that has the potential to change the way researchers, prescribers and pharmacists identify prescription drug abuse is state operated prescription drug monitoring programs (PDMPs). PDMPs are electronic databases which collect specific data on CSPs dispensed within the respective state. Currently, 49 states have an operational PMDP (U.S. Department of Justice Drug Enforcement Administration Office of Diversion Control, 2011). The specific data that PDMPs collect vary by state, however most databases contain the patient's name, age, address, information on their CSP utilization and specific information about each dispensed prescription (drug name, national drug code (NDC), quantity dispensed), prescription fill dates, information of the prescriber and pharmacy dispensing each CSP (National Alliance for Model State Drug Laws, 2014d). Unlike other large claims databases, PDMP databases capture all outpatient CSPs dispensed regardless of payment type used to purchase the prescription (e.g., insurance, cash) (Clark et al., 2012). CSP data is provided only to authorized users (dictated by state statue) by the individual program, such as prescribers, pharmacists and often times law enforcement. Additionally, some PDMPs also provide data for research purposes. PDMP data can be used within daily clinical practice and for research purposes allowing for both individual patient's CSP utilization history to be examined and to examine utilization patterns and prescribing practices (The PDMP Training and Technical Assistance Center, 2014).

Utility of PDMP Data

Clinical Utilization

The extant literature has illustrated that data acquired via PDMPs have the capability to improve clinical decision-making, reduce excessive CSP prescribing, and decrease prescription drug abuse and doctor shopping (Haffajee et al., 2015; PDMP Center of Excellence, 2014a; Simeone et al., 2006; U.S. General Accounting Office, 2002; United States General Accounting Office, 2002). PDMP data can be a powerful clinical tool, as study results have reported changes in provider prescribing behavior and reduced opioid consumption after implementation of this program (DF Baehren et al., 2010; Feldman et al., 2012; Morgan, Weaver, Sayeed, & Orr, 2013; Thomas et al., 2014). Thomas et al. (2014) found that among prescribers in Massachusetts who reviewed their patient's PDMP data, 78.5% took further action, such as adding the prescription history to the patient's file, discussing the report with other prescribers and discussing the report with the patient (Thomas et al., 2014). The same study found that upon reviewing PDMP data, only 8.4% of prescribers were aware of most of the other prescribers that were listed on the individual patient's report (Thomas et al., 2014). Baehren et al. also reported that within their prospective study, physicians who reviewed patient PDMP data prescribed 61% fewer opioids than originally planned.(D Baehren et al., 2010)

State PDMP: Program Utility

Currently available in 38 state PDMPs is the generation of *unsolicited or proactive reports* based on PDMP data. This data can specifically be utilized by state

programs to identify the aforementioned aberrant behaviors. PDMPs with this feature have the capability to generate proactive or unsolicited reports for prescribers and pharmacists based on PDMP data that may suggest aberrant behavior (PDMP Center of Excellence, 2014c). PDMP reports use predetermined criteria established by the specific program to identify at-risk patients or questionable activity based on their CSP utilization (e.g., utilizing ≥5 prescribers and ≥5 pharmacies in 12 months) (PDMP Center of Excellence, 2014c). Simoene and Holland reported that state PDMPs which are proactive in their reporting were effective in reducing the per capita supply of opioids and stimulants, as compared to states without this feature (Simeone et al., 2006).

Research Purposes: PDMP Data as a Public Health Tool

Establishing an evidence-based consensus on well-known aberrant behaviors associated with abuse can also help local public health authorities and researchers accurately define the populations most at risk for prescription drug abuse. More importantly, better understanding of at risk populations would lead to more efficient allocation of resources related to prescription drug abuse prevention and treatment.

Indicators of Aberrant Behavior

There are several aberrant behaviors that suggest CSP misuse or abuse that are readily identifiable by reviewing PDMP data. Aberrant behavior can be defined as patient behaviors that may indicate prescription medication abuse or behaviors that are more likely to be associated with misuse/abuse (National Institute on Drug Abuse). This paper aims to highlight aberrant CSP behavior which can be identifiable through PDMP data. Three aberrant behaviors discussed in this paper include: receiving inappropriate

and/or overlapping combinations of CSPs; utilizing multiple providers (i.e., doctor shopping) to obtain prescription opioids and other CSPs; and receiving a high daily morphine equivalents dose (MED).

Multiple Provider Episodes (MPEs)

Individuals who obtain prescriptions for the same CSPs from multiple prescribers without the prescribers' knowledge of the other prescriptions are often referred to as doctor shoppers, pharmacy shoppers, or as having a multiple provider episode (Centers for Disease Control and Prevention National Center for Injury Prevention and Control Division of Unintentional Injury Prevention, 2012; McDonald & Carlson, 2013; Sansone & Sansone, 2012). While only a relatively small proportion of patients are representative of this behavior, moreover, they represent a significant contribution to diversion rates and fill a disproportionately large number of CSPs (Cepeda, Fife, Berwaerts, Yuan, & Mastrogiovanni, 2014; M. Cepeda, D. Fife, Y. Yuan, et al., 2013). Additionally, the Department of Justice reported that shopping behavior is the primary method used to obtain opioids for illegitimate means (U.S. Government Accountability Office, 2011).

Studies analyzing patients who utilize multiple providers to obtain CSPs (e.g., opioids) have varied regarding their operational definitions and indicators of aberrant behavior. Various classifications are based on the numbers of pharmacies visited; numbers of prescribers used; prescriptions that are overlapping; using more than one class of CSP from different providers; early refills of prescriptions; and excess doses over different periods of time (Buurma et al., 2008; Cepeda et al., 2014; M. Cepeda, D. Fife, Y. Yuan, et al., 2013; AM Gilson et al., 2012; Hall et al., 2008; Katz et al., 2010; Peirce

et al., 2012; Wilsey et al., 2010; Yang et al., 2015). Given that prescribers and pharmacists may not be aware of all the CSPs that patients have filled or the number of other prescribers and pharmacies filling other prescriptions, PDMP data can assist providers by providing a summary of the patient's CSP history.

Simultaneous or Overlapping Prescriptions

A second aberrant behavior identifiable with PDMP data is patients receiving overlapping prescriptions for CSPs. Patients receiving overlapping prescriptions for CSPs have an increased risk for not only MPEs, but also for overdose deaths and serious adverse events (M.B Forrester, 2011; Liu, Logan, Paulozzi, Zhang, & Jones, 2013; U.S. Department of Health and Human Services, 2013; Wunsch, Nakamoto, Behonick, & Massello, 2009). One combination of CSPs popular among abusers is the concomitant use of opioids, muscle relaxants and benzodiazepines, due to the euphoric sensation or high that the combinations produce and also for their high street value (M.B Forrester, 2011; U.S. Drug Enforcement Administration, 2013b). While the literature reveals little medical justification for this combination, studies have found a high prevalence of this inappropriate combination (M.B Forrester, 2011; Liu et al., 2013; Olsen, 2010; Volkow, 2014). Additionally, in 2009 the majority of prescription drug-related ED visits were attributed to opioids alone and in combination with benzodiazepines (Substance Abuse and Mental Health Services Administration, 2010b).

As can be expected, the aberrant behaviors discussed in this paper have been found to be highly correlated. Wilsey et al. reported that the greatest predictor of having a MPE was simultaneously receiving prescriptions for different CSPs (Wilsey et al.,

2010). This study found that individuals who were prescribed simultaneous prescriptions for stimulants/anorectics, benzodiazepines and opioids had a 25.1 times increased odds of having an MPE (Odds Ratio [OR])=25.10, 95% Confidence Interval [CI]=22.73-27.72) (Wilsey et al., 2010). While simultaneously using CSPs has dire consequences, there are few clinical guidelines regarding overlapping CSP use and which specific combinations should be avoided.

PDMP data can help to identify individuals with overlapping and medically unnecessary prescriptions for controlled substances. This practice can not only assist with identification of aberrant CSP use, but also harmful drug-drug interactions which could lead to an adverse event or even death.

High Daily Morphine Equivalent Dosage

One of the gold standards for comparing doses across different opioids is by measuring the daily morphine equivalent dose (MED) (Boudreau et al., 2009; AM Gilson et al., 2013; Manchikanti, Abdi, et al., 2012; Prescription Drug Monitoring Program Training and Technical Assistance Center, 2013). Daily dosage among chronic users of opioids has been found to increase with continued use over time (Cepeda et al., 2010; LJ Paulozzi, Zhang, Jones, & Mack, 2014). These findings suggest that chronic opioid users experience tolerance to their opioids and require higher daily MED. Guidelines vary concerning threshold levels for daily MED in patients with nonmalignant pain, however several official guidelines, including The Agency for Healthcare Research and Quality and the Washington State Opioid Guidelines, recommend using caution when the average daily MED doses exceed 120 mg (National Guideline Clearinghouse (NGC)) (Agency

Medical Directors Group, 2010; Group Health Cooperative, 2014). Opioid overdoses have also been found to be highly correlated with a high average daily opioid dose (LJ Paulozzi et al., 2012). Bohnert et al. and Dunn et al. found that patients receiving >100 mg/day had an exponential increase in the risk of overdose death and accounted for approximately 40% of opioid overdoses (Bohnert et al., 2011; Dunn et al., 2010). Dunn et al., also found that as compared to patients receiving an average daily opioid dose of 1-20 mg per day, those receiving 100mg or more per day had an 8.9 fold increase in overdose risk and a 1.8% annual overdose rate (Dunn et al., 2010). Moreover, research has found that even doses as low as 40 or 50 mg of daily MEDs may be responsible for a large number of ED admissions (Manchikanti, Abdi, et al., 2012).

PDMP data can be used to identify individuals with dangerous levels of daily MED or with rapid dose escalation. This data can also help prescribers identify individuals who may not be responding to opioids even at high dosage levels, who may benefit from an alternative pain therapy. Additionally, patients identified as highly dependent on opioids may indicate the presence of a comorbid mental health disorder (National Institute on Drug Abuse, 2011c). Patients on high dose opioids have been found to have higher rates of mental health problems (Kobus et al., 2012; Merrill et al., 2012; Seal et al., 2012).

Discussion

PDMP Utilization and Mandates

A prerequisite to the potential positive effects of PDMP data and unsolicited reporting is increasing utilization of these databases. Unfortunately, due to factors such

as limited resources, unawareness of the programs and legislative policies, PDMPs are not currently being utilized to their full potential (PDMP Center of Excellence, 2014c). Currently, only 22 PDMPs mandate prescribers to use the system in certain circumstances before prescribing CSPs (Haffajee et al., 2015). In Ohio Baehren et al. found that a large portion of prescribers reported reviewing PDMP data for only 1-10% of their patients receiving prescribed CSPs (DF Baehren et al., 2010). In states where PDMP use is not mandated, estimates of prescriber registration with their respective PDMP is approximately 35% (Kreiner, Nikitin, & Shields, 2014). Other research has indicated a high lack of awareness of PDMPs among nonusers (ML Fleming, Hatfield, Wattana, & Todd, 2014).

While the Centers for Disease Control and Prevention, The PDMP Center of Excellence and the National Alliance for Model State Drug Laws recommend sending unsolicited reports to end users as a best practice, of the 45 states that have the capability to send unsolicited reports, only 53% of the programs were utilizing this practice (National Alliance for Model State Drug Laws, 2012; PDMP Center of Excellence, 2014c). Additionally, as of 2014, only 19 states were sending unsolicited reports to all authorized users (e.g., prescribers, pharmacists, law enforcement and licensing entities) (National Alliance for Model State Drug Laws, 2014e). However, the inclusion of unsolicited reports could assist in CSP prescribing practices, taking the guess work out of identifying aberrant CSP utilization behaviors and function as a valuable clinical tool in a busy healthcare or pharmacy practice.

Limitations of PDMP Data

One major disadvantage of using PDMP data for identifying aberrant behavior is their lack of patient clinical data. While establishing validated criteria for identifying aberrant CPS use is the first step to addressing this problem, dispensing and utilization data cannot definitively confirm abuse. Prescribers and pharmacists should follow up with patient medical records for verification of medically warranted use. Therefore, PDMP data needs to be integrated with electronic health records (EHRs) to properly identify the patient's medically justified or aberrant CSP use.

Future Direction

Moving forward, future research is needed to examine the effectiveness of PDMPs regarding identifying individuals with aberrant behaviors, such as receiving overlapping combinations of CSPs, utilizing multiple providers to obtain CSPs, and consuming a high daily MED.

Conclusions

PDMPs are a powerful clinical and public health surveillance tool that can be used to identify aberrant CSP behaviors among individuals and populations. Proactively using PDMP data and unsolicited reporting provides prescribers and pharmacists an opportunity to educate patients on their CSP utilization and intervene when appropriate. Utilizing PMDPs to their full potential will be essential to addressing the current prescription drug abuse epidemic.

MANUSCRIPT 2

Prevalence and Factors Associated with Patients Receiving Potentially Inappropriate Overlapping Controlled Substance Prescriptions

Abstract

Introduction: Controlled substance prescription (CSP) use and abuse in the U.S. has reached unprecedented levels. One common method of abuse is the use of overlapping or concomitant use of certain CSPs.

Methods: This was a retrospective, cohort analysis of data from the 2013-2014 Texas Prescription Drug Monitoring Program Database (PDMP). Logistic regression analysis was employed to examine the patient-level and prescription utilization factors associated with patients utilizing overlapping CSPs.

Results: Among all Texas patients utilizing CSPs, 1,660,015 patients (15.99%) had at least one episode of utilizing one of the five overlapping CSPs combinations discussed in this manuscript. Overlapping opioid prescriptions were found to be the most prevalent combination among Texas patients (17.23%, n=1,574,572). Utilization of opioids, being ≥18 years of age, utilizing CSPs for >30 days, utilizing greater than one CSP, having a multiple provider episode, and traveling >25 miles to obtain CSPs were all statistically significant predictors of utilizing overlapping CSPs.

Conclusion: This study found a high prevalence of patients utilizing overlapping CSPs. This practice is concerning for patient safety and public health in Texas. Programs such as the Texas Prescription Drug Monitoring Program should be utilized to address prescription drug abuse behaviors, such as utilization of overlapping CSPs.

Introduction

Controlled substance prescriptions (CSPs) have become a fundamental in the US healthcare system, with over 259 prescriptions written for opioid prescriptions alone in 2012 (Centers for Disease Control and Prevention). Classified based on their high potential for dependence, the abuse and misuse of CSPs, such as opioids and benzodiazepines, contributes significantly to morbidity and mortality rates in the US (U.S. Department of Health and Human Services, 2013; U.S. Department of Justice Drug Enforcement Administration Office of Diversion Control, 2014). While the increased availability and consumption of these prescription medications has contributed to elevated overdose rates and adverse events, there are several aberrant CSP utilization behaviors that responsible for a disproportionate percentage of these statistics and also may indicate abuse (Volkow, 2014). One such behavior is the concomitant use of different or the same controlled substance prescriptions. Concurrent or overlapping use of CSPs can be dangerous, resulting in unintended adverse events (AEs) or overdose deaths (Dunn et al., 2010; Hall et al., 2008; Wunsch et al., 2009).

According to the Substance Abuse and Mental Health Services Administration (SAMHSA) and the Drug Abuse Warning Network (DAWN), the use of prescription opioids alone and in combination with other CSPs is responsible for half of the 1.2 million ER visits associated with the nonmedical use of pharmaceuticals (Substance Abuse and Mental Health Services Administration, 2012a). A 2015 study from Jones and McAninch found an almost three times increase in drug overdose deaths from 2004 to 2011 from overlapping use of opioids and benzodiazepines (Jones & McAninch, 2015). A nationwide study from Calcaterra et al. also reported that the concurrent use of opioids

and benzodiazepines was the most common cause of multi-drug overdose death (Calcaterra, Glanz, & Binswanger, 2013).

The most common practice of concomitant use related to or associated with CSPs are patients taking two or more overlapping opioids (Express Scripts, 2014). A 2013 study from Express Scripts found that almost 60% of patients utilizing opioids were taking a combination of prescription drugs that are associated with serious safety risks and adverse events (e.g., cardiovascular risks). The majority of these patients were taking either benzodiazepines, muscle relaxants or both with their opioids and were largely female (62.3%) (Express Scripts, 2014).

Overlapping prescriptions, especially for opioids, have been shown in previous studies as having a strong association with other indicators of prescription drug abuse, such as doctor shopping, the utilization of a high daily dosage (e.g. >100mg/day), and long-term use of CSPs (Bohnert et al., 2011; M. Cepeda, D. Fife, W. Chow, G. Mastrogiovanni, & S. Henderson, 2013; Dunn et al., 2010; Express Scripts, 2014; White et al., 2009; Wilsey et al., 2010). Wilsey et al. found that individuals who had received stimulants and benzodiazepines concurrently had a 20 times increased odds of having a multiple provider episode (MPE), also known as *doctor shopping* (Wilsey et al., 2010). Utilizing overlapping opioids increases a patient's daily morphine equivalent dose (MED) (calculated to convert opioid dose to standard dose based on type and quantity of opioid dispensed) (PDMP Training and Technical Assistance Center, 2013b). This practice is especially concerning given that previous research reported that patients receiving 100 mg of opioids or more per day had an 8.9 fold increase in overdose risk, as compared to receiving 1-20 mg per day (Dunn et al., 2010). Additionally, while the

utilization of overlapping prescriptions is often the result of inappropriate prescribing, certain combinations of CSPs are also obtained aberrantly by patients due to the heroin like effect they produce when taken concurrently, and also for their high street value (M.B Forrester, 2011; U.S. Drug Enforcement Administration, 2013a).

This study aimed to identify the prevalence and factors associated with patients receiving inappropriate overlapping CSPs in the State of Texas. Texas, specifically the Houston area, is a national hotspot for patients consuming the deadly combination of opioids, benzodiazepines and muscle relaxants, also known as the *Triple Cocktail* (M.B Forrester, 2011; Horswell, 2010; Olsen, 2010).

Methods

Design

This was a retrospective, cohort analysis using data from the Texas Prescription Drug Monitoring Program Database (PDMP). The Texas PDMP database is operated by the Texas Department of Public Safety (DPS). The researchers obtained deidentified data based on all CSPs dispensed from outpatient pharmacies in the State of Texas. This study included prescriptions dispensed from June 1, 2013 to June 1, 2014, which was comprised of 38,350,287 CSPs consumed by 10,381,532 unique patients (Texas Department of Public Safety Regulatory Services Division).

Dependent Variable

The binary (0/1) dependent variable was the presence of receiving at least one inappropriate combination of CSPs. The following three combinations were included as

the dependent variable in a logistic regression analysis: 1) overlapping opioid prescriptions; 2) overlapping opioid, stimulant, and benzodiazepine prescriptions; 3) overlapping opioid, muscle relaxant, and benzodiazepine prescriptions (*Triple Cocktail)*.

Independent Variables

The patient-level variables included: patient age category; the number of CSPs utilized in the 12-month study period; the duration of CSP utilization (total days of use); daily MED (for opioid prescriptions); the distance between the patient's zip code and CSP prescriber's zip code; the distance between the patient's zip code and the filling pharmacy's zip code; and the distance between the prescriber's zip code and the filling pharmacy's zip code; MPE (defined as utilizing ≥5 prescribers and 5≥ pharmacies in 12-month period).

Statistical Analysis

The prevalence of patients receiving overlapping CSPs was conducted among the entire cohort of CSP utilization patients residing in Texas and among the cohort of patients with a MPE. The prevalence of the following combinations was identified: 1) overlapping opioid, muscle relaxant, and benzodiazepine prescriptions (*Triple Cocktail)*; 2) overlapping opioid and benzodiazepine prescriptions; 3) overlapping opioid, stimulant, and benzodiazepine prescriptions; 4) overlapping stimulant and benzodiazepine prescriptions; and 5) overlapping opioid prescriptions. Overlapping use was defined as having prescriptions with ≥7 days of overlap (Liu et al., 2013). Overlapping opioid prescriptions were further analyzed by opioid type: long-acting/extended release and

short-acting/immediate release. Descriptive statistics were conducted on the main CSP utilization cohort and among the cohort of CSP utilization patients with one of the five potentially inappropriate overlapping CSPs.

The association between individual-level variables and the utilization of an inappropriate combination of CSPs were examined using logistic regression modeling. This study and its research activities were approved by The Institutional Review Board at the University of Houston.

Results

Among all Texas patients utilizing CSPs there were 1,660,015 patients (15.99%) with at least one episode of utilizing one of the five overlapping CSPs combinations. Within the MPE cohort, 17,878 patients (93.00%) had at least one overlapping use episode. While 17.23% (n=1,574,572) of all Texas patients utilizing CSPs had at least one episode of overlapping opioid prescriptions, alarmingly so did 90.78% (n=17,450) of patients in the MPE cohort (Table 2.1). The vast majority (95.17%) of overlapping opioid prescriptions were for two short-acting opioids (e.g., hydrocodone combination products) (Table 2.2). Within the MPE cohort, overlapping use of opioids and benzodiazepines and stimulants and benzodiazepines was prevalent, 12.23% and 11.57%, respectively.

Patients in both the main cohort and the overlapping use cohort were mostly between the ages of 18-64 (Table 2.3). A much higher percentage of patients in the overlapping use cohort had a higher daily MED, with 7.43% of the patients utilizing ≥100 mg per day, compared with only 2.34% of patients in the main cohort. Patients with overlapping CSP use also consumed a higher mean number of CSPs during the 12

months of analysis (M±SD, 9.40 ± 9.61 vs. 3.62 ± 5.42, respectively) and for a longer duration (>150 days, 33.85% vs. 12.49%, respectively). A larger proportion of patients in the CSP overlapping use cohort also had at least one MPE during the study analysis (1.08% vs. 0.18%).

Logistic Regression

Among the CSP overlap cohort, 1,581,274 (95.25%) patients had at least one of the three inappropriate combinations used in the logistic analysis (Table 2.4). All patients over the age of 18 had an increased odds of having an overlapping CSP, as compared to those under the age of 18. A strong association was found between utilizing opioids and having overlapping CSPs, especially for those patients using an average MED of >100 mg per day (adjusted odds ratio [OR]=140.44 [95% CI: 139.65-141.23]). The distance between the patient's zip code and the CSP prescriber's zip code and filling pharmacy's zip code were not significant predictors of utilizing overlapping CSPs. Having a MPE increased the patient's odds of using overlapping CSPs by two and half times (OR= 2.55 [95% CI: 2.51-2.58]). The model was a strong predictor of patient's receiving inappropriate combinations of CSPs, with a c-score of 0.91.

Discussion

In this study the prevalence of patients receiving prescriptions for inappropriate combinations of CSPs, especially overlapping opioids, was alarming given the lack of clinical evidence for their concomitant use and their strong association with AEs. The prevalence of overlapping opioids was driven almost completely by patients obtaining overlapping prescriptions for two short-acting opioids, which was comprised mostly of

prescriptions for short-acting hydrocodone. Thus this overlapping opioid phenomenon was not driven by patients requiring a long-acting opioid with a short-acting opioid for breakthrough pain, which is often justified in the management of severe chronic pain (Argoff & Viscusi, 2014). Short-acting opioids are more frequently prescribed in emergency room settings and hydrocodone specifically has been found to be the most commonly abused opioid (Drug Enforcement Administration; Nawar, Niska, & Xu, 2007). Long-acting opioids however, are less frequently prescribed and generally reserved for use when other treatment options have failed (U.S. Food and Drug Administration, 2013). Nevertheless, regardless of the opioid's formulation, the results of the daily MED in the logistic model revealed that using any type of opioid increased a patient's odds of utilizing overlapping CSPs drastically.

While this study did not capture a large number of demographic characteristics, the relatively evenly distributed association between patient age category and utilization of overlapping CSPs demonstrates the vast nature of aberrant CSP utilization behavior. This finding highlights the challenge of targeting drug abuse prevention efforts to a specific demographic or age category and the immense nature of this epidemic.

Given the high prevalence of patients with an MPE who also utilized overlapping CSPs and the sizeable association found between the two variables, this may indicate that patients with an MPE are doctor shopping for CSPs with intention to take them concurrently. This hypothesis has also been supported by the findings of Wilsey et al.. (Wilsey et al., 2010). Therefore, when doctor shopping is suspected, prescribers should also examine the patient's CSP fill history, corresponding dates, and vise versa.

There are currently programs and polices in place to help detect aberrant CSP use and indicators of abuse prior to issuing prescriptions for pain management. One such program is the Texas Prescription Drug Monitoring Program (PDMP), which is a statewide program that collects data on all CSPs dispensed within the state (U.S. Department of Justice Drug Enforcement Administration Office of Diversion Control, 2011). Prescribers and pharmacists can review a patient's CSP dispensing history within the PDMP to determine if a patient has inappropriate and/or overlapping CSP use (PDMP Center of Excellence, 2014a). This program can also help prescribers prevent future AEs and even facilitate an intervention regarding the patient's aberrant CSP utilization when needed.

As aforementioned the greatest limitation of this study is the lack of patient demographic and clinical data available in the database. However, given that several of the predictors were significantly associated with overlapping CSP use, CSP utilization behavior can be sufficiently used to identify aberrant behavior.

Conclusion

Polypharmacy of CSPs is a dangerous practice, which should be avoided when not medically necessary. Given the high prevalence of Texas patients utilizing overlapping CSPs, this could result in very serious implications for patient health outcomes. Through the implementation of policies and programs, such as state PDMPS, patients with aberrant CSP utilization behaviors, such as utilizing overlapping CSPS, can be identified and future adverse events can be avoided.

Tables

Table 2.1 Prevalence of Potentially Inappropriate Overlapping[1] Controlled Substance Prescription Utilization				
Overlapping Combination	**All CSP[2] Utilization Patients (10,381,532)**		**MPE[3] Cohort (19,223)**	
	Frequency[4]	**Percent**	**Frequency[4]**	**Percent**
Opioids, benzodiazepines, muscle relaxants[5]	7,077	0.07	290	1.51
Opioids and benzodiazepines	73,266	0.71	2,351	12.23
Opioids, benzodiazepines, stimulants[5]	25,178	0.24	1,563	8.13
Stimulants and benzodiazepines	108,346	1.04	2,224	11.57
Overlapping opioid use[5]	1,574,572	17.23	17,450	90.78

[1]Overlapping defined as ≥7 days of concurrent use
[2]Controlled Substance Prescription
[3]MPE: Patients utilizing ≥5 prescribers and 5≥ pharmacies in 12-month period
[4]Frequencies not mutually exclusive
[5]Overlapping combinations used in final logistic model

Table 2.2 Prevalence of Overlapping Opioids by Opioid Type		
Overlapping Combination	**Overlapping Opioid Use Patients (1,574,572)**	
	Frequency	**Percent**
1 Short-Acting + 1 Long-Acting Opioid Overlap	447	0.03
2 Long-Acting Opioids Overlap	75,572	4.80
2 Short-Acting Opioids Overlap	1,498,553	95.17

[1]Overlapping defined as ≥7 days of concurrent use

Table 2.3 Descriptive Statistics of All Patients Utilizing CSP[1] in Texas and Among Overlapping CSP Use Cohort					
		All CSP Utilization in Texas (10,381,532)		**Any Overlapping Use[2] Cohort** (1,660,015)[3]	
Variable		**Frequency**	**Percent**	**Frequency**	**Percent**
Age Distribution	<18	927,144	8.93	24,484	1.47
	18-34	2,248,759	21.66	261,278	15.74
	35-44	1,619,562	15.60	250,379	15.08
	45-64	3,528,745	33.99	698,688	42.03
	65-74	1,139,414	10.98	238,137	14.35
	≥75	917,908	8.84	188,049	11.33
Average Daily Morphine Equivalent (MED)	0	5,163,761	49.74	145,600	8.77
	1-19mg	1,519,756	14.64	399,502	24.07
	20-49	2,621,524	25.25	759,049	45.73
	50-99	833,655	8.03	232,332	14.00
	≥100	242,484	2.34	123,262	7.43
Number of Controlled Substance Prescriptions (mean)		3.62 ± 5.42		9.40 ± 9.61	
Total Days with CSP (during 365 days of analysis)	1-30	4,849,813	46.72	366,456	22.08
	31-60	2,904,381	27.98	380,630	22.93
	61-90	627,818	6.05	153,538	9.25
	91-149	703,287	6.77	197,722	11.91
	>150	1,296,233	12.49	561,669	33.84
Distance Between Patient Zip and Prescriber Zip (mean in miles)		25.59 ± 119.07		27.78 ± 106.50	
Distance Between Patient Zip and Pharmacy Zip (mean in miles)		30.56 ± 142.91		25.51 ± 131.05	
Distance Between Prescriber and Pharmacy (mean in miles)		44.46 ± 178.92		40 ± 163.37	
Multiple Provider Episode (MPE)		19,223	0.18	17,878	1.08

[1]Controlled Substance Prescription
[2]Overlapping defined as ≥7 days of concurrent use
[3]Numbers may not add up to 1,660,015 due to missing values

Table 2.4 Patient Factors Associated with Use of Overlapping Controlled Substance Prescriptions			
Patient-Level Variables			
	Variable	**Odds Ratio**	**95% C.I.[1]**
Age category (<18 reference)	18-34	2.36	2.34-2.38
	35-44	2.60	2.58-2.63
	45-64	2.97	2.95-3.00
	65-74	3.22	3.19-3.25
	>75	3.15	3.12-3.18
Distance Between Patient Zip and Prescriber Zip (1-25 miles reference)	26-99 miles	1.15	1.14-1.6
	>=100	1.07	1.06-1.08
Distance Between Patient Zip and Pharmacy Zip (1-25 miles reference)	26-99 miles	0.96	0.95-0.97
	>=100	0.93	0.92-0.94
Distance Between Prescriber and Pharmacy (1-25 miles reference)	26-99 miles	1.01	1.01-1.02
	>=100	0.94	0.93-0.95
Number of CSPs[2]	continuous	1.11	1.10-1.12
Daily Morphine Equivalent (0 mg reference)	1-19mg	65.76	65.50-66.03
	20-49mg	71.19	70.92-71.46
	50-99mg	70.91	70.60-71.22
	>100mg	140.44	139.65-141.23
Total Study Days with CSPs (<30 reference)	31-60	2.49	2.48-2.50
	61-90	3.49	3.48-3.51
	91-149	3.11	3.09-3.12
	>150	2.42	2.41-2.42
Multiple Provider Episode (MPE)[3]		2.55	2.51-2.58

[1]Confidence interval
[2]Controlled Substance Prescription
[3]MPE: Patients utilizing ≥5 prescribers and 5≥ pharmacies in 12-month period

MANUSCRIPT 3

Prevalence and Factors Associated with Multiple Provider Episodes in Texas: An Epidemiological Analysis of Prescription Drug Monitoring Program Data

Abstract

Background: Prescription drug abuse has reached epidemic levels, leading to dire health outcomes and economic implications. Both patient-level and environmental-level factors are believed to contribute to higher rates of prescription drug abuse. While national estimates of abuse have been extensively studied, this phenomenon has not been examined in the State of Texas. The objective of this research was to determine the prevalence and factors associated with multiple provider episodes in Texas.

Methods: This study was a retrospective, cohort analysis of data obtained from the Texas prescription drug monitoring database (PDMP) which was linked with Texas county-level census data. Descriptive statistics and multi-level model regression analysis were employed to determine the prevalence of multiple provider episodes (MPE) and analyze the association between patient-level, prescription utilization and county-level factors with MPEs.

Results: Opioid prescriptions, especially hydrocodone-combination products (38.64%), were the most frequently utilized controlled substance prescriptions (CSPs) dispensed. The prevalence of MPEs was 185.16 per 100,000 population. Among those identified in the MPE cohort, 76.98% utilized CSPs >150 days and 11.48% had a daily morphine equivalent (MED) ≥100 mg/day. Residing in metropolitan areas, traveling >100 miles to obtain prescriptions, chronic use of CSPs, younger age, and high daily MED were all factors significantly associated with an increased risk of MPE.

Conclusion: Prescription drug abuse has been identified as a major public health problem in Texas. Prescription drug abuse prevention efforts need to be addressed at both the patient-level and through legislation regarding public health and policy.

Introduction

Prescription drug misuse and abuse in the U.S. has reached epidemic levels (Centers for Disease Control and Prevention, 2013b; S. E. McCabe et al., 2008). This epidemic has resulted in unprecedented morbidity and mortality and may be indicative of the high utilization of prescription opioids in the US. Reports concerning international drug consumption showed that the US accounted for almost all hydrocodone consumption (99%) and the vast majority of oxycodone consumption (83%), globally (International Narcotics Control Board, 2013). The Substance Abuse and Mental Health Services Administration (SAMHSA) 2013 National Survey on Drug Use and Health (NSDUH) indicated that 15.7 million persons aged 12 or older reported using pharmaceutical nonmedically within the past year (Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality, 2013a). The National Institute on Drug Abuse (NIDA) defines the nonmedical use as using prescriptions in a way other than as prescribed (National Institute on Drug Abuse, 2014d). Additionally, 4.5 million persons reported nonmedical use of opioids within the past month in 2013, an over 75% increase from 2002 (Jones, 2012; Substance Abuse and Mental Health Services Administration, 2014a). One report from NIDA found opioids to be present in 50% of cases seen in emergency departments related to nonmedical-use of pharmaceuticals (National Institute on Drug Abuse, 2011d). Drug overdoses were found to be the leading cause of injury related deaths in the United States in 2012, outnumbering the number of deaths due to motor vehicle accidents (Centers for Disease Control and Prevention, 2014d). The mortality associated specifically with prescription drug abuse is estimated at 46 deaths per day, with the majority of cases attributed to

prescription opioids (Centers for Disease Control and Prevention, 2014c; LJ Paulozzi et al., 2011; Substance Abuse and Mental Health Services Administration, 2014a). Moreover, the economic impact of prescription drug abuse is vast, considering that abuse of opioids alone results in approximately $53-$72 billion in societal and medical costs each year (Birnbaum et al., 2011; Coalition Against Insurance Fraud, 2007; Hansen et al., 2011).

Previous literature has shown that both patient-level factors and environmental factors contribute to an increased likelihood of developing prescription drug misuse and abuse (Buurma et al., 2008; Fishman, 2010; Han et al., 2012; Jones, 2012; Wilsey et al., 2010). Patient-level factors include younger age (e.g., 18-25),(Buurma et al., 2008; Fishman, 2010; Han et al., 2012; Peirce et al., 2012; Wilsey et al., 2010) being male,(Substance Abuse and Mental Health Services Administration, 2014a; U.S. Department of Health and Human Services, 2013) and the number and type of controlled substance prescriptions (CSPs) utilized (Fishman, 2010; Hall et al., 2008; Han et al., 2012; Katz et al., 2010; Kim et al., 2014; Rosenblum et al., 2007; White et al., 2005; Wilsey et al., 2010). Environmental factors, such as a patient's region or county, are also believed to play a role in the propensity for abuse, given that individuals in the same geographic region often have comparable access to healthcare resources and share similar sociodemographic characteristics (Fishman, 2010; Hall et al., 2008; Han et al., 2012; PDMP Center of Excellence, 2012; Simeone et al., 2006). For example, the increased availability of healthcare providers in a region has been highly correlated with an elevated propensity for behaviors associated with abuse (e.g., utilizing multiple providers to obtain CSPs) (Curtis et al., 2006; Han et al., 2012).

The Centers for Disease Control (CDC) has recommended that prescription drug abuse prevention efforts target patients at highest risk in terms of prescription opioid dosage and the numbers of CSPs and prescribers utilized (Centers for Disease Control and Prevention, 2013b). This includes patients who obtain CSPs from multiple prescribers without the prescriber's knowledge of the other prescriptions (Centers for Disease Control and Prevention National Center for Injury Prevention and Control Division of Unintentional Injury Prevention, 2012; McDonald & Carlson, 2013; Sansone & Sansone, 2012). This patient behavior is often referred to as *doctor shopping*, *pharmacy shopping,* or as having *multiple provider episodes (MPEs)*, which recognizes the combination of both definitions. More importantly, patients identified with a MPE often represent a significant contribution to prescription drug diversion rates. The aforementioned high-risk utilization of CSPs is considered aberrant CSP utilization behavior. Aberrant use is defined as using CSPs in a way other than intended by the original prescriber (Back et al., 2010; National Institute on Drug Abuse).

Contemporary PDMPs are designed to address issues of prescription drug abuse and diversion (Astho, 2014). PDMPs are statewide electronic databases which collect designated data on CSPs dispensed within the respective state. One benefit of PDMPs is their capability to track patients' CSP history longitudinally (U.S. Department of Justice Drug Enforcement Administration Office of Diversion Control, 2011). Data collected by PDMPs can be utilized as a public health surveillance tool if the appropriate resources are designated. Ideally, PDMPs would be utilized as a public health tool to reduce morbidity, mortality and to improve health outcomes regarding pain management (Centers for Disease Control and Prevention, 2001). Using the California PDMP, Wilsey

et al. was able to identify the CSPs most frequently associated with MPEs (Wilsey et al., 2010). Also in California, Gilson et al. examined the effect of policy changes on opioid prescribing behavior following the implementation of the state's electronic PDMP system (AM Gilson et al., 2012).

In prior research, physicians' access of PDMP data was shown to impact their clinical decision-making, reduce excessive CSP prescribing, and reduce prescription drug abuse and doctor shopping (Haffajee et al., 2015; PDMP Center of Excellence, 2014a; Simeone et al., 2006; U.S. General Accounting Office, 2002). Moreover, studies have reported that in an emergency department setting, after reviewing PMDP data, providers changed their clinical management plan in 41% of the cases (D Baehren et al., 2010). A survey from Green at al. also found that pharmacists were utilizing PDMP data to screen their patients for abuse and doctor shopping (Green et al., 2013).

The current extent of prescription drug abuse and overdose deaths in Texas is not well known, and is believed to be drastically underestimated (Olsen & Roser, 2015). However, Harris County, home to Houston which is the fourth largest city in the US, has been identified as one of the nation's top hotspots for prescription drug abuse (Horswell, 2010, 2012). Therefore, this study used MPEs to assess the magnitude of prescription drug abuse and the associated factors in Texas. The objective of this study was to examine the prevalence and individual-level and regional-level factors associated with patients having an MPE.

Methods

Study Design and Data Source

This was a retrospective cohort epidemiological analysis of data from the Texas PDMP database. The Texas PDMP database is operated under the authority of Texas Department of Public Safety (DPS) and contains information on all outpatient CSPs dispensed from outpatient and community pharmacies in the state. This study included all prescriptions filled from June 1, 2013 to June 1, 2014 (Texas Department of Public Safety Regulatory Services Division). Patients in this database filled at least one CSP during the data analysis period. This database consists of 39,904,964 CSPs, obtained by 10,688,720 patients, written by 113,143 prescribers, and dispensed at 5,155 pharmacies. The data was deidentified by the PDMP vendor prior to data acquisition. After data cleaning, removing missing and implausible observations, and restricting the analysis to only Texas patients, a total of 38,350,287 CSPs obtained by 10,381,532 patients were included in the descriptive statistics and final analysis. The patient-level data from the Texas PDMP was also linked with Texas Census Data to obtain county level data on the 254 counties in Texas (Texas Association of Counties, 2014; Texas Department of State Health Services, 2013a, 2013b; Texas Education Agency, 2014; United States Department of Labor, 2013).

This study examined two CSP utilization cohorts for descriptive purposes and analysis. The first cohort consisted of all Texas patients utilizing CSPs during the 12-month study period (n=10,381,532). The second cohort was comprised of patients with at least one MPE during the study period.

Dependent Variable

The dependent variable employed in this study was presence of MPEs, which was defined as utilizing ≥5 prescribers and ≥5 pharmacies within a 12-month period. Prior research by Hall et al. and the Bureau of Justice also similarly operationalized MPE by the aforementioned definition (i.e., ≥5 prescribers and ≥5 pharmacies) (Bureau of Justice Assistance, 2013; Hall et al., 2008). However, within the extant literature, there is no agreed upon gold standard for defining shopping behavior or MPE (Buurma et al., 2008; Cepeda et al., 2014; M. Cepeda, D. Fife, Y. Yuan, et al., 2013; AM Gilson et al., 2012; Hall et al., 2008; Katz et al., 2010; Peirce et al., 2012; Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality, 2013b; Wilsey et al., 2010). Therefore, a sensitivity analysis was conducted based on other previously utilized definitions of MPE (e.g., ≥4 doctors and ≥4 prescribers, ≥5 doctors and/or ≥5 prescribers) to determine the prevalence of MPEs based on the defined criteria.

Independent Variables

The independent variables in the analysis included both patient-level variables and county-level variables, as detailed below. The patient-level covariates included: patient age category; the number of CSPs utilized in the 12-month study period; the duration of CSP utilization (total days of use); average daily morphine equivalent dose (MED); the distance between the patient's zip code and CSP prescriber's zip code; the distance between the patient's zip code and the dispensing pharmacy's zip code; and the distance between the prescriber's zip code and the dispensing pharmacy's zip code.

County-Level Factors

The county-level variables included in the analysis were: county population; race (percent nonwhite population); percent uninsured; percent unemployed; high school graduation rate; ratio of direct patient care clinicians per 100,000 population; and ratio of pharmacists per 100,000 population.

Statistical Analysis

Descriptive statistics were conducted on both the main cohort of Texas patients utilizing CSPs and also among the MPE cohort. The association between patient-level, prescription utilization and county-level factors and having a MPE were examined using multilevel logistic regression modeling. Multilevel modeling takes into account the similarities and correlations of patients clustered within counties (Snijders & Bosker, 2012). The PDMP data was also mapped spatially by Texas zip code. This technic allowed for the authors to visually identify the prevalence of MPEs and hot spots for utilization of multiple providers across the state. All statistical analyses were conducted using SAS Statistical Software 9.3. This study and its research activities were approved by The Institutional Review Board at the University of Houston.

Results

Descriptive statistics of the main cohort and among the MPE cohort are provided in Table 3.1. The prevalence of MPEs based on differently defined criteria (e.g., ≥4 prescribers and ≥ pharmacies) is provided in Table 3.2. In general, patients utilizing

CSPs displayed conservative behavior in their prescription and healthcare provider utilization. During the 12 months of analysis, patients filled a mean (M±SD) 3.62 ± 5.42 for CSPs, utilized a M = 1.39 ± 0.88 prescribers and M = 1.19 ± 0.58 pharmacies to obtain their CSPs. However, patients with indicators of aberrant behavior contributed significantly to the number of CSPs filled and to healthcare provider utilization. At least one patient was identified with 473 CSPs during the study period; two other patients utilized up to 43 different prescribers and filled prescriptions at 39 different pharmacies.

This study identified 19,223 patients with a MPE, equivalent to 185.16 MPEs per 100,000 population. Almost 24% of all MPEs occurred in Harris County (home to Houston), producing a rate of 104.93 per 100,000 population within the county. The most frequently utilized CSPs were opioids (e.g., oxycodone) in both the main cohort (38.64%) and the MPE cohort (64.93%). Utilization of a high daily dosage was relatively low in the main cohort with only 2.34% of patients utilizing a daily MED ≥100 mg, however, 11.48% of patients in the MPE cohort utilized greater than 100 mg daily. Additionally, a much larger percentage of patients in the MPE cohort utilized CSPs for a longer duration compared to the those without a MPE (>150 days, 76.98% vs 12.49%, respectively) and traveled further to obtain prescriptions from prescribers (28.75 miles vs. 25.59 miles).

Patient-Level Factors Associated with MPE

The multilevel model produced a McFaden pseudo-R^2 of 0.24, which indicates a good model fit based on the assumptions of this model (McFadden, 1979). As compared to patients under the age of 18, patients in the 18-34 years of age category had a 6.35

times (adjusted odds ratio [OR] = 6.35 [95% CI = 6.01-6.70]) increased odds of having a MPE and patients in the 35 to 44 years of age category had a 5.12 times [95% CI = 4.90-5.47] increased odds (Table 3.3). An exponential relationship was also found between MPE and increasing number of days with CSPs, with patients taking CSPs for greater than five months having a 76.34 times [95% CI = 72.86-80.00] increased odds of having an MPE.

As compared to patients not utilizing prescription opioids, all categories of daily MED were at an increased odds of having an MPE. However, having a daily MED between 20 to 99 mg produced the greatest odds of MPE (20 to 49mg, OR = 16.48 [95% CI = 16.48-17.01]; 50 to 99 mg, OR = 14.72, [95% CI = 14.48-14.98]). Patients traveling further than 25 miles from their home to visit a prescriber and pharmacy were also at an increased risk of having an MPE. However, traveling further than 100 miles to receive a CSP from a prescriber or to obtain it from a pharmacy had the greatest odds of having MPEs (distance to prescriber, OR = 2.02 [95% CI = 1.97-2.06]; distance to pharmacy, OR = 1.48 [95% CI = 1.46-1.51]).

County-Level Factors Associated with MPE

Among the county-level variables, patients living in a metropolitan area (>1,000,000 population) were found to have a 7.30 times [95% CI = 7.06-7.55] increased odds of having MPEs, when compared to those in living in rural counties (<15,000 population). Counties with higher educational attainment exhibited increased odds of its residents having MPEs (>90% graduation rate (OR= 1.60 [95% CI = 1.53-1.67]). Counties with higher uninsured patients (>30%) and a higher pharmacy ratio (>100 per

100,000 population) were found to have a reduced odds of having MPEs (OR = 0.67 [95% CI = 0.66-0.69]; OR = 0.74 [95% CI = 0.72-0.77], respectively). Race distribution and unemployment rates within counties were not found to have a statistically significant relationship with having MPEs. The results of the spatial mapping indicate a high prevalence of MPEs in the metropolitan areas of Texas, including areas within Houston, Dallas, San Antonio and Austin (see Figure 3.1).

Discussion

This study is one of the first epidemiological analyses of prescription drug abuse (i.e., MPEs) in Texas. The utilization of PDMP data gives new insight into CSP utilization and abuse within the state. After analyzing the Texas PDMP data in conjunction with county census data, the prevalence of CSP utilization and MPEs were identified, as well as factors which may put patients at an increased risk for prescription drug abuse. While this study identified 185.16 MPEs per 100,000 population, these results may also be conservative due to observations that were deleted due to missing values. In comparison, a study conducted among Washington patients which employed the analysis of PDMP data and utilized the same definition for MPE (i.e., ≥5 doctors and/or ≥5 prescribers) found that 7.3 per 100,000 population were involved in MPEs (PDMP Center of Excellence, 2015).

Among the main cohort (all CSP utilization patients) and especially in the MPE cohort, opioids, particularly hydrocodone-combination products, were the most frequently utilized Scheduled prescriptions. This finding is consistent with opioid prescribing trends across the US (IMS Institute for Healthcare Informatics, 2014). Also

similar to this study, an association was found between higher daily MED and MPEs in this analysis (Han et al., 2012). Han et al (2012) conducted an analysis of California PDMP data and also found a strong association between the utilization of as little as >40 mg of opioids per day and use of new providers. While utilization of opioids at any dose was found to increase a patient's odds of an MPE, both this study and the study conducted by Han et al. have demonstrated a linear relationship between increasing MED and odds of MPE.

Another alarming finding from this study was the high prevalence of patients receiving chronic CSP therapy. With 12.5% of the main cohort and over 75% of the MPE cohort utilizing CSPs for greater than five months, this raises concerns about the current culture in which patients rely heavily on CSP therapy, which can increase their risks for tolerance and dependence. Similar to findings reported by NIDA, the results of this year-long study also highlight the extensive utilization of opioids in pain management over the past decade (Volkow, 2014).

The main cohort and the MPE cohort were both comprised of less than 25% of individuals under the age of 35; however patients in the 18-34 years of age category had the greatest association with having a MPE. This finding is consistent with previous studies which examined factors associated with prescription drug abuse (Buurma et al., 2008; Fishman, 2010; Han et al., 2012; Peirce et al., 2012; Wilsey et al., 2010). Also consistent with the findings from Cepeda et al., is the association found between patients traveling further distances to obtain CSPs from prescribers and pharmacies had an increased odds of MPEs (M. Cepeda, D. Fife, Y. Yuan, et al., 2013). This trend may be indicative of doctor shopping patients trying to avoid detection by traveling to prescribers

and pharmacies in different locations. Although, this study did not include out of state patients traveling to Texas to fill their CSPs in the analysis, these findings further support the need for PDMPs not only to be utilized, but to be interconnected with other PDMPs, especially in bordering states.

As revealed from the results of both the spatial mapping and the multilevel logistic model, residing in metropolitan areas (>1,000,000 residents) increased the odds of MPEs, which is consistent with findings from Hal et al. (Han et al., 2012). Identifying that metropolitan areas have the greatest proportion of MPEs can assist with the allocation of resources for prescription drug abuse prevention efforts by targeting these high risk metropolitan areas and communities. Two noteworthy findings from this study were that counties with higher educational attainment have increased odds of MPEs and the variable capturing racial distribution and unemployment rates within counties were found to be insignificant. This highlights the need for prescribers and pharmacists to be aware that no longer are stereotypical drug abuser profiles the norm, but recognize that the problem is now more widespread across diverse populations.

Prescription drug abuse has serious public health implications and not identifying and addressing these issues could have catastrophic effects. This issue is heightened to an even greater extent given that opioid dependence is believed to a significant predictor of future heroin abuse and is one of the factors that have led to the recent increase in heroin use (American Society of Addiction Medicine, 2015; Lakey & Lewis, 2014; Muhuri et al., 2013). Previous surveys have found that up to 80% of heroin users have also reported engaging in prior abuse of prescription drugs (Lakey & Lewis, 2014). Given the magnitude of heroin overdose, prescriber, pharmacist and patient education

regarding opioid use and pain management is imperative in order to mitigate the prescription drug abuse epidemic. Opioid dependence remains a serious public health issue that should be addressed with patients, but just as important through public policy and legislation that focuses on substance treatment.

Professional healthcare organizations and healthcare provider educational programs need to provide prescribers and pharmacists with more resources and training in prescription drug abuse intervention efforts. Patients in this study were able to receive up to 473 CSPs from up to 43 prescribers and fill at 39 different pharmacies, thus it is evident that the Texas PDMP is not being utilized to its full potential. Currently, pharmacists in Texas are required to report dispensing information on all CSPs within seven days of the fill date to the state PMDP (National Alliance for Model State Drug Laws, 2014c). However, prescribers and pharmacists in Texas are not currently required to check the patient's profile in the PDMP database before dispensing CSPs. Therefore, state legislation should make it mandatory for prescribers and pharmacists to query the state's PDMP database to examine patients' CSP history before issuing prescriptions or dispensing CSPs. Finally, more epidemiological studies addressing issues related to CSP use is warranted in Texas. Local public health authorities can more readily and efficiently serve populations through resource allocation, prevention and treatment efforts if they understand the prevalence and distribution of MPEs. One recommendation based on the results of this study would be the creation of yearly reports from the state PDMP data which are based on the current standards created by the Prescription Behavior Surveillance System (PBSS). This reporting system acts as a early warning and surveillance tool to assess trends in CSP prescribing, dispensing practices and indicators

of prescription drug abuse (PDMP Center of Excellence, 2015). Future epidemiological studies conducted using PDMP data will help identify health outcomes, prescribing behavior, the effectiveness of initiatives and policies, utilization rates and quantification of behaviors associated with abuse.

Limitations

The results of this study should be interpreted in the context of several limitations. One limitation of utilizing PDMP data is the lack of patient clinical and diagnostic information. Therefore, the appropriateness of all CSP use cannot be readily determined. Clinical data may verify that a patient has a diagnosis (e.g., cancer) warranting elevated CSP use. When abuse is suspected, prescribers consult the patient's clinical information and pharmacists should follow up with the patient's prescribers. Additionally, given the lack of a standard definition for MPE, setting a specific threshold of 5 doctors and 5 pharmacies in 12 months may result in the unintended consequence of a high risk for false negatives. However, this study addressed this issue by expanding the definition of doctor shopping to include utilizing both multiple prescribers and multiple pharmacies. The statistically significant variables based on these analyses did not differ across definitions, nor did their effect sizes differ significantly. This study may also lack generalizability to states other than Texas. PDMP programs operate under different conditions within each specific state and may collect different data. Not to mention state policies influencing the prescribing and availability of CSPs may vary across states. This analysis only included patients residing in Texas; therefore patients traveling to Texas from outside the state to obtain prescriptions from multiple providers were not examined.

Despite the limitations cited, this study is one of the first epidemiological analyses of CSP utilization in Texas. To the authors knowledge this is also the first examination of the prevalence of MPEs and association between patient-level and county-level factors with utilization of multiple providers within the state. While future research utilizing PMDP data containing more extensive patient-level data is needed, this study highlighted how aberrant CSP utilization behaviors, such as MPEs, can be identified through patient prescription utilization data such as PDMP data.

Conclusion

While there are no set standards for identifying prescription drug abuse, PMDP data can be utilized to ascertain well-known indicators of abuse and help quantify an individual's propensity for abuse. The findings of this study suggest that the major issues with prescription drug abuse afflicting this country are also very present in Texas. Prescription drug abuse prevention efforts need to be focused at the individual level and through legislation and public policy due to the far-reaching extent of the problem. Recognizing the often dire consequences associated with prescription drug abuse, this study calls for policy changes which promote the safe and responsible prescribing of CSPs both in Texas and nationwide.

Tables and Figures

Table 3.1. Descriptive Statistics of All Controlled Substance Prescription Utilization in Texas and Among a Multiple Provider Episode Cohort

		All CSP[1] Utilization in Texas (10,381,532)			MPE[2] Cohort (19,223)	
Variable		Frequency	Percent		Frequency	Percent
Number of Prescriptions Accounted For		38,350,287	100		492,931	1.28
Age Distribution	<18	927,144	8.93		89.0	0.46
	18-34	2,248,759	21.66		4,655	24.22
	35-44	1,619,562	15.60		5,041	26.22
	45-64	3,528,745	33.99		8,319	43.28
	65-74	1,139,414	10.98		893	4.65
	≥75	917,908	8.84		226	1.18
Frequency by Class of Medication	Opioids	14,510,859	38.64		319,854	64.93
	Benzodiazepines	8,229,548	21.92		56,536	11.49
	Sedative	3,421,778	9.11		25,419	5.16
	Stimulants	4,367,227	11.63		20,871	4.24
	Muscle Relaxant	870,440	2.32		18,009	3.66
	Steroids/Hormones	788,834	2.10		1,821	0.37
	Barbiturates	229,949	0.61		1,425	0.29
	Other	5,931,652	13.67		48,996	9.86
Top CSPs Dispensed (by drug name, any strength)	Hydrocodone-APAP	13,246,938	34.54	Hydrocodone - APAP	193,888	39.33
	Xanax® (alprazolam)	3,411,191	9.01	Xanax® (alpraxolam)	36,554	8.62
	Ambien® (zolpidem tartrate)	3,058,117	8.08	Ambien® (zolpidem tartrate)	32,646	6.62
	Klonopin® (clonazepam)	1,889,166	5.00	Soma® (carisoprodol)	31,788	6.45
	Ativan® (lorazepam)	1,385,439	3.67	Klonopin® (clonazepam)	22,833	4.63
	Mixed Ampethamine Salts (Adderall®)	1,199,943	3.12	Mixed Ampethamine Salts (Adderall®)	14,606	2.96
Average Daily Morphine Equivalent	0	5,163,761	49.74		818	4.26
	1-19mg	1,519,756	14.64		2,092	10.88
	20-49	2,621,524	25.25		10,788	56.13
	50-99	833,655	8.03		3,317	17.26
	≥100	242,484	2.34		2,206	11.48
Total Days with CSP (during 365 days of analysis)	1-30	4,849,813	46.72		252	1.31
	31-60	2,904,381	27.98		747	3.89
	61-90	627,818	6.05		911	4.74
	91-149	703,287	6.77		2,516	13.09
	>150	1,296,233	12.49		14,797	76.98

[1]Controlled Substance Prescriptions

[2] Multiple Provider Episode (Utilizing ≥5 prescribers and ≥5 pharmacies in 12-months

Table 3.2. Prevalence of Multiple Provider Episodes based on Various Definitions

Cohort	Frequency of Patients	Frequency of CSP[1] Prescriptions Utilized	Percent of all prescriptions in whole dataset
≥3 Prescribers and ≥3 Pharmacies	187,667 (1.81%)	2,898,677	7.72%
≥4 Prescribers and ≥4 Pharmacies	53,643 (0.50%)	1,131,939	3.01%
≥5 Prescribers and ≥5 Pharmacies[2]	19,223 (0.18%)	492,931	1.31%
≥6 Prescribers and ≥6 Pharmacies	8,243 (0.08%)	246,035	0.65%

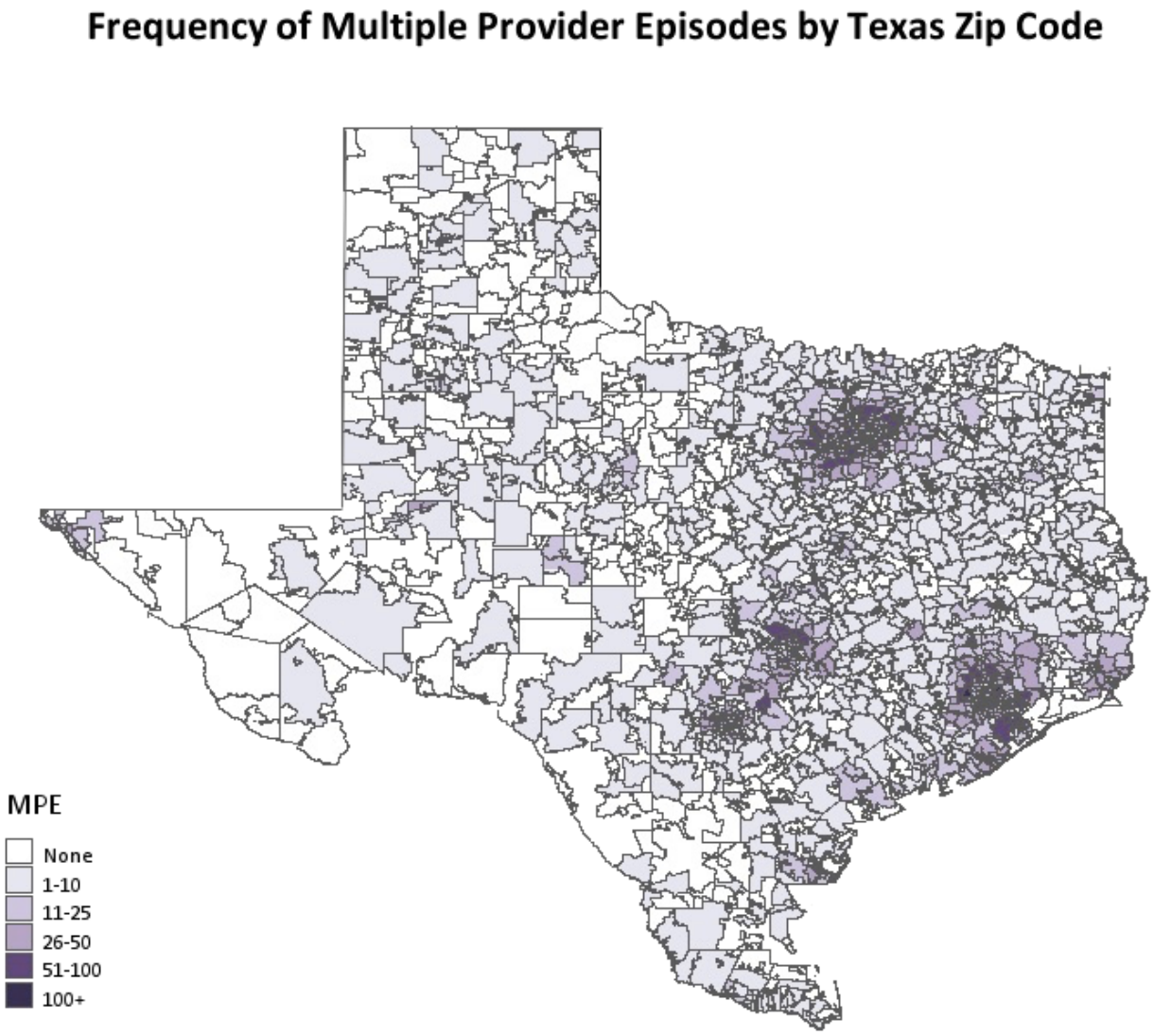
[1]Controlled Substance Prescriptions
[2]Definition used for statistical analysis

Table 3.3 Patient and County-Level Factors Associated with Multiple Provider Episodes

	Variable	Odds Ratio	95% C.I.
Patient-Level Variables			
Age category (<18 reference)	18-34	6.35	6.01-6.70
	35-44	5.12	4.90-5.47
	45-64	2.61	2.47-2.75
	65-74	0.91	0.86-0.96
	>75	0.31	0.29-0.33
Distance Between Patient Zip and Prescriber Zip (1-25 miles reference)	26-99 miles	1.64	1.61-1.66
	>=100	2.02	1.97-2.06
Distance Between Patient Zip and Pharmacy Zip (1-25 miles reference)	26-99 miles	1.45	1.43-1.7
	>=100	1.48	1.46-1.51
Distance Between Prescriber and Pharmacy (1-25 miles reference)	26-99 miles	0.70	0.69-0.71
	>=100	0.75	0.74-0.76
Number of Controlled Substance Prescriptions (continuous)	1.024	1.023-1.025	
Daily Morphine Equivalent (0 mg reference)	1-19mg	8.40	8.24-8.54
	20-49mg	16.74	16.48-17.01
	50-99mg	14.72	14.48-14.98
	>100mg	10.14	9.96-10.32
Total Study Days with CSPs[1] (<30 reference)	31-60	7.29	6.92-7.68
	61-90	22.21	21.13-23.35
	91-149	39.01	37.20-40.91
	>150	76.34	72.86-80.00
County-Level Variables			
Population (<15,000 reference)	15,000-99,999	1.68	1.63-1.73
	100,000-1,000,00	3.21	3.11-3.31
	>1,000,000	7.30	7.06-7.55
Race (Percent nonwhite) (<10 reference)	11-19%	0.97	0.96-0.98
	>20%	0.96	0.94-0.97
Percent Uninsured (<20% reference)	21-29	0.59	0.58-0.59
	>30%	0.67	0.66-0.69
Ratio of Direct Patient Care Clinicians (per 100,000) (<20 reference)	21-99	0.89	0.86-0.91
	>100	0.98	0.95-1.01
Percent Unemployed (<10% reference)	>10%	1.00	0.98-1.02
High School Graduation Rate (<=75 reference)	76-90%	1.34	1.31-1.43
	>90%	1.60	1.53-1.67
Pharmacist Ratio per 100,000 Population (<25 reference)	26-99	0.76	0.74-0.78
	>100	0.74	0.72-0.77

[1]Controlled Substance Prescriptions

Figure 3.1. Frequency of Multiple Provider Episodes by Texas Zip Code



SUMMARY OF FINDINGS

Objective I

Aberrant CSP[1] behavior which can be identifiable through PDMP[2] data
▪ Multiple provider episodes (MPEs): individuals who obtain prescriptions for the same medications and/or CSPs from multiple prescribers without the prescribers' knowledge of the other prescriptions. ▪ Represent a significant contribution to diversion rates and are responsible for a disproportionately large number of CSPs.
▪ Simultaneous and/or overlapping CSPs ▪ Responsible for an excess of overdose deaths, serious adverse events, emergency room visits
▪ High daily dosage ▪ Associated with an increased risk for overdose death, emergency room visits and likelihood of having mental health problems
▪ Using PDMP data to identify patients with aberrant CSP utilization behaviors can be beneficial for both clinical care and for public health surveillance practices.

[1]Controlled substance prescription
[2]Prescription drug monitoring program data

Objective II

Prevalence of patients receiving potentially inappropriate overlapping CSPs[1] in the State of Texas
▪ There were 1,660,015 patients (15.99%) with one of the following inappropriate combinations of CSPs: 1) overlapping opioid, muscle relaxant, and benzodiazepine prescriptions (*Triple Cocktail)*; 2) overlapping opioid and benzodiazepine prescriptions; 3) overlapping opioid, stimulant, and benzodiazepine prescriptions; 4) overlapping stimulant and benzodiazepine prescriptions; and 5) overlapping opioid prescriptions
▪ 17.23% (n=1,574,572) of all CSP use patients had overlapping opioid prescriptions and 90.78% (n=17,450) of patients in the MPE[2] cohort
▪ 95.17% of overlapping opioid prescriptions were for 2 short acting opioids
Factors associated with patients receiving potentially inappropriate overlapping CSPs in the State of Texas
▪ Age categories between >18 years of age ▪ Traveling >25 miles to obtain prescriptions for CSPs ▪ Obtaining more than one CSP ▪ Daily MED[3] ≥1mg/day ▪ Utilizing CSPs >30 days ▪ Having MPEs

[1]Controlled substance prescription
[2]Multiple provider episode

Objective III

Identify the current state and burden of CSP[1] use and abuse in Texas
▪ 38.64% of all CSPs dispensed were for opioids
▪ Hydrocodone combination products were the most frequently prescribed CSP (34.54%)
Prevalence and individual-level and regional-level factors associated with patients having an MPE[1] in the State of Texas
▪ 19,223 patients with a MPE (185.16 MPEs per 100,000 population)
▪ Individual-level variables that are significantly associated with an increased risk for MPE: ▪ age categories between 18-64 years of age ▪ traveling >25 miles to obtain prescriptions for CSPs ▪ traveling >25 to fill CSPs at a pharmacy ▪ Obtaining more than one CSP ▪ Daily MED[3] ≥1mg/day ▪ Utilizing CSPs >30 days
▪ County-level variables that are significantly associated with patients having an MPE[1] in the State of Texas: ▪ Residing in county with population >15,000 ▪ County high school graduation rate >76%
▪ MPEs were highly centralized in Texas metropolitan areas (e.g., Houston, Dallas, San Antonio)

[1]Controlled substance prescription
[2]Multiple provider episode
[3]Morphine equivalent dose

CONCLUSIONS

This research study was a foundation for establishing the current state of CSP use and abuse in the State of Texas. A high prevalence of aberrant CSP utilization behaviors was found among Texas patients, such as the use of multiple providers to obtain CSPs, overlapping prescriptions for CSPs, and utilization of a high daily morphine equivalent dose (MED). However, utilizing both logistic regression and multilevel modeling this study also identified both patient-level and regional-level factors significantly associated with these aberrant behaviors. This research will also allow for patients in these high-risk categories to be more readily identifiable using a combination of individual-level variables, CSP utilization behaviors and county-level characteristics. The utilization of PDMP data in this study also demonstrated the utility of this relatively underutilized type of data for both clinical and epidemiological purposes. The findings of this research support the future utilization of the Texas PDMP not only as a clinical tool for both prescribers and pharmacists, but for future research purposes, particularly those which address the prescription drug abuse epidemic in Texas

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