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Dated: August 12, 2016

Assessing the Impact of Multiple Levels of Influence on the Use of Hydrocodone Combination Products and Buprenorphine as Opioid Addiction/Dependence Treatment

by

Mark D. Hatfield, MS

A dissertation submitted in partial fulfillment of

the requirement for the degree of

DOCTOR OF PHILOSOPHY

IN

PHARMACEUTICAL HEALTH OUTCOMES AND POLICY

University of Houston

College of Pharmacy

August 12, 2016

Assessing the Impact of Multiple Levels of Influence on the Use of Hydrocodone Combination Products and Buprenorphine as Opioid Addiction/Dependence Treatment

To the Faculty of the University of Houston, College of Pharmacy:
The members of the committee appointed to examine the dissertation of Mark D. Hatfield find it satisfactory and recommend that it be accepted on July 14, 2016. [Signatures on file with the department of Pharmaceutical Health Outcomes and Policy]

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ACKNOWLEDGEMENTS

This dissertation was the culmination of a great deal of effort and support on behalf of many people. I have done my best to do their work justice with this brief acknowledgement.

My deepest gratitude to my advisor and committee chair, Dr. Marc Fleming. His mentorship, guidance, insight, and generosity were invaluable throughout this journey. I had the opportunity to serve as his research assistant during my time in the department, and learned early about his passion for improving patient care, which will continue to serve as an inspiration to me. His leadership, infectious positive attitude toward this work and life in general, and willingness to go out of his way to help students succeed, impacted me greatly, and I will be forever grateful to him for these experiences.

I was honored to have such a strong and supportive committee. A huge thanks to Dr. Sujit Sansgiry, my PhD co-advisor and advisor for my master's work. His advice over the years has, and will continue, to serve me well. Dr. Michael Johnson was a tremendous source of support to me as a student. He was always available to guide and help me in any way, and has served as an excellent role model for me with his ability to make the complex understandable and his innate ability to inspire others. I also had the good fortune to have had Dr. E. James Essien serve on my committee for both my PhD and my master's work. He was always available to consult with and mentor me through my time in the department. I will always be grateful for his wisdom and incredible ability to focus on the key issue at hand, and offer much-needed advice exactly when I needed it most. I would also like to thank Dr. Knox Todd, whom I had the privilege of working with on this and other projects. His knowledge in this area is second to

none. Additionally, his ability to understand the most important elements of the topic, which were not readily obvious to virtually anyone else, was remarkable, not to mention vital, to the successful completion of this study.

I would also like to thank my other esteemed professors in the department of Pharmaceutical Health Outcomes and Policy, the terrific staff, and my fellow students – past and present. Too many to name, but without whose support, friendship, and encouragement, this would not have been possible. Thank you one and all.

Most of all, I would like to thank my family. My children, Sam, Will, and Leah have always been the inspiration for everything that I do. I love you each so much and am so proud to be called your Dad. To my wife, Catherine – where do I start to express my thanks for all that you have done? Suffice it to say your support, encouragement, and patience with me through all of this means everything to me. Thank you, family, for being so supportive and your willingness to sacrifice through this whole phase – we made it! Now on to the next chapter…

Dedicated to
Catherine,
Sam,
Will,
&
Leah

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DEFINITIONS

Abuse and misuse: "Prescription drug misuse and abuse is the intentional or unintentional use of medication without a prescription, in a way other than prescribed, or for the experience or feeling that it causes" (Substance Abuse and Mental Health Services Administration, 2016).

Acute pain: "Pain that comes on quickly, can be severe, but lasts a relatively short time" (American Chronic Pain Association, 2016).

Addiction: "Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death" (American Society of Addiction Medicine, 2016).

Breakthrough pain: "Breakthrough pain is a flare of pain that happens even though you are taking pain medicine regularly for chronic pain. It's called breakthrough pain because it 'breaks

through' the pain relief you get from the regular pain medicine. Breakthrough pain is not controlled by the regular doses of pain medicines. It varies in intensity and usually cannot be predicted" (American Cancer Society, 2014).

Chronic pain: "Described as ongoing or recurrent pain, lasting beyond the usual course of acute illness or injury or more than 3 to 6 months, and which adversely affects the individual's well-being. A simpler definition for chronic or persistent pain is pain that continues when it should not" (American Chronic Pain Association, 2016).

Chronic cancer pain: "Many people with chronic cancer pain have two types of pain – persistent (chronic) pain and breakthrough pain" (American Cancer Society, 2014).

Complementary and alternative medicine (CAM): "The term for medical products and practices that are not part of standard care. Standard care is what medical doctors, doctors of osteopathy and allied health professionals, such as registered nurses and physical therapists, practice. Alternative medicine means treatments that you use instead of standard ones. Complementary medicine means nonstandard treatments that you use along with standard ones. Examples of CAM therapies are acupuncture, chiropractic and herbal medicines" (American Chronic Pain Association, 2016).

Dependence: "A state of adaptation that is manifested by a withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or

administration of an antagonist. In the management of acute pain, physical dependence usually does not develop because of the limited duration of opioid use. Physical dependence is not addiction" (American Chronic Pain Association, 2016).

Illicit drug use: "Illicit drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics (pain relievers, tranquilizers, stimulants, and sedatives) used non-medically" (Substance Abuse and Mental Health Services Administration, 2014).

Non-medical use: "Use [of drugs] without a prescription of the individual's own or simply for the experience or feeling the drugs caused" (Substance Abuse and Mental Health Services Administration, 2014).

Opioid: "Any group of endogenous neural polypeptides that bind especially to opiate receptors and mimic some of the pharmacological properties of opiates. Also a synthetic drug (as methadone) possessing narcotic properties similar to opiates but not derived from opium; broadly: opiates" (*Merriam-Webster's Medical Dictionary: New Edition*, 2006).

Pain: "A usually localized physical suffering associated with bodily disorder (as a disease or injury)" (*Merriam-Webster's Medical Dictionary: New Edition*, 2006).

Pain medicine: “The specialty of Pain Medicine is a discipline within the field of medicine that is concerned with the prevention of pain, and the evaluation, treatment, and rehabilitation of persons in pain” (American Chronic Pain Association, 2016).

Pseudoaddiction: “Relief-seeking behaviors misinterpreted as drug-seeking behaviors that resolve upon institution of effective analgesic therapy” (Jackman, Purvis, & Mallett, 2008).

Recurrent pain: “Acute pain can be a *recurrent* problem, with episodes being interspersed with pain-free periods, as in the case of dysmenorrhea, migraine, and sickle-cell disease” (Pizzo et al., 2011a).

Tolerance: “A phenomenon or adaptation of the body over a period of time in which one or more effects of a drug become less with repeated use at the same dose. Analgesic tolerance is not addiction” (American Chronic Pain Association, 2016).

ACRONYMS AND ABREVIATIONS

C-II to C-V: Schedule II to Schedule V

CDC: Centers for Disease Control and Prevention

CPD: Controlled prescription drug

CSA: Controlled Substances Act of 1970

DATA: Drug Addiction Treatment Act of 2000

DEA: Drug Enforcement Administration

DPS: Department of Public Safety

DSaRM: Drug Safety and Risk Management Advisory Committee

ED: Emergency department

FDA: Food and Drug Administration

HCP: Hydrocodone combination product

NDC: National Drug Code

NSAID: Nonsteroidal anti-inflammatory drug

NSDUH: National Survey on Drug Use and Health

OUD: Opioid use disorder

PDMP: Prescription drug monitoring program

SAMHSA: Substance Abuse and Mental Health Services Administration

SUD: Substance use disorder

CHAPTER 1: INTRODUCTION

1.1 Background

The perception of pain is very personal, subjective, and can be complex. A multitude of factors, including an individual's physiology, past experiences, psychological background, and social environment, influence how pain is perceived. Additionally, the consequences of pain can vary from relatively insignificant to completely debilitating. Pain can also significantly affect an individual's quality of life.

The medical treatment of pain is as old as the medical profession itself. Relief from pain can come in the form of a wide variety of treatments, from meditation therapy, to surgery, to the use of prescription opioid analgesics. Prescription opioid analgesics have been shown to effectively alleviate pain when used appropriately. However, when improperly used, these medications can lead to serious negative outcomes for the individual and to society. Common adverse events associated with prescription opioids include sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression (Benyamin et al., 2008). Public health issues include abuse and diversion of these medications, which has reached epidemic levels (Benyamin et al., 2008; Centers for Disease Control and Prevention, 2013; National Institute on Drug Abuse, 2014; National Prevention Council, 2011; Leonard J. Paulozzi, Jones, Mack, & Rudd, 2011).

Patients, prescribers, pharmacists, and other stakeholders continue to be challenged by the complexity of the problem of treating pain while simultaneously preventing abuse. On the one hand, a patient's relief from pain needs to be appropriately addressed. At the same time,

abuse and diversion need to be minimized. Striking a balance between these two interconnected issues is the goal, though in practice it is not as straightforward.

Interventions aimed to address the abuse epidemic have been enacted targeting various aspects of the issue and come from various levels of influence. Patients with pain are at the center of the issue. Also involved are additional levels of influence including family, friends, healthcare providers, communities, counties, states, and the federal government. Interventions (e.g., legal policy) can be initiated at any of these interconnected levels. An example of a recent federal intervention was the Ensuring Patient Access and Effective Drug Enforcement Act of 2016, aimed at improving collaboration between healthcare providers and law enforcement regarding controlled substances (US Congress, 2016). Two other federal interventions relate directly to this study.

One recent federal intervention was the rescheduling of hydrocodone combination products (HCPs) by the Drug Enforcement Administration (DEA) which took effect on October 6, 2014 (Federal Register, 2014b). HCPs contain hydrocodone, an opioid analgesic. From 2008 to 2012, HCPs were the most prescribed drugs in the US (IMS Health, 2013). Changing the controlled drug schedule for HCPs from schedule III to the most restrictive schedule II set in place additional restrictions for distribution, storage, prescribing, and dispensing. This regulation would effectively restrict the use of HCPs, thereby limiting the potential for abuse and diversion.

Another federal intervention was the enactment of the Drug Addiction Treatment Act of 2000 (DATA) (US Congress, 2000). This legislation provided for buprenorphine to be used as opioid addiction/dependence treatment on an outpatient basis with DATA-certified physicians. Prior to this law, treatment for opioid addiction/dependence had been with methadone on an inpatient basis. This regulation would improve access for patients to opioid addiction treatment. Although the two aforementioned interventions occurred at different points in time, they are interconnected because if HCPs are a gateway drug to further opioid abuse, which has been suggested, then restricted access may lead to more patients seeking drug addiction treatment.

Additionally, the environment of the patient influences their behavior, such as prescription opioid use based on availability and opioid addiction/dependence treatment use. Variation exists between states, counties, cities, and communities regarding prescribing patterns, treatments, and access. This study evaluated the impact of multiple levels of influence on the use of prescription opioid analgesics and the use of buprenorphine as opioid addiction/dependence treatment.

1.2 Statement of Purpose

The purpose of this study was to apply an ecological model to assess the impact of multiple levels of influence on the use of HCPs and the use of buprenorphine as opioid addiction/dependence treatment. Further, this study assessed the trends of use of these and other opioid analgesic medications in the context of rescheduling HCPs.

1.3 Statement of Problem

The treatment of pain with opioid analgesics and the risk of opioid addiction/dependence are interconnected issues. As long as opioids are prescribed to alleviate pain, the potential for addiction/dependence exists. Therefore, stakeholders have a responsibility to maintain an environment in which appropriate prescribing can exist while removing barriers to allow for access to addiction/dependence treatment as needed. Since variation exists within the US and across multiple levels of influence in society, interventions can target the appropriate level to maximize its impact. This study seeks to assess the variation which exists both across and within states for two medications – one an opioid analgesic aimed at treating pain, and the other aimed at treating opioid addiction/dependence.

1.4 Significance of Objectives

The significance of this study is to apply an ecological model to identify and better understand the variation that exists between multiple levels of influence on the use of HCPs, a type of widely used opioid analgesic medications. Additionally, buprenorphine as used in an outpatient setting for the treatment of opioid addiction/dependence will similarly be evaluated. This study could inform policymakers, healthcare providers, patients, and other stakeholders of the potential levels of influence which could be targeted by future interventions in order to improve patient care.

This was the first known study to use data from the Texas and Louisiana prescription drug monitoring programs (PDMPs) to assess prescription opioid use in each state. This data

contains all schedule II to V drugs dispensed within these states. Texas and Louisiana are bordering states with many similar characteristics, culture, and values. These states also have many differences regarding prescribing patterns, including different regulations concerning opioid prescribing. Comparing these two states could highlight state, local, and prescriber level variation. The study will also relate the differences that a national intervention – HCP rescheduling – has on opioid analgesic use in two neighboring states.

CHAPTER 2: LITERATURE REVIEW

2.1 Overview of Pain

Pain in the US is a significant health concern. Many in the medical community believe that "effective pain management is a moral imperative, a professional responsibility, and the duty of people in the healing professions" (Pizzo et al., 2011a). Payne et al. stated that physicians have the "moral and ethical obligation to treat pain" with opioids when necessary, regardless of external influences in the form of law enforcement and/or medical boards (Payne et al., 2010).

Indeed, pain is the most common reason for patients to seek care in the emergency department (Cordell et al., 2002). Alternative treatments exist for the treatment of pain, though prescription opioid analgesics are among the most common option. The section below will highlight the prevalence and impact of pain in the US and discuss pain treatment options.

2.1.1 Prevalence of Pain

An estimated 100 million Americans suffer from chronic pain, more than the total affected by heart disease, cancer, and diabetes combined (Gaskin & Richard, 2012; Pizzo et al., 2011a; Tsang et al., 2008). A Gallup Poll from 2011 found that an average of 31% reported neck or back pain, 26% with knee or leg pain, and 18% with another condition causing pain (Brown, 2012). As a part of the 2012 National Health Interview Survey, it was estimated that over the previous three months, 126.1 million of US adults experienced at least some pain, 25.5 million

(11.1%) experienced pain on a daily basis, and 23.4 million (10.3%) experienced “a lot” of pain during their most recent episode (Nahin, 2015).

2.1.2 Impact of Pain

The total cost of pain in the US ranges from $560 to $635 billion in 2010, exceeding that of heart disease ($309 billion), cancer ($243 billion), and diabetes ($188 billion) (Gaskin & Richard, 2012). The impact of pain on the individual is highly personalized, subjective, and complex. A number of factors influence the extent to which an individual perceives pain. The factors include, but are not limited to an individual’s physiology, biology, psychological background (Ochsner et al., 2006), and social environment (Pizzo et al., 2011a). Pain, in turn, can affect a person’s emotional status, cognition, and behavior (Gatchel, Peng, Peters, Fuchs, & Turk, 2007). The extent to which an individual is affected by pain varies from person to person. Consequently, pain can significantly affect an individual’s quality of life and ability to function.

2.1.3 Treatment Options for Pain

Health care providers, specifically physicians and pharmacists, are charged with balancing the need for appropriate pain control and the potential for abuse within the system currently in place (K. H. Todd, 2010; Wilsey, Fishman, & Ogden, 2005). A variety of treatments exist to treat pain, including: medications, surgery, behavioral interventions, psychological counseling, rehabilitative and physical therapy, and complementary or alternative treatments (Jackman et al., 2008; Pizzo et al., 2011b). Of note, a national survey of former emergency department (ED) patients by Todd et al. (2010) found that approximately one-half of the

patients had not received information regarding pain management or specialist referrals (Knox H. Todd, Cowan, Kelly, & Homel, 2010). A list of common treatment options for chronic nonmalignant pain is shown in Table 2.1.

Table 2. 1. Treatment Options for Chronic Nonmalignant Pain

Treatment Type	Options
Non-Pharmacological	
Lifestyle	Cessation of tobacco products, weight loss
Physical	Exercise, manipulation, physical therapy, stretching and yoga, surgical therapies (nerve blocks, trigger point injections, spinal infusion or stimulation), transcutaneous electric nerve stimulation
Psychologic	Biofeedback, cognitive behavior therapy, counseling, hypnosis, music, relaxation
Complementary or alternative	Acupuncture, herbal remedies, massage, mindfulness meditation, reflexology
Occupational	Occupational therapy, work conditioning programs
Pharmacological	
Non-opioid analgesics	Acetaminophen, NSAIDs, salicylates (aspirin)
Opioid medications	Combination opioid and non-opioid medications (codeine, hydrocodone [Hycodan®], or oxycodone [Roxicodone®] plus acetaminophen, aspirin, or an NSAID)
	Non-combination or "strong" opioid medications, such as morphine (MS Contin®) and its derivatives (butorphanol [Stadol®], codeine, fentanyl [Duragesic®], hydrocodone, hydromorphone [Dilaudid®], levorphanol [Levo-Dromoran®], methadone, oxycodone)
	Tramadol (Ultram®)
Adjuvant medications	Anticonvulsant medications (carbamazepine [Tegretol®], gabapentin [Neurontin®], lamotrigine [Lamictal®], phenytoin [Dilantin®], pregabalin [Lyrica®], valproic acid [Depakene®])
	Antidepressants (selective serotonin reuptake inhibitors, tricyclic)
	Atypical antidepressants (duloxetine [Cymbalta®], venlafaxine [Effexor®]
	Topical lidocaine (Xylocaine®)
	Others (topical capsaicin, cyclobenzaprine [Flexeril®], lidocaine patches)

Source: (Jackman et al., 2008)

2.1.3.1 Non-Pharmacological

Studies have shown that chronic pain can be effectively treated using multiple modalities, including psychological, physical rehabilitative, and surgery (National Pharmaceutical Council, 2001). Typically, these modalities are used to supplement pharmacological strategies. The goal these non-pharmacological treatments are pain reduction, improved physical and mental functioning, and improved quality of life (Marcus, 2000).

2.1.3.2 Pharmacological Agents

Pharmacological treatments can be categorized as non-opioid analgesics, opioid analgesics, and adjuvant medications. Analgesic medications are specifically aimed at pain relief. Other medications which provide pain relief are adjuvant medications (e.g., gabapentin) such as those listed in Table 2.1. These medications are drugs which are prescribed for a primary indication other than pain (Lussier, Huskey, & Portenoy, 2004).

Non-opioid analgesics include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and salicylates (aspirin). These medications are typically classified as over-the-counter medications, with minimal potential for abuse. However, as with most medications, non-opioid analgesics also have the potential for unwanted adverse events.

2.1.3.2.1 Opioids

Opioid analgesics are commonly prescribed for the treatment of pain. Opioid analgesics can be effective for pain when used appropriately. The effectiveness of prescription opioids for

the relief of pain is well established, but of late, controversial due to their inherent potential for addiction/dependence. The prevalence of opioids has also increased significantly over the past two decades. From 1997 to 2006, use of prescription opioids increased 327% (Manchikanti, Benyamin, Datta, Vallejo, & Smith, 2010).

Morphine and codeine are examples of opioids extracted from poppy seeds (Jamison & Mao, 2015). Oxycodone and hydrocodone are examples of semisynthetic opioids (L. J. Paulozzi, Mack, & Hockenberry, 2014). Tramadol is considered a synthetic opioid (L. J. Paulozzi et al., 2014), and is associated with an increased potential for abuse and addiction/dependence compared to non-opioid analgesics (e.g., acetaminophen, NSAIDs). For this reason, the Drug Enforcement Administration (DEA) classified tramadol as a schedule IV medication as of August 18, 2014 (Federal Register, 2014a). For a more complete list of opioids by schedule, refer to Table 2.2.

Table 2. 2. Prescription Opioid Medications by Controlled Substance Schedule

Generic Name	C-II	C-III	C-IV	C-V	Brand Name/Other Names
codeine single-entity	X				
fentanyl	X				Duragesic®, Oralet®, Actiq®, Sublimaze®, Innovar®
hydrocodone	X				Zohydro®, Hysingla®, dihydrocodeinone
hydrocodone combination product	X[a]	X[a]			Vicodin®, Lorcet®, Lortab®, Lortab ASA®, Vicoprofen®, Hycomine®
hydromorphone	X				Dilaudid®, Palladone®, dihydromorphinone
meperidine	X				Demerol®, Mepergan®
methadone	X				Dolophine®, Methadose®
morphine	X				MS-Contin®, Kadian®, MSIR®, Oramorph SR, RMS®, Roxanol®
oxycodone	X				OxyContin®, OxyIR®, Percocet®, Percodan®, Tylox®
buprenorphine		X			Buprenex®, Temgesic®, Subutex®, Suboxone®
codeine combination product		X		X	Tylenol #3® (codeine/APAP): C-II. Low dose: C-V
dihydrocodeine combination product		X			Trezix®
pentazocine (non-opioid)			X		Talacen®, Talwin®, Talwin NX®
tramadol (>8/18/14) (non-opioid)			X[b]		ConZip®, Rybix ODT®, Ryzolt®, Ultram®
butorphanol (non-opioid)			X		Stadol®, Stadol NS®, Torbugesic®, Torbutrol®

[a]Hydrocodone combination products were rescheduled from C-III to C-II as of October 6, 2014
[b]Tramadol was changed from not being scheduled to C-IV as of August 18, 2014

2.1.3.2.1.1 Opioid Abuse

Prescription drug abuse and overdose is a significant national public health issue, which has rapidly increased in size and scope since the 1990s, fueled greatly by prescription opioids (Leonard J. Paulozzi et al., 2012; Leonard J. Paulozzi et al., 2012). From 1996 to 2011, non-medical use of opioids increased 4,680% (Atluri, Sudarshan, & Manchikanti, 2014). For the time period from 2001-2002 to 2012-2013, non-medical use of opioids more than doubled (National Institute of Health, 2016). In 2012-2013, nearly 10 million Americans (4.1% of the adult population) used opioids non-medically, up from 1.8% of the adult population in 2001-2002 (National Institute of Health, 2016). Over 11% of the adult population in 2012-2013 reported non-medical use of prescription opioids at least once during their lifetime, compared to 4.7% ten years earlier (National Institute of Health, 2016).

Death from prescription opioid overdose has become a top public health issue, and was labeled by the Centers for Disease Control and Prevention as an epidemic (Leonard J. Paulozzi et al., 2011). From 1999 to 2011, mortality associated with prescription analgesic use increased by four times (Levi, Segal, & Martin, 2015). As of 2013, drug overdoses were the leading cause of injury deaths in the US, with approximately 36% associated with prescription analgesics (Centers for Disease Control and Prevention, 2015a; Levi et al., 2015).

2.1.3.2.1.2 Scheduling of Opioids

The use of prescription opioids has serious risks, such as abuse, addiction, dependence, and other potentially severe adverse outcomes. As a result, these drugs are classified as controlled substances, also referred to as controlled prescription drugs (CPDs).

In 1970, the Controlled Substances Act (CSA) was passed by Congress (US Congress, 1970). It established the classification of controlled substances (including analgesics such as HCPs) into five categories, termed schedules, namely schedules I to V (C-I to C-V) (Table 2.3). In practical terms, the differences between schedule II and schedules III to V are significant and affect every phase of the drug delivery process, including manufacturing, delivery, prescribing (Table 2.4), and dispensing (Table 2.5). By design, schedule II drugs are the most restrictive prescription drugs to access.

Table 2. 3. Characteristics of Controlled Substances by Schedule

Schedule (Abbreviation)	Currently Accepted Medical Use in the US	Potential for Abuse	Abuse of the Substance may lead to _____ Physical Dependence	Abuse of the Substance may lead to _____ Psychological Dependence
I (C-I)	No	High	[a]	[a]
II (C-II)	Yes, or it has a currently accepted medical use with severe restrictions	High	Severe	Severe
III (C-III)	Yes	Less than that of drugs in Schedules I & II	Low or moderate	High
IV (C-IV)	Yes	Less than that of drugs in Schedule III	Limited (relative to drugs in Schedule III)	Limited (relative to drugs in Schedule III)
V (C-V)	Yes	Less than that of drugs in Schedule IV	Limited (relative to drugs in Schedule IV)	Limited (relative to drugs in Schedule IV)

[a]The law does not address this characteristic
Source: (US Congress, 1970)

Table 2. 4. Prescribing Regulation Differences between Schedule II and Schedules III to V

	Schedule II	Schedules III to V
Type of prescription	Written, e-prescribe	Written, verbal, fax, e-prescribe
Serialized prescription pad requirement	No (Fed); Yes (TX); No (LA)	No
Refills allowed	No, but 2 additional prescriptions can be post-dated	Yes, up to 5 months
Record-keeping requirements	Yes, plus additional requirements	Yes
Practitioners able to prescribe • **Dentists** • **Nurse Practitioners**	• Yes, though many did not have the DEA narcotic registration • Yes (Fed); No (TX); Yes (LA)	• Yes • Yes

Abbreviations: Fed=Federal; TX=Texas; LA=Louisiana
Sources: (Texas Department of Public Safety, 2015; Texas State Board of Pharmacy, 2014; US Congress, 1970)

Table 2. 5. Dispensing Regulation Differences between Schedule II and Schedules III to V

	Schedule II	Schedules III to V
Type of prescription	Written, e-prescribe	Written, verbal, fax, e-prescribe
Refills allowed	No, but 2 additional prescriptions can be post-dated	Yes, up to 5 months
Record-keeping requirements	Yes, plus additional requirements	Yes
Emergency fills	Allowed with limitations	Yes
Transfers allowed to another pharmacy	No	Yes (1 time only)
Ordering requirements	DEA Form 222 or Controlled Substance Ordering System (CSOS)	May be ordered with other inventory
Separate prescription file requirements	No (Fed); No (TX); Yes (LA)	No
Storage requirements	Secured area (Fed); Separate and locked safe (TX); May be stored with other inventory (LA)	May be stored with other inventory
Real-time perpetual inventory	No (Fed); Yes (TX); No (LA)	No
Additional labeling requirements	No (Fed); No (TX); Yes (LA)	No

Abbreviations: Fed=Federal; TX=Texas; LA=Louisiana
Sources: (Texas Department of Public Safety, 2015; Texas State Board of Pharmacy, 2014; US Congress, 1970)

2.2 Hydrocodone Combination Products

Hydrocodone is a semisynthetic opioid designed for relieving moderate to severe pain (*Pharmacotherapy Handbook, 8th Edition*, 2012). HCPs have a relatively favorable profile with relatively fewer adverse effects than other opioids, accounting for the high rate of use in the

US. It is a viable alternative to patients who cannot tolerate natural opioids such as codeine (Food and Drug Administration, 2013b).

2.2.1 Prevalence of Hydrocodone Combination Products

Hydrocodone combination products (HCPs) were the most prescribed drugs in the US from 2008 to 2012 (IMS Health, 2013). HCPs accounted for 135.3 million prescriptions dispensed (25.9% more than the second most dispensed drug) (IMS Institute for Healthcare Informatics, 2012). Moreover, the US consumed 99% of the world's hydrocodone supply in 2012 (International Narcotics Control Board, 2013).

2.2.2 Rescheduling Hydrocodone Combination Products

Since the differences between schedule II and schedules III to V are significant, specifically regarding regulations concerning healthcare providers (e.g., physicians, mid-level practitioners such as nurse practitioners, and pharmacists), patients may be affected. Rescheduling could result in: additional physician and pharmacist oversight; the under treatment of pain (if a patient was switched from a HCP treatment plan which was effective); increased addiction treatment; or additional burdens on physician and pharmacist workflow influencing pain treatment.

From a medical perspective, some physicians and other prescribers (e.g., mid-level practitioners, optometrists, and dentists) historically did not typically prescribe C-II drugs, for a variety of reasons. These reasons could include, but are not limited to: C-IIs cannot be refilled; state requirements for prescribers to use serialized prescription pads for C-IIs (required in

Texas, but not in Louisiana) (Food and Drug Administration; Center for Drug Evaluation and Research, 2013); the inability to prescribe C-II drugs (e.g., nurse practitioners in some states); the additional administrative burden associated with prescribing C-IIs (Food and Drug Administration; Center for Drug Evaluation and Research, 2013); additional record-keeping requirements for physicians; and state regulations for mid-level practitioners (mid-level practitioners cannot prescribe C-IIs in Texas, but they can in Louisiana) (Stokowski, 2015). These additional requirements for C-IIs translate to additional time and burden on the part of the physician.

From a pharmacist's perspective, the storage, handling, and dispensing of C-IIs is much more involved than that of the other scheduled drugs (Food and Drug Administration; Center for Drug Evaluation and Research, 2013). Some of the additional steps required of a pharmacist for the dispensing of C-IIs include, but are not limited to: since refills are not permitted on C-IIs, additional prescriptions will need to be processed versus refills allowed on C-III to C-V drugs; transferring a prescription to another pharmacy is not permitted; ordering C-IIs from the wholesaler requires a separate DEA form which can only be completed by the pharmacist; some states require C-IIs to be stored in a locked safe (which may need to be upsized, due to the additional volume of HCPs); C-II inventory needs to be updated daily; and other additional administrative and recordkeeping requirements. Similar to physicians, these additional requirements for C-IIs translate to additional time and burden on the part of pharmacists.

From the patient perspective, rescheduling of HCPs could impact access. Since refills are not allowed with C-IIs, the patient will have to visit the physician more often to get the same

medication. It is also possible that a patient could be switched to an alternative pain treatment, either another C-II such as an oxycodone combination product (which is stronger and arguably more susceptible to abuse), or a C-III or C-IV analgesic (note that C-V does not contain analgesics per se, but rather cough preparations predominantly). Other scenarios exist, including: use of addiction treatment medications; switching to over-the-counter (OTC) analgesics; or a patient could decide to forego medical treatment and turn to an illicit drug, such as heroin (Food and Drug Administration; Center for Drug Evaluation and Research, 2013).

2.2.2.1 History of Rescheduling

Single-entity hydrocodone has always been classified as schedule II, though it was not commercially available in this form until recently (Food and Drug Administration, 2013a; US Congress, 1970). HCPs were originally classified as schedule III (US Congress, 1970). In 1999, the US Drug Enforcement Administration (DEA) received a petition to reschedule HCPs from schedule III to schedule II (Federal Register, 2014b). In 2004, the DEA requested a scientific and medical evaluation and scheduling recommendation for HCPs from the Department of Health and Human Services (HHS). In 2008, the HHS responded with a recommendation that HCPs should remain schedule III. The DEA requested a re-evaluation in 2009. In 2012, President Obama signed the Food and Drug Administration Safety and Innovation Act, which included a directive for the Food and Drug Administration (FDA) to hold a public hearing regarding rescheduling HCPs to schedule II. In January 2013, the FDA held a Drug Safety and Risk Management Advisory Committee (DSaRM) meeting (Food and Drug Administration; Center for

Drug Evaluation and Research, 2013). The committee voted 19 to 10 in favor of recommending HCPs be rescheduled to schedule II (Federal Register, 2014b). The HHS and DEA elicited further comments and ultimately published a ruling to reschedule HCPs to schedule II on August 22, 2014. The ruling took effect on October, 6, 2014.

2.3 Addiction and Dependence

The American Society of Addiction Medicine defines addiction as "Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by the inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death." (American Society of Addiction Medicine, 2016) Dependence is a related condition, although different from addiction. The American Chronic Pain Association defines dependence as "A state of adaptation that is manifested by a withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. In the management of acute pain, physical

dependence usually does not develop because of the limited duration of opioid use. Physical dependence is not addiction." (American Chronic Pain Association, 2016)

Addiction and dependence are separate conditions from tolerance, which is found when an individual adapts to drug exposure, thus reducing the drug effect over time (American Chronic Pain Association, 2016). A significant issue concerning tolerance is that if the dosage is increased, the risk of negative side effects can increase.

2.4 Medication-Assisted Treatment

Treatment for drug addiction and dependence (specifically for opioids) used to be solely an inpatient process. Methadone served as typical treatment. Methadone clinics remain an option for opioid addiction/dependence treatment.

Buprenorphine-naloxone and single-entity buprenorphine (hereafter referred to as "buprenorphine as opioid addiction/dependence treatment") have been shown to effectively treat opioid addiction/dependence (Fiellin et al., 2006; Fudala et al., 2003; Johnson et al., 1995; Kosten, Schottenfeld, Ziedonis, & Falcioni, 1993; Ling, Wesson, Charuvastra, & Klett, 1996). The Drug Addiction Treatment Act of 2000 (DATA) allowed for buprenorphine to be used as opioid addiction/dependence treatment on an outpatient basis (Drug Enforcement Administration, 2013; US Congress, 2000). This was a significant step towards decreasing barriers to improve access for patients seeking treatment for opioid addiction/dependence. Physicians are certified to administer buprenorphine on an outpatient basis through the Substance Abuse and Mental

Health Services Administration (SAMHSA). Physicians can be certified with either a 30-patient or 100-patient limit.

Buprenorphine was the first medication allowed to be used for the treatment of opioid addiction/dependence on an outpatient basis. This was achieved due to the relatively low risk of respiratory depression and abuse of buprenorphine (Walsh, Preston, Stitzer, Cone, & Bigelow, 1994). It has also been shown to be as effective at treating opioid addiction/dependence as methadone (Fudala et al., 2003; Johnson et al., 1995; Kosten et al., 1993; Ling et al., 1996).

Medication-assisted treatment (MAT) includes a multi-disciplinary approach to treatment of opioid addiction/dependence. MAT includes the use of medication coupled with counseling. This approach improves the success rate of opioid addiction/dependence treatment (National Institute on Drug Abuse, 2009). US Department of Health and Human Services (HHS) Secretary Sylvia M. Burwell declared addressing opioid abuse, dependence, and overdose a priority for the agency in March 2015 (US Department of Health and Human Services, 2015). Further, expanding the use of MAT was one of the three priority areas identified by HHS to tackle the crisis.

2.4.1 Prevalence of Medication-Assisted Treatment

The use of buprenorphine as opioid addiction/dependence treatment in an outpatient setting has increased steadily since its inception. From 2003 to 2013, buprenorphine as opioid addiction/dependence treatment use increased from 0.16 million visits to 2.1 million visits

(Turner, Kruszewski, & Alexander, 2015). The same study found that there was a significant shift regarding physician specialty. In 2003, 92.2% of DATA certified physicians were psychiatrists and 6.0% were primary care physicians. By 2013, 32.8% were psychiatrists and 63.5% were primary care physicians. Table 2.6 shows the number of DATA certified physicians with 30-patient and 100-patient limits as of September 2015.

Table 2. 6. Number of DATA-Certified Physicians with 30-Patient and 100-Patient Limits as of September 2015

Area	30-Patient Certified	30-Patient Limit Met	30-Patient Certified/ 100,000 Population	100-Patient Certified	100-Patient Limit Met	100-Patient Certified/ 100,000 Population
United States	20,723	N/A	6.56	9,801	N/A	3.10
Texas	411	1	1.55	366	0	1.38
Louisiana	103	0	2.23	165	0	3.57

Source: (Substance Abuse and Mental Health Services Administration, 2015b)

2.5 Summary of Literature Review

Pain affects a large number of individuals in the US. Numerous treatments for the relief of pain exist, most notably the use of prescription opioid analgesics. Due to the potential for abuse and addiction/dependence, opioids are classified as controlled substances. Due to wide accessibility, the prescription opioid abuse problem in the US has reached epidemic levels. Interventions have been implemented to curb the problem, notably HCP rescheduling.

The DEA rescheduled HCPs in October 2014 to further restrict access. The other notable intervention occurred in 2000 with the passage of the Drug Addiction Treatment Act, allowing

physicians to prescribe and administer buprenorphine for the treatment of opioid addiction/dependence on an outpatient basis.

This study aimed to quantify the impact of rescheduling HCPs in terms of opioid use with the application of a social ecological model. This model provided an assessment of the impact of multiple levels of influence (local, state, and national) on the use of HCPs in light of rescheduling. Additionally, this study assessed the impact of the same multiple levels of influence on buprenorphine as used for opioid addiction/dependence treatment.

CHAPTER 3: THEORY

3.1 Rationale of Study

Behavioral research studies are conducted for different purposes. Purposes include prediction or explanation of behavior. This study was conducted to explain the behavior of individuals in the context of their environment.

Environments are defined as outside influences affecting an individual's perceptions which influence behavior. Three types of environments are identified by the Social Cognitive Theory proposed by Albert Bandura: 1) Imposed (environments not under the control of an individual); 2) Selected (environments chosen by an individual); and 3) Created (environments created by an individual) (Bandura, 1986). It should be noted that the environment is composed of two elements: physical and social. The physical environment encompasses physical characteristics, such as facilities, equipment, and geographic areas, in addition to policies and programs. The social environment includes influences from family, friends, and the community. From the public health perspective selected for this study, the imposed physical environment is the focus (specifically the multiple interconnected layers of the nation's geopolitical system).

The prescription opioid abuse problem in the US has become a national epidemic (Benyamin et al., 2008; Centers for Disease Control and Prevention, 2013; National Institute on Drug Abuse, 2014; National Prevention Council, 2011; Leonard J. Paulozzi et al., 2011). Solutions in the form of interventions need to be implemented to combat the crisis. Since

different areas of the country have different needs regarding this issue, the development of interventions should account for the unique characteristics of the area being targeted. A theoretical framework using a social ecological model was selected to explain behaviors in the context of multiple levels of environmental influences in order to potentially identify areas as targets of future interventions.

3.2 Theoretical Models Used to Explain Behavior

One of the goals of behavioral research is to explain behavior. Multiple theories have been successfully applied to different behaviors of interest (e.g., Theory of Planned Behavior, Social Cognitive Theory, Transtheoretical Model of Change) (Ajzen & Fishbein, 1980; Bandura, 1986; Prochaska, 1984). Many of these theories involve the individual directly, by assessing the individual's perceptions and attitudes, for example. One of the primary applications associated with the use of a particular theory is to understand the cognition behind a specific behavior (e.g., attitude) so that an intervention to change those attitudes or perceptions can be developed and implemented. This would, in turn, lead to a change in an individual's behavior.

The focus of this study, however, was at a much broader level – that of the environment. This study aimed to assess the impact of multiple environmental levels on health behaviors. Specifically, these layers are geopolitical boundaries. The reason for choosing these levels was to assess variation and identify appropriate levels of government which could feasibly implement interventions targeted at the behavior of concern. With limited resources, the more informed the developers of the intervention are of the targeted population, the more

successful and efficient the intervention will be. It should be noted that geopolitical areas are only one type of environment which could be assessed. Other environments could include: physician professional organizations, managed care environments, or workplace environments.

3.3 Social Ecological Model

Urie Bronfenbrenner proposed a social ecological model in 1979 consisting of nested and interconnected levels termed: 1) micro (e.g., individual knowledge, skills, attitudes, values); 2) meso (interaction of two or more micros); exo (external environments); and macro (e.g., organizations, schools, workplaces) (Bronfenbrenner, 1977, 1979). Other social ecological models have been proposed, similar in concept to Bronfenbrenner's model (McLeroy, Bibeau, Steckler, & Glanz, 1988; Stokols, 1996).

The four core principles of ecological models are: 1) a specific health behavior is affected by multiple levels of influence; 2) interactions across these multiple levels of influence affect health behavior; 3) the health behavior must be specific; and 4) interventions should be introduced at multiple levels to be most effective (Sallis, Owen, & Fisher, 2008). The multiple levels of influence typically include intrapersonal, interpersonal, organizational, community, physical environmental, and policy. Different versions of ecological models have been applied to many health promotion studies, including violence prevention (Centers for Disease Control and Prevention, 2015c), reducing HIV incidence (Sweat & Denison, 1995), diabetes management (Fisher et al., 2005), and promotion of healthy nutrition (Glanz, Sallis, Saelens, &

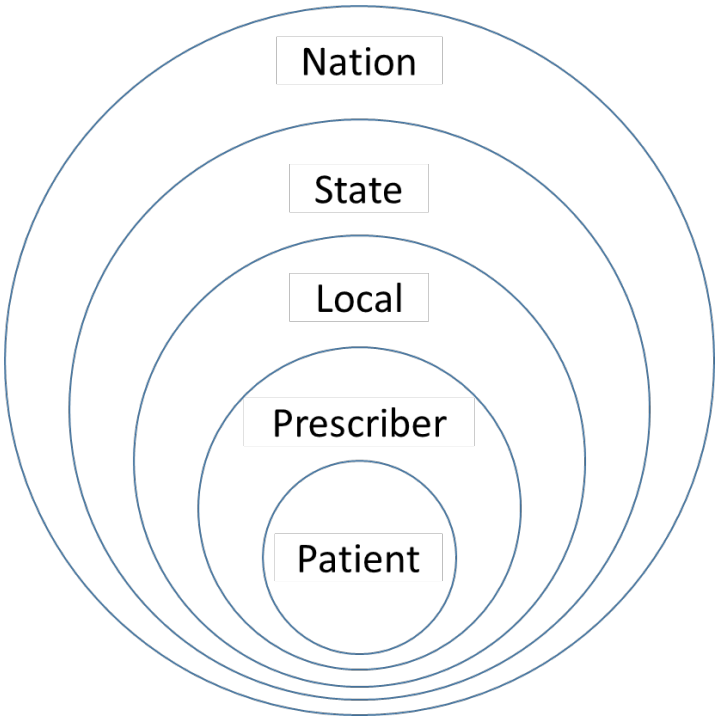
Frank, 2005). Additionally, social ecology theory is recognized by the Institute of Medicine (IOM) as an essential health promotion theory (*Who Will Keep the Public Healthy? Educating Public Health Professionals for the 21st Century*, 2003).

3.4 Theoretical Framework

The model used for this study was primarily based on social ecological models (Bronfenbrenner, 1979; McLeroy et al., 1988; Sweat & Denison, 1995). The following are the levels identified by this study (Figure 3.1):

1. Nation
2. State
3. Local
4. Prescriber
5. Patient

Figure 3. 1. Proposed Social Ecological Model



The national, state, and local levels represent not only different geographic boundaries, but different political, legal, and cultural influences. The national level represents the nation as a whole, and encompasses its collective system of federal laws, rules, regulations, governing bodies (e.g., FDA, DEA, and Congress), FDA-regulated controlled prescription drug (CPD) production quotas, and programs (e.g., federal drug take-back programs, DEA law enforcement). This level also includes the national culture (e.g., pain management and treatment, medical and pharmacy credentialing requirements, national prescription drug abuse), and national professional organizations (e.g., the American Medical Association, the American Pharmacists Association) and their formal guidelines and perspectives on healthcare

issues. It also accounts for the supply of CPDs, including possible backorders, or other supply issues.

The state level represents the collective characteristics of each individual state. Regarding healthcare issues, such as rescheduling hydrocodone, there exist regional differences as well, which could encompass more than one state. However, each state has its own characteristics, including its own laws (e.g., which practitioners are allowed to prescribe C-IIs), rules, regulations, governing bodies (e.g., Texas Medical Board, Texas State Board of Pharmacy), and programs (e.g., Texas prescription drug monitoring program). This level also includes a broad statewide culture towards certain healthcare issues (e.g., pain treatment, prescription drug abuse). Professional organizations also operate and influence healthcare providers at the state level (e.g., Texas Medical Association, Texas Society of Health-System pharmacists). The supply (including shortages) of HCPs and other drugs from the manufacturers also impact pain treatment across the nation.

The local level represents the collective characteristics of a patient's surrounding environment, and includes three sublevels: 1) community; 2) physician; and 3) pharmacy. The community sublevel was the smallest environment assessed in this study. For this study, the community sublevel consisted of population demographics at the zip code level. The physician sublevel includes the characteristics of a particular physician (e.g., CPD prescription history). The pharmacy sublevel includes the characteristics of a particular pharmacy (e.g., CPD dispensing history).

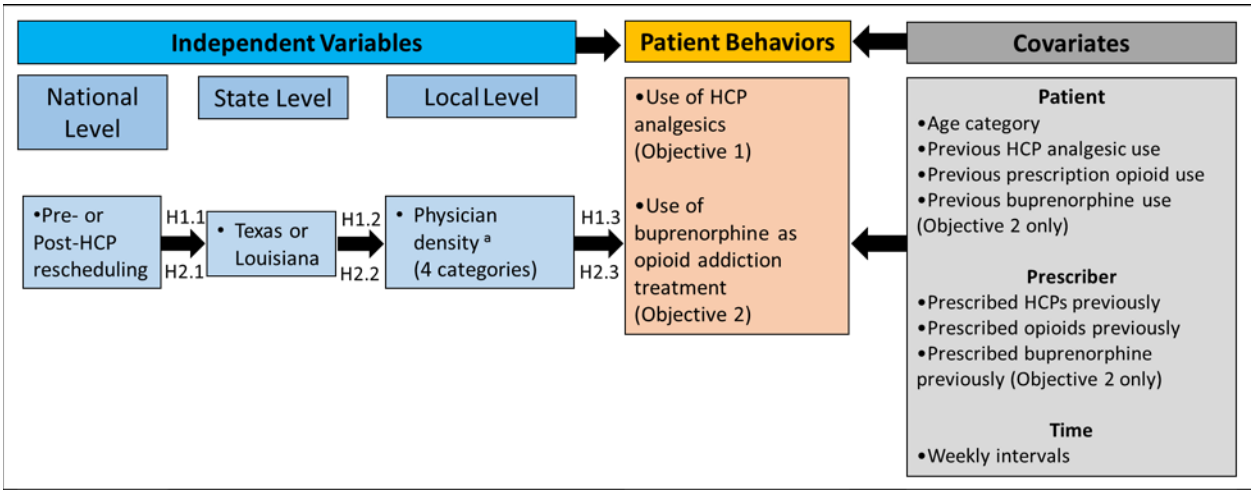
The patient level represents the individual impacted by the environment. In this study, some of the patient characteristics included, but were not limited to: age and use of other opioid analgesics.

Each of these levels can be influenced and affected by another. This study addressed the four core principles of an ecological model (Sallis et al., 2008).

1. A specific health behavior is affected by multiple levels of influence. HCP use and buprenorphine used as opioid addiction/dependence treatment were proposed to be affected by multiple levels of influence.
2. Interactions across these multiple levels of influence affect health behavior. Each of these multiple levels were proposed to be influenced by one another and consequently influenced health behavior.
3. The health behavior must be specific. This study addressed HCP use and buprenorphine used as opioid addiction/dependence treatment.
4. Interventions should be introduced at multiple levels to be the most effective. This study focused on the impact of these multiple levels on health behaviors.

Accounting for these levels of environmental influence, this study assessed the use of HCPs and buprenorphine as used for opioid addiction/dependence treatment. See Figure 3.2 for the operationalization of the model to this study.

Figure 3. 2. Operationalization of the Model



[a]Physician density (4 categories) assessed for each geographic area (TX: county; LA: 3-digit zip code)

Abbreviations: HCP=hydrocodone combination product; TX=Texas; LA=Louisiana

3.5 Objectives and Hypotheses

The objectives of this study were to assess the impact of multiple levels of influence.

Objective 1. Determine the impact of multiple levels of influence on the use of hydrocodone combination products (HCPs).

H1.1. Environmental factors at the national level will explain a significant amount of variance of HCP use.

H1.2. Environmental factors at the state level will explain a significant amount of variance of HCP use.

H1.3. Environmental factors at the local level will explain a significant amount of variance of HCP use.

Objective 2: Determine the impact of multiple levels of influence on the use of buprenorphine as opioid addiction treatment.

H2.1. Environmental factors at the national level will explain a significant amount of variance of use of buprenorphine as opioid addiction/dependence treatment.

H2.2. Environmental factors at the state level will explain a significant amount of variance of buprenorphine as opioid addiction/dependence treatment.

H2.3. Environmental factors at the local level will explain a significant amount of variance of buprenorphine as opioid addiction/dependence treatment.

3.6 Summary

Theory is used to explain behavior and to guide research. The selection of an appropriate theory requires consideration of multiple factors, including the nature of the study and its objectives. For this study, the use of a social ecological model should be both applicable to the nature of the study and explain the behaviors outlined in the objectives. Specific environments representing multiple layers of influence could affect two related behaviors. Further, the impact of each of these layers on behaviors were quantified to identify targets for future interventions.

CHAPTER 4: MANUSCRIPT 1

Use of Hydrocodone Combination Products Pre- and Post-Rescheduling: Assessing the Impact Using a Social Ecological Model

Abstract

Background: The use of opioid analgesics, specifically hydrocodone combination products (HCPs), which were the most prescribed drugs in the US from 2008 to 2012, is influenced by not only a patient's medical condition, but also multiple levels of external influence to a patient. One example of a level of external influence was the federal regulation to reschedule HCPs from C-III to the more restrictive C-II in October 2014. The objective of this study was to assess the impact of multiple levels of influence on HCP use, through application of a social ecological model.

Methods: A retrospective cohort design was employed using data from the Texas and Louisiana prescription drug monitoring programs. This data contained prescription level information for all controlled substances dispensed from community pharmacies from June 2, 2014 to July 22, 2015 in Texas and June 1, 2013 to April 8, 2015 in Louisiana.

The dependent variable was HCP use. Logistic regression analysis was used to assess the effect of the independent variables from the national, state, and local levels while controlling for interactions and other covariates.

Results: At the national level, HCP rescheduling reduced HCP use for both states and for each of four types of local areas (based on physician density). At the state level, the inherent characteristics of Texas (including policies regarding C-II prescribing) were associated with a reduction of HCP use of 84.7% (OR=0.153, $p<0.0001$) and a reduction of HCP use in Louisiana of 42.4% (OR=0.576, $p<0.0001$) on a pre- versus post-rescheduling basis. The impact of local areas based on physician density was limited.

Conclusion: Multiple levels of influence impacted the use of HCPs. The federal intervention of rescheduling HCPs reduced HCP use for both Texas and Louisiana. The inherent characteristics of Texas (including the requirement of physicians to use state-mandated C-II prescription pads) were possibly the most influential in reducing the likelihood of HCP use.

Introduction

Factors which influence health behavior come from both the patient and external environmental factors. Prescription opioid use, specifically the use of hydrocodone combination products (HCPs), is no exception. Certainly a patient's medical condition influences the decision of whether to prescribe opioids or not. Additionally, environmental factors influencing HCP use are found at different levels. Specifically, federal and state regulations and policies, local environmental characteristics, and prescriber behavior can all influence HCP use.

Over the past couple of decades, opioid use for the treatment of pain has increased dramatically in the US. From 1997 to 2006, prescription opioid use had increased by 327%

(Manchikanti, Benyamin, et al., 2010). By 2011, prescription analgesic use, of which most were opioids, increased by four times that of 1999 (Levi et al., 2015). Leading this trend were HCPs which were the most prescribed drugs in the US from 2008 to 2012 (IMS Health, 2013).

Additionally, since the late 1990s, concerns have been mounting regarding prescription opioid abuse, prompting the Centers for Disease Control and Prevention (CDC) to classify it as a public health epidemic (Centers for Disease Control and Prevention, 2013). Regulation and policy changes at the federal and state levels have been enacted over the years to target the growing problem. In August 2014, the Drug Enforcement Administration (DEA) rescheduled HCPs from schedule III to the most restrictive schedule II as of October 6, 2014 (Federal Register, 2014b). This regulation was targeted at further restricting access to prescription opioids.

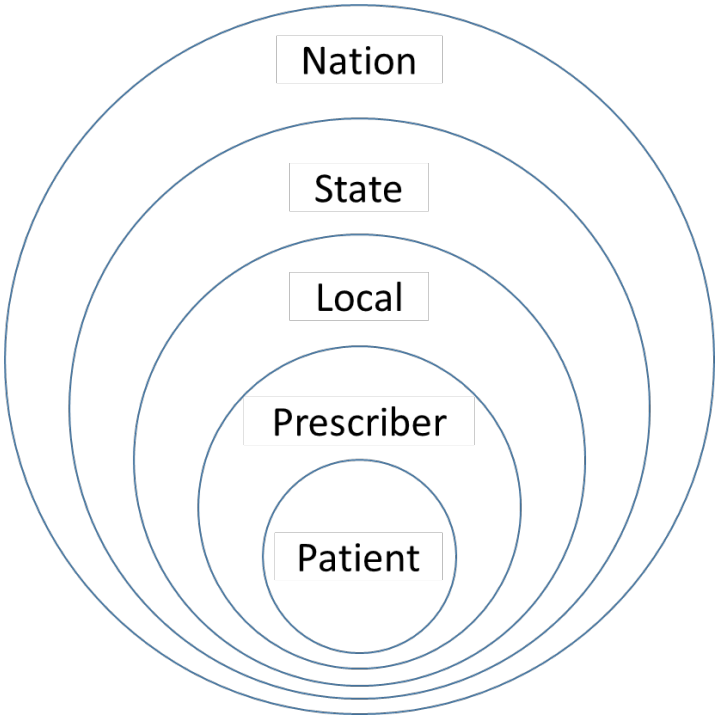
It should be noted that state regulations regarding scheduled drugs vary, whereby some state laws are more stringent than the federal law. For example, Texas requires the use of serialized prescription pads (formerly triplicate forms) for C-IIs and mid-level practitioners are not allowed to prescribe C-IIs in Texas, except for specific practice settings (State of Texas, 1989). Louisiana does not share these additional restrictions. This variation between these two states may highlight the impact that different regulations at the state level have on opioid prescribing.

Local characteristics and prescriber behavior are additional factors which influence HCP use. Physician density has been found to have a greater correlation with opioid use, compared

to other county level characteristics such as population, race distribution, and urban versus rural designation (McDonald & Carlson, 2013).

Social ecological models propose that multiple interconnected levels of influence affect behaviors (Bronfenbrenner, 1977, 1979). These levels interact between one another and influence a specific behavior of interest. Additionally, interventions should be targeted at multiple levels in order to be the most effective (Sallis et al., 2008). This study proposed a social ecological model to explain HCP use (Figure 4.1), using the following levels: national, state, local, prescriber, and patient. The objective of this study was to assess the impact of multiple levels of influence on HCP use, through application of a social ecological model.

Figure 4. 1. Proposed Social Ecological Model



Methods

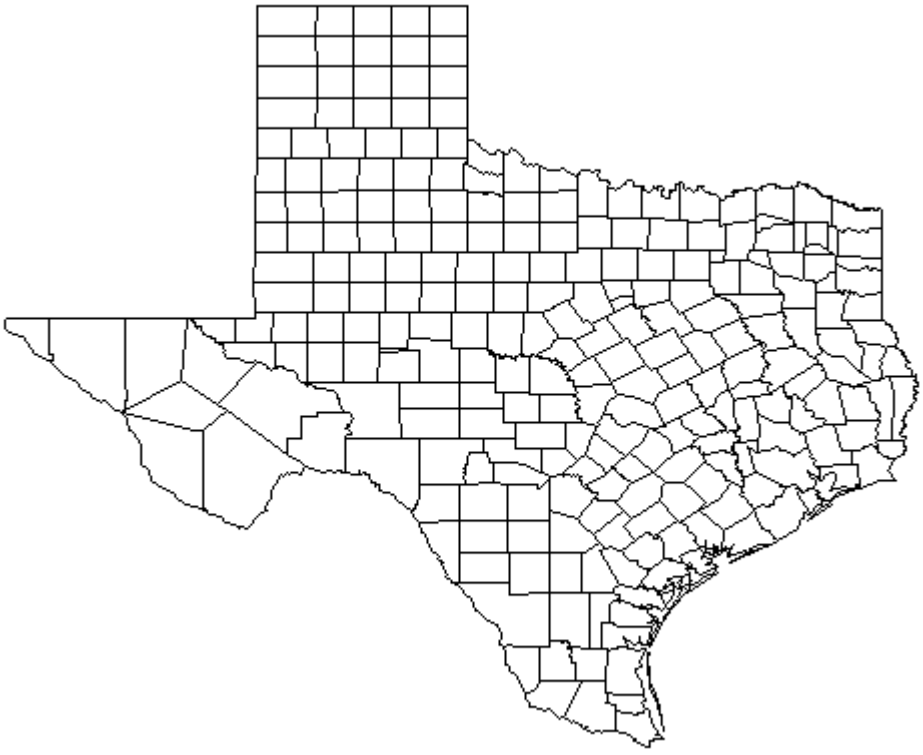
A retrospective cohort design was used. De-identified data used were from the Texas and Louisiana prescription drug monitoring programs (PDMPs). PDMPs are administered by individual states and collect information on every controlled substance prescription dispensed from community pharmacies. De-identified data from the Texas and Louisiana PDMPs were available to a limited number of researchers with the prior authorization of the PDMP administrators.

Short-acting opioid analgesics with a normal route (e.g., oral) to be dispensed from a community pharmacy were included. Medications not intended specifically for the treatment of pain (e.g., cough and cold syrups), opioids with non-normal routes (e.g., intravenous, intramuscular, epidural) to be dispensed from a community pharmacy, and buprenorphine used as treatment for opioid addiction/dependence were excluded.

PDMP variables required for the analysis included drug name, National Drug Code (NDC), de-identified patient ID, patient zip code (Texas data included the five digit zip code and Louisiana data included the first three digits of the zip code for confidentiality of patients within sparsely populated areas), patient year of birth, de-identified prescriber ID, and date dispensed. Other required variables (e.g., drug route, drug schedule, patient county, number of physicians per local area) came from different publically available resources. Each observation was grouped into one of five opioid categories based on NDC: 1) HCPs; 2) schedule II opioids; 3) acetaminophen/codeine; 4) tramadol; and 5) other scheduled opioid analgesics. Each patient

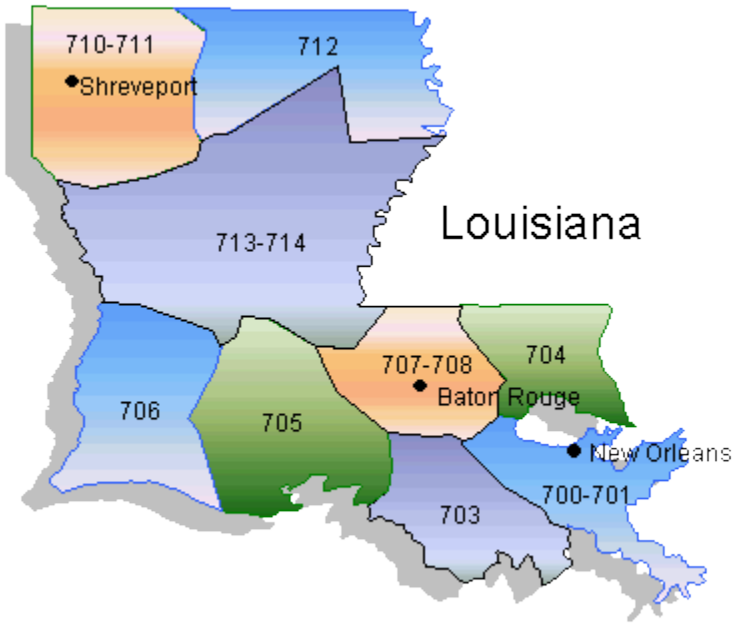
was assigned a local area (county for Texas [Figure 4.2], based on patient zip code, and 3-digit zip code area for Louisiana patients [Figure 4.3]). Physician density (number of physicians per 100,000 population) was calculated for each local area, and grouped into one of four categories: 1) <150; 2) 150-199; 3) 200-249; and 4) ≥250.

Figure 4. 2. Texas Counties (N=254)



Source: (Texas Association of Counties, 2016)

Figure 4. 3. Louisiana Local Areas Using 3-Digit Zip Code (N=13)



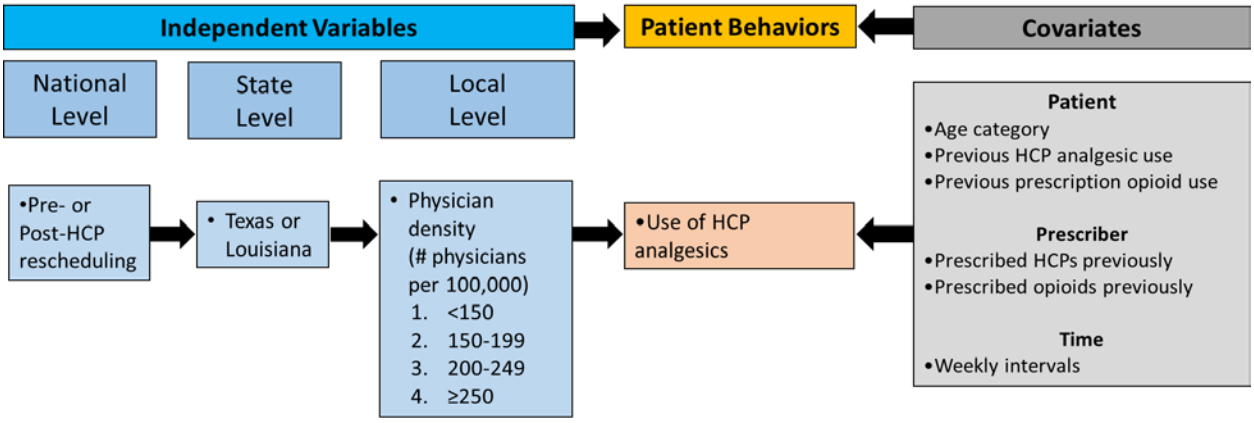
Louisiana Local Areas:

Local Area 1=700
Local Area 2=701
Local Area 3=703
Local Area 4=704
Local Area 5=705
Local Area 6=706
Local Area 7=707
Local Area 8=708
Local Area 9=710
Local Area 10=711
Local Area 11=712
Local Area 12=713
Local Area 13=714

Logistic regression was used to model HCP use (Figure 4.4). Independent variables represented the multiple levels of influence: pre- or post-rescheduling (national level); Texas or Louisiana (state level); and four categories of physician density (local level). Covariates included patient characteristics (age, previous use of the five opioid categories), prescriber

characteristics (prescribed any of the five opioid categories previously), and time (number of weeks since start of data). Two interactions were assessed between: 1) the nation and state levels; and 2) the state and local levels. SAS version 9.3 (SAS Institute Inc., Cary, NC) was used. Statistical significance was set at $p \leq 0.05$.

Figure 4. 4. Operationalization of a Social Ecological Model



Results

Texas data covered June 2, 2014 to July 22, 2015 and Louisiana data covered June 1, 2013 to April 8, 2015. Of the total number of prescriptions (n=22,147,055), most were dispensed in Texas (63.2%). The most dispensed opioids were HCPs (57.8%) (Table 4.1). More patients (n=9,859,311) were from Texas (67.3%) and most were over 65 years of age (22.4%) (Table 4.2).

The logistic regression analysis modeled the probability of a patient to receive a prescription for HCPs among a cohort of patients who received a prescription for an opioid analgesic (Table 4.3). The likelihood of a patient to receive a prescription for an HCP decreased

in both Texas (OR=0.153, 95% CI=0.152-0.154) and Louisiana (OR=0.576, 95% CI=0.573-0.579) on a post-HCP-rescheduling versus pre-HCP-rescheduling basis. Prior to HCP rescheduling, the likelihood of a patient to receive a prescription for an HCP was greater in Texas versus Louisiana for each of the local area categories. After HCP rescheduling, the likelihood of a patient to receive a prescription for an HCP was less in Texas versus Louisiana for local areas with a physician density of less than 199 per 100,000 population, and greater in Texas versus Louisiana for local areas with a physician density of more than 200 per 100,000 population.

Prescribers who had previously prescribed HCPs were more likely to prescribe HCPs than prescribers who had not. Previous prescribing of schedule II opioids, acetaminophen/codeine, and other opioids was associated with a lower likelihood of prescribing HCPs than not.

Patients who previously received an HCP prescription were less likely to receive an HCP prescription (OR=0.092, 95% CI=0.091-0.092) than patients who had not. Patients who previously received a prescription for a schedule II opioid, acetaminophen/codeine, tramadol, or other opioid were more likely to receive a prescription for an HCP than patients who had not received a prescription for that particular opioid. Patients who were under 44 years of age or over 65 and older were less likely to receive a prescription for an HCP versus patients aged 45-54.

Table 4. 1. Number of Prescriptions, Patients, and Prescribers by Opioid Category

Opioid Category	Number of Prescriptions, N (%)	Number of Patients, N (%) [a]	Number of Prescribers, N (%)[b]
HCP	12,801,041 (57.8)	5,913,036 (60.0)	85,684 (73.3)
C-II	2,520,567 (11.4)	1,125,925 (11.4)	30,995 (26.5)
APAP/codeine	2,731,355 (12.3)	2,042,803 (20.7)	67,298 (57.6)
Tramadol	3,757,356 (17.0)	2,167,213 (22.0)	70,739 (60.5)
Other opioid[c]	336,736 (1.5)	101,244 (1.0)	10,230 (8.8)
Total	22,147,055 (100.0)	9,859,311 (100.0)	116,881 (100.0)

[a]Percentages do not sum to 100% since patients could be taking opioids from more than one opioid category

[b]Percentages do not sum to 100% since prescribers could prescribe opioids from more than one opioid category

[c]Other opioid=Opioid analgesic not included in other categories (e.g., pentazocine)

Abbreviations: HCP=hydrocodone combination product; APAP=acetaminophen

Table 4. 2. Number of Prescriptions and Patients by Age

Variable	Categories	Number of Prescriptions, N (%)	Number of Patients, N (%)
Age	Under 18	592,348 (2.7)	496,987 (5.0)
	18 – 24	909,312 (4.1)	670,908 (6.8)
	25 – 34	2,510,109 (11.3)	1,445,651 (14.7)
	35 – 44	3,148,331 (14.2)	1,479,514 (15.0)
	45 – 54	4,388,122 (19.8)	1,745,976 (17.7)
	55 – 64	4,927,514 (22.3)	1,809,548 (18.4)
	Over 65	5,671,319 (25.6)	2,210,727 (22.4)
	Total	22,147,055 (100.0)	9,859,311 (100.0)

Table 4. 3. Results of Logistic Regression Analysis Modeling the Use of Hydrocodone Combination Products[a]

Category	Independent Variable	Estimate (SE)	Wald Chi-Square	OR (95% CI)
	Intercept	-4.354 (0.011)[b]	152344.7	-
National	Nation (Post- vs. Pre-[c] HCP rescheduling)	-0.552 (0.003)[b]	43027.3	-
State	State (Texas vs. Louisiana[c])	1.288 (0.004)[b]	128358.3	-
Local	Local (Number of Physicians per 100,000 population [150 - 199 vs. <150[c]])	0.231 (0.003)[b]	6175.2	-
	Local (Number of Physicians per 100,000 population [200 - 249 vs. <150[c]])	0.034 (0.003)[b]	171.3	-
	Local (Number of Physicians per 100,000 population [>250 vs. <150[c]])	-0.124 (0.003)[b]	2236.0	-
National & State Interaction	Nation (Post- vs. Pre-[c] HCP rescheduling) * State (Texas vs. Louisiana[c])	-1.326 (0.004)[b]	178001.5	Post vs. Pre, TX: 0.153 (0.152-0.154) Post vs Pre, LA: 0.576 (0.573-0.579)
National, State, & Local Interaction	-	-	-	TX vs. LA, Pre, Local (<150): 3.628 (3.603-3.654) TX vs. LA, Post, Local (<150): 0.963 (0.958-0.969) TX vs. LA, Pre, Local (150-199): 2.767 (2.746-2.788) TX vs. LA, Post, Local (150-199): 0.735 (0.730-0.739)

				TX vs. LA, Pre, Local (200-249): 3.822 (3.795-3.849) TX vs. LA, Post, Local (200-249): 1.015 (1.009-1.100) TX vs. LA, Pre, Local (>250): 4.125 (4.099-4.152) TX vs. LA, Post, Local (>250): 1.095 (1.090-1.100)
State & Local Interaction	State (Texas vs. Louisiana[c]) * Local (Number of Physicians per 100,000 population [150 - 199 vs. <150[c]])	-0.271 (0.004)[b]	5251.9	Local (150 - 199 vs. <150), TX: 0.960 (0.956-0.956) Local (150 - 199 vs. <150), LA: 1.259 (1.252-1.266)
	State (Texas vs. Louisiana[c]) * Local (Number of Physicians per 100,000 population [200 - 249 vs. <150[c]])	0.052 (0.003)[b]	225.0	Local (200 - 249 vs. <150), TX: 1.089 (1.084-1.094) Local (200 - 249 vs. <150), LA: 1.034 (1.029-1.039)
	State (Texas vs. Louisiana[c]) * Local (Number of Physicians per 100,000 population [>250 vs. <150[c]])	0.128 (0.003)[b]	1691.7	Local (>250 vs. <150), TX: 1.005 (1.001-1.008) Local (>250 vs. <150), LA: 0.883 (0.879-0.888)
Prescriber History	Prescribed HCPs previously (Yes vs. No[c])	0.995 (0.008)[b]	14749.2	2.704 (2.661-2.748)
	Prescribed C-II opioids previously (Yes vs. No[c])	-0.025 (0.003)[b]	7376.1	0.778 (0.773-0.782)

Prescriber History (cont.)	Prescribed acetaminophen/codeine previously (Yes vs. No[c])	-0.177 (0.002)[b]	6872.0	0.838 (0.834-0.841)
	Prescribed tramadol previously (Yes vs. No[c])	0.170 (0.003)[b]	3487.6	1.185 (1.178-1.191)
	Prescribed other opioids previously (Yes vs. No[c])	-0.120 (0.002)[b]	2470.7	0.887 (0.883-0.891)
Patient History	Received HCPs previously (Yes vs. No[c])	-2.391 (0.002)[b]	2136281.6	0.092 (0.091-0.092)
	Received C-II opioids previously (Yes vs. No[c])	1.880 (0.002)[b]	885777.5	6.554 (6.528-6.580)
	Received acetaminophen/codeine previously (Yes vs. No[c])	2.203 (0.002)[b]	1238185.2	9.053 (9.018-9.088)
	Received tramadol previously (Yes vs. No[c])	1.802 (0.002)[b]	1134844.2	6.060 (6.040-6.080)
	Received other opioids previously (Yes vs. No[c])	1.674 (0.006)[b]	78591.0	5.334 (5.272-5.397)
Patient Age	< 18 years (vs. 45 – 54 years[c])	-0.930 (0.004)[b]	46780.5	0.395 (0.391-0.398)
	18 – 24 years (vs. 45 – 54 years[c])	-0.462 (0.003)[b]	18021.0	0.630 (0.626-0.634)
	25 – 34 years (vs. 45 – 54 years[c])	-0.290 (0.002)[b]	18182.4	0.749 (0.745-0.752)
	35 – 44 years (vs. 45 – 54 years[c])	-0.128 (0.002)[b]	4432.1	0.880 (0.876-0.883)
	55 – 64 years (vs. 45 – 54 years[c])	0.022 (0.002)[b]	181.5	1.023 (1.019-1.026)
	≥ 65 years (vs. 45 – 54 years[c])	-0.069 (0.002)[b]	1803.3	0.934 (0.931-0.937)
Time	Week Number	-0.008 (0.000042)[b]	38207.9	0.992 (0.992-0.992)

[a]Modeling use of hydrocodone combination products (Yes vs. No[c])

[b]$p<0.0001$ for all estimates

[c]Category reference

Abbreviations: SE=standard error; OR=odds ratio; CI=confidence interval; HCP=hydrocodone combination product; TX=Texas; LA=Louisiana

Notes: Logistic model c-statistic=0.860. The "Local" category was defined as physician density (number of physicians per 100,000 population).

Discussion

Results reinforced the application of a social ecological model to assess the impact of multiple levels of influence on HCP use. Levels included national, state, and local environments. At the national level, HCP rescheduling was associated with a significant reduction in HCP use. This effect was evident at the state and local levels. This was the original intention of the DEA, and the impact was evident at both the state and local levels. The impact on patient care has yet to be assessed in the literature. Patient outcomes such as pain control, addiction, and mortality have not yet been assessed. However, evidence of patients substituting heroin or other illicit drugs for prescription opioids in an effort to relieve pain have surfaced in the literature (Cicero, Ellis, & Harney, 2015; Compton, Jones, & Baldwin, 2016; Levi et al., 2015; Rudd, Aleshire, Zibbell, & Gladden, 2016). Additionally, HCP rescheduling was temporarily associated with a decrease in HCP exposures and an increase in codeine, oxycodone and tramadol exposures reported to Texas Poison Centers (Haynes, Kleinschmidt, Forrester, & Young, 2016). Long-term effects of HCP rescheduling will need to be assessed in the future.

At the state level, HCP use was influenced by regulations concerning controlled substance prescribing which varied between the states of Texas and Louisiana. The decision to use these two states was to underscore differences at the state level of schedule II prescribing regulations. While these states share many of the same inherent characteristics, regulations regarding C-IIs are quite different. Schedule II prescribing in Texas is more conservative than most states, while Louisiana is more similar to most other states. Specifically, Texas requires prescribers to use serialized prescription pads (i.e., triplicate forms) and mid-level practitioners

are not able to prescribe C-IIs. These two regulations further restrict C-II prescribing in Texas, which was evident in the differences across the states found in the interaction of the nation and state in the model. On a post- versus pre-rescheduling basis, the likelihood of a patient to receive an HCP prescription was less for Texas than Louisiana (OR=0.153 versus OR=0.576), due at least in part to the differences in state regulations regarding controlled substance prescribing. It should be noted that other inherent differences between Texas and Louisiana exist and are part of the effect found in the model. However, since these controlled substance prescribing regulations specifically target C-II prescribing, these regulations may be the most influential single difference between the two states regarding prescription opioid use.

At the local level, physician density was a significant predictor of HCP use, though the effect was limited. Within the state of Texas, the difference of the effect of physician density between local areas was within 9%. Within the state of Louisiana, the difference in the effect of physician density between local areas was within 26%. Additionally, the effect of a local area with a physician density of 150-199 per 100,000 versus a local area with less than 150 physicians per 100,000 was associated with a reduction of HCP use of 4% in Texas and an increase of 25.9% in Louisiana. This shows that the effect of local areas on HCP use was not consistent across states. This could have multiple explanations, including: multi-county areas used in Louisiana versus the county level basis in Texas; other local characteristics not assessed in the model were factors; local areas should be matched on variables other than physician density alone; or local areas grouped by population level characteristics may not be as impactful as state and national level characteristics. This last explanation is aligned with the

discussion by Paulozzi et al., who stated that population level characteristics, including available prescribers, ethnicity, and socioeconomic status only explained a small amount of variation in opioid prescribing rates (Leonard J. Paulozzi, Strickler, Kreiner, & Koris, 2015). It should be noted that in a study examining geographic variation in opioid prescribing, it was found that physician density was the most impactful factor associated with opioid prescribing (McDonald, Carlson, & Izrael, 2012).

This study proposed a social ecological model using levels which were both meaningful and actionable. Federal regulations concerning prescription opioids apply to all states. Similarly, state regulations concerning prescription opioids affect all areas within the state. Local areas, such as counties or areas grouped by zip code do not necessarily have the ability to enact regulations, though similar areas may have certain characteristics which could influence opioid prescribing. Other population or group level organizations influence opioid prescribing, including physician organizations, managed care organizations, and patient advocacy organizations. With a c-statistic of 0.860, the measure of discrimination of the model was considered good. This helps to justify the potential appropriate application of a social ecological model with this population level data. It should be noted that this model was intended to explain, rather than to predict HCP use.

The inclusion and exclusion criteria for the study were chosen to create of cohort of patients with similar characteristics, specifically patients who received a prescription for either an HCP or similar opioid. Long-acting opioids or opioids administered through a route other

than that typically dispensed from a community pharmacy were not considered similar enough to HCPs.

The findings of the study should be understood in light of several limitations. Limited patient (e.g., diagnosis, comorbidities, health insurance status, level of pain control) and prescriber (e.g., type [medical doctor, physician assistant], specialty, experience) characteristics were available in the dataset, leading to a limited ability to control for confounders for patients and prescribers. Data from Louisiana was not able to be attributed to a particular parish, limiting the ability to generalize the concept of the "local area" to be county or parish-specific. Data was obtained from Texas and Louisiana, so the ability to generalize the results to other states is limited.

Conclusion

The proposed social ecological model was applicable in assessing the influence of multiple levels (national, state, and local) on HCP use. At the national level, HCP rescheduling was associated with a reduction in HCP use for the cohort. At the state level, schedule II prescribing regulation differences between Texas and Louisiana were associated with a greater reduction in HCP use in Texas versus that of Louisiana. At the local level, limited variation in local areas grouped by physician density was found. The impact of population level interventions implemented at multiple levels can be assessed using a social ecological model. Future studies are warranted to assess the application of the model to other populations, and the impact of reduced HCP use on patient care.

CHAPTER 5: MANUSCRIPT 2

Use of Buprenorphine as Opioid Addiction/Dependence Treatment: Assessing the Impact of Multiple Levels of Influence

Abstract

Background: Factors from multiple levels of external influence impact the use of medication therapy, including federal interventions, state policies, local environment, physician prescribing patterns, pharmacy characteristics, patient behavior, and other factors. The use of buprenorphine as opioid addiction/dependence treatment is also influenced by these factors. With the epidemic of opioid abuse in the US, the use of buprenorphine on an outpatient basis is an effective option for patients suffering from opioid addiction/dependence. The objective of this study was to assess the impact of these multiple levels of external influence on buprenorphine use, through application of a social ecological model.

Methods: A retrospective cohort design was employed using data from the Texas and Louisiana prescription drug monitoring programs (PDMPs). This data contains prescription level information for all controlled substances dispensed from community pharmacies for the time period covered. The dependent variable was the use of buprenorphine as opioid addiction/dependence treatment. Logistic regression analysis was used to assess the effect of the independent variables from the national, state, and local levels.

Results: The c-statistic for the model was 0.917. The effect of hydrocodone combination product (HCP) rescheduling at the national level was associated with an increase of

buprenorphine as opioid addiction/dependence treatment in Texas, and a decrease of buprenorphine in Louisiana. Prescribers who previously prescribed HCPs were less likely to prescribe buprenorphine as opioid addiction/dependence treatment. Patients who were previously prescribed HCPs, C-IIs, acetaminophen/codeine, or tramadol were more likely to receive a prescription of buprenorphine than if they had not received prior. Patients aged ≤45 or ≥65 years were more likely to receive a buprenorphine prescription.

Conclusion: Use of buprenorphine as opioid addiction/dependence treatment depended on multiple factors from multiple levels of external influence. A national intervention, state characteristics, and local area DATA-certified physician density were all influential on the use of buprenorphine as opioid addiction/dependence treatment. The design of future interventions should take into consideration the targeted level of external influence in order to maximize its effectiveness.

Introduction

The drug abuse problem in the US has reached epidemic levels according to the Centers for Disease Control and Prevention (Leonard J. Paulozzi et al., 2012). Fueling much of the problem is the escalating non-medical use of prescription analgesic opioids (Levi et al., 2015). Prescription opioid analgesic use increased by over four times from 1999 to 2011, and mortality from prescription analgesic use increased a similar amount over the same timeframe (Levi et al., 2015).

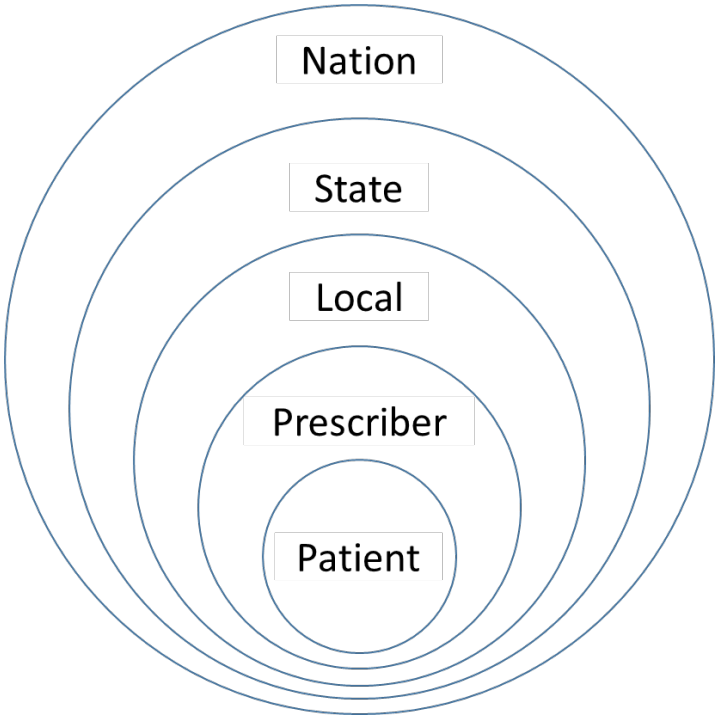
One of the key interventions to counter the inevitable consequence of opioid addiction/dependence was to remove barriers to increase access to treatment. In 2000, the Drug Addiction Treatment Act (DATA) was signed into law (US Congress, 2000). This law allowed buprenorphine to be used for the treatment of opioid addiction/dependence in an outpatient setting, which had previously only been available as inpatient therapy. Physicians who meet the qualifications can become DATA certified with either a 30 patient or 100 patient limit through the Substance Abuse and Mental Health Services Administration (SAMHSA) (Substance Abuse and Mental Health Services Administration, 2015a). Buprenorphine was shown to be associated with a relatively low risk of respiratory depression and abuse (Walsh et al., 1994), yet still as effective at treating opioid addiction/dependence as methadone (Fudala et al., 2003; Johnson et al., 1995; Kosten et al., 1993; Ling et al., 1996).

With different priorities and challenges facing different parts of the country, governments at different levels (e.g., state, county) are also able to target specific aspects of drug abuse. For example, Texas had a relatively low age-adjusted drug overdose mortality rate of 8.2/100,000 population versus Louisiana with a relatively elevated drug overdose mortality rate of 17.9/100,000 population in 2007 (Manchikanti, Fellows, Ailinani, & Pampati, 2010).

The study purpose was to identify the impact of multiple levels of influence on the use of buprenorphine as opioid addiction/dependence treatment in the context of a social ecological model. The theory of social ecology has successfully been applied since the 1980s to explain the interconnected nature of different environments and their respective influence on behaviors (Figure 5.1) (Bronfenbrenner, 1977, 1979, 1994; Centers for Disease Control and

Prevention, 2015c; McLeroy et al., 1988; Stokols, 1996; Sweat & Denison, 1995). Variation between different environments were assessed in terms of use of buprenorphine as opioid addiction/dependence treatment, with the intention of identifying possible levels of future interventions and the areas of influence to be targeted by these interventions. The objective of this study was to assess the impact of different levels of governmental influence on the use of buprenorphine as opioid addiction/dependence treatment, specifically in the neighboring states of Texas and Louisiana.

Figure 5. 1. Proposed Social Ecological Model



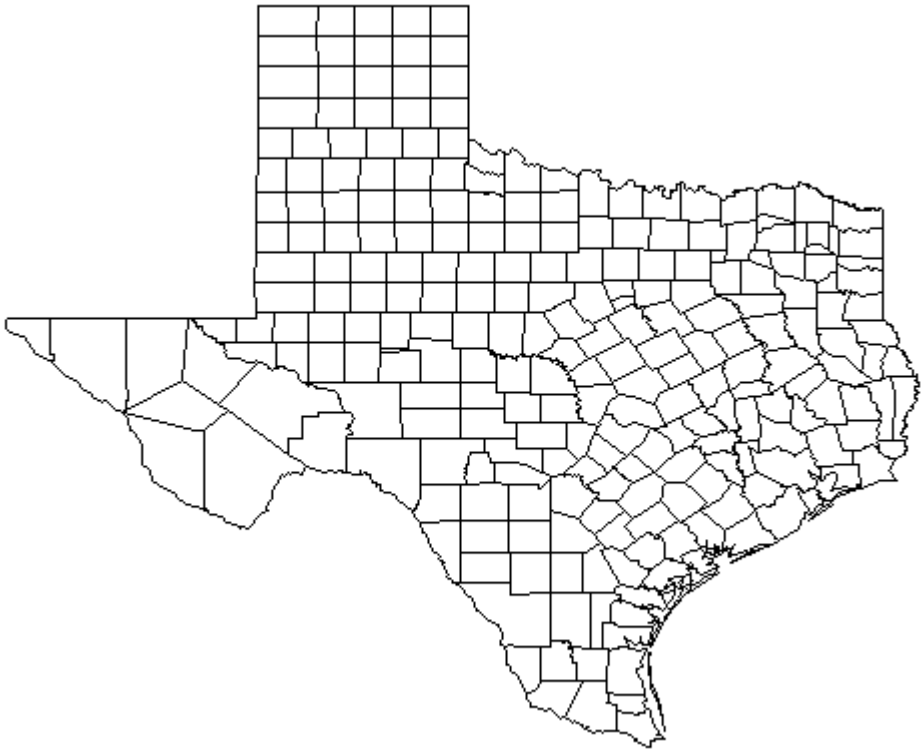
Methods

A retrospective cohort study design was employed using de-identified data from the Texas and Louisiana prescription drug monitoring programs (PDMPs). PDMPs are state operated electronic databases which collect prescribing and dispensing information related to controlled prescription drugs dispensed within the state from community and outpatient pharmacy settings. Administrators of the PDMPs from Texas and Louisiana are authorized to make available de-identified information to a limited number of requestors for the purposes of research.

All prescriptions of opioid analgesics were included in the analysis. Variables included in the analysis were drug name, National Drug Code (NDC), de-identified patient ID, patient zip code (Texas supplied the 5-digit zip code and Louisiana supplied the first three digits of the zip code for confidential purposes of patients in sparsely populated areas), patient year of birth, de-identified prescriber ID, and date dispensed. Other variables included in the analysis (e.g., patients' county of residence, drug schedule, number of DATA-certified physicians per local area) were collected from publically available resources. Each prescription was grouped into one of six opioid categories, based on NDC: 1) buprenorphine as opioid addiction/dependence treatment (e.g., Suboxone®, Subutex®); 2) hydrocodone combination products (HCPs); 3) schedule II opioids; 4) acetaminophen/codeine; 5) tramadol; and 6) other scheduled opioid analgesics. Each patient was assigned a local area (county for Texas [Figure 5.2], based on patient zip code, and a 3-digit zip code area for Louisiana patients [Figure 5.3]). DATA-certified physician density (number of DATA-certified physicians per 100,000 population) was calculated

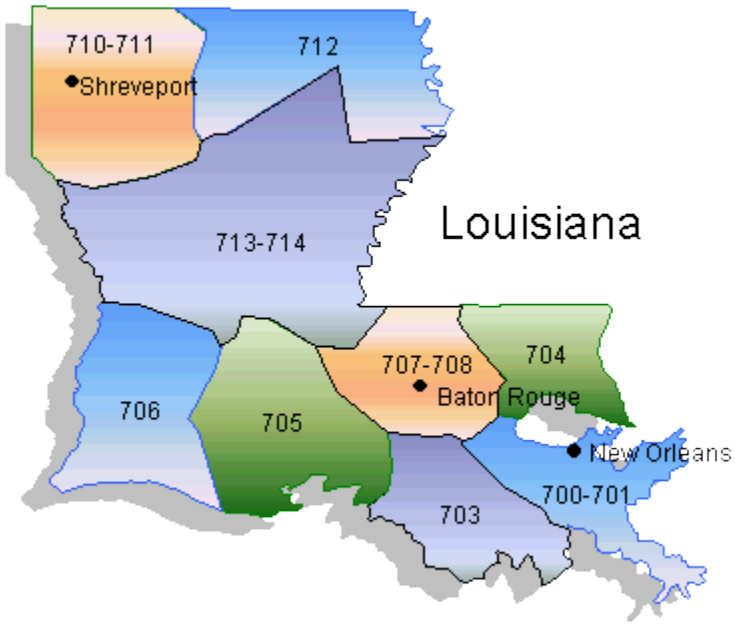
for each local area, and subsequently grouped into one of four categories: (1) <1.0; (2) 1.0-1.9; (3)2.0-3.5; and (4) ≥ 3.5.

Figure 5. 2. Texas Counties (N=254)



Source: (Texas Association of Counties, 2016)

Figure 5. 3. Louisiana Local Areas Using 3-Digit Zip Code (N=13)



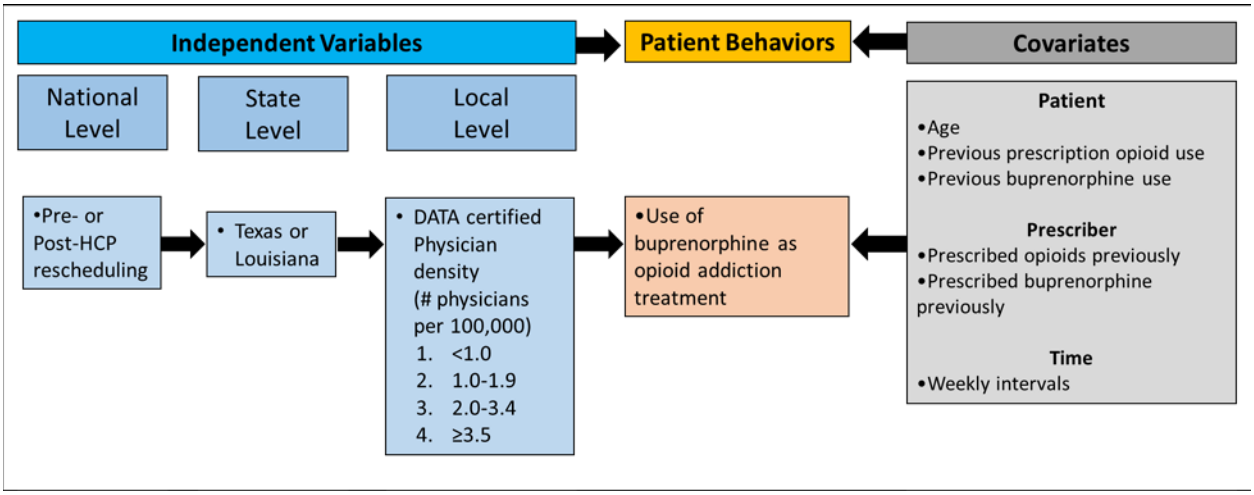
Louisiana Local Areas:

Local Area 1=700
Local Area 2=701
Local Area 3=703
Local Area 4=704
Local Area 5=705
Local Area 6=706
Local Area 7=707
Local Area 8=708
Local Area 9=710
Local Area 10=711
Local Area 11=712
Local Area 12=713
Local Area 13=714

Logistic regression was used to model the binary dependent variable - the prescription of buprenorphine as opioid addiction/dependence treatment - among a cohort of patients taking prescription opioids (Figure 5.4). Independent variables represented the multiple levels of influence: pre- or post-HCP rescheduling (national level); Texas or Louisiana (state level); and

four categories of DATA-certified physician density per 100,000 population (local level). Covariates included patient characteristics (age, previous use of the six opioid categories), prescriber characteristics (previously prescribed any of the six opioid categories), and time (number of weeks since start of data). Two interactions were assessed between: 1) the national and state levels; and 2) the state and local levels. SAS version 9.2 (SAS Institute Inc., Cary, NC) was used. Statistical significance was set at $p \leq 0.05$.

Figure 5. 4. Operationalization of a Social Ecological Model



Results

The final cohort included 25,727,238 opioid prescriptions (59.8% from Texas). Texas data covered a timeframe from June 2, 2014 to July 22, 2015 and Louisiana data covered June 1, 2013 to April 8, 2015. Most patients who were prescribed opioids were over age 65 (22.6%) (Table 5.1). Across all opioid categories, most prescriptions were for HCPs (49.8%) (Table 5.2).

Of the 101,490 patients who were prescribed buprenorphine as opioid addiction/dependence treatment, 45.6% were from Texas. Most patients who were prescribed

buprenorphine were aged 25 to 34 (37.9%) for both states (Table 5.3). The logistic regression model accounted for interactions between the national, state, and local levels. The results of the model are shown in Table 5.4. The overall model resulted with a c-statistic of 0.917.

Rescheduling hydrocodone combination products (HCPs) was associated with an increase of buprenorphine prescriptions in Texas (OR=1.091, 95% CI=1.078 – 1.105) and a decrease of buprenorphine prescriptions in Louisiana (OR=0.986, 95% CI=0.975 – 0.998).

The inherent characteristics of the state of Texas were associated with a lower likelihood to receive a prescription of buprenorphine as opioid addiction/dependence treatment versus Louisiana, prior to HCP rescheduling, for each of the four local areas. The effect of the inherent characteristics of the state of Texas were associated with a lower likelihood to receive a prescription of buprenorphine as opioid addiction/dependence treatment versus Louisiana, after HCP rescheduling, for three of the four local areas (1.0-1.9, 2.0-3.4, and ≥3.5).

The effect of the inherent characteristics of each local area with a DATA-certified physician density of ≥ 1.0 per 100,000 population, for each state, was associated with an increased likelihood to receive a prescription of buprenorphine as opioid addiction/dependence treatment versus local areas with a DATA-certified physician density of < 1.0 per 100,000.

Prescribers who previously prescribed buprenorphine as opioid addiction/dependence treatment were more likely to prescribe buprenorphine as opioid addiction/dependence treatment versus physicians who did not.

Patients who were previously prescribed HCPs, C-II opioids, acetaminophen/codeine, tramadol, or other opioids were more likely to receive buprenorphine prescriptions than patients who had not. Patient who were <24, 25-34, and ≥65 years were more likely to receive a prescription for buprenorphine as opioid addiction/dependence treatment than patients who were 45-54 years.

Table 5. 1. Number of Prescriptions and Patients by Age Category

Variable	Categories	Number of Prescriptions, N (%)	Number of Patients, N (%)
Age	Under 24	1,595,931 (6.2)	1,201,972 (11.6)
	25 – 34	2,993,558 (11.6)	1,531,439 (14.7)
	35 – 44	3,721,970 (14.5)	1,536,282 (15.0)
	45 – 54	5,113,318 (19.9)	1,842,991 (17.7)
	55 – 64	5,735,785 (22.3)	1,911,730 (18.4)
	Over 65	6,566,676 (25.5)	2,350,868 (22.6)
	Total	25,727,238 (100.0)	10,402,282 (100.0)

Table 5. 2. Number of Prescriptions, Patients, and Prescribers by Opioid Category

Opioid Category	Number of Prescriptions, N (%)[a]	Number of Patients, N (%)[b]	Number of Prescribers, N (%)[c]
HCP	12,801,041 (49.8)	5,913,036 (56.8)	91,663 (74.6)
C-II	4,128,496 (16.1)	1,379,002 (13.3)	36,675 (29.8)
APAP/codeine	2,731,355 (10.6)	2,042,803 (19.6)	69,147 (56.2)
Tramadol	4,987,736 (19.4)	2,695,955 (25.9)	82,019 (66.7)
Other opioid[d]	336,736 (1.3)	101,244 (1.0)	11,248 (9.2)
Buprenorphine (as opioid addiction treatment)	741,874 (2.9)	110,490 (1.1)	3,739 (3.0)
Total	25,727,238 (100.0)	10,402,282 (100.0)	122,955 (100.0)

[a]Percentages do not sum to 100% due to rounding
[b]Percentages do not sum to 100% since patients could be taking opioids from more than one opioid category
[c]Percentages do not sum to 100% since prescribers could prescribe opioids from more than one opioid category
[d]Other opioid=Opioid analgesic not included in other categories (e.g., pentazocine)
Abbreviations: HCP=hydrocodone combination product; APAP=acetaminophen

Table 5. 3. Number of Prescriptions and Patients with Buprenorphine as Opioid Addiction/Dependence Treatment by Age

Variable	Categories	Number of Prescriptions, N (%)	Number of Patients, N (%)[a]
Age	Under 24	31,603 (4.3)	6,733 (6.1)
	25 – 34	289,593 (39.0)	41,906 (37.9)
	35 – 44	236,180 (31.8)	32,212 (29.2)
	45 – 54	120,699 (16.3)	17,893 (16.2)
	55 – 64	54,764 (7.4)	9,795 (8.9)
	Over 65	9,035 (1.2)	1,951 (1.8)
	Total	741,874 (100.0)	110,490 (100.0)

[a]Percentages do not sum to 100% due to rounding

Table 5. 4. Results of Logistic Regression Analysis Modeling the Use of Buprenorphine as Opioid Addiction/Dependence Treatment[a]

Category	Independent Variable	Estimate (SE)	Wald Chi-Square	OR (95% CI)
	Intercept	-10.889 (0.034)[b]	101365.6	-
National	Nation (Post- vs. Pre-[c] HCP rescheduling)	-0.014 (0.006)[d]	5.5158	-
State	State (Texas vs. Louisiana [c])	-0.054 (0.016)[e]	11.9056	-
Local	Local (Number of DATA-certified physicians per 100,000 population [1.0 – 1.9 vs. < 1.0[c]])	0.994 (0.014)[b]	5082.9	-
	Local (Number of DATA-certified physicians per 100,000 population [2.0 – 3.4 vs. < 1.0[c]])	1.121 (0.015)[b]	5795.0	-
	Local (Number of DATA-certified physicians per 100,000 population [> 3.5 vs. < 1.0[c]])	1.179 (0.013)[b]	7947.3	-
National & State Interaction	Nation (Post- vs. Pre-[c] HCP rescheduling) * State (Texas vs. Louisiana[c])	0.101 (0.007)[b]	194.8	Post vs. Pre, TX: 1.091 (1.078-1.105) Post vs Pre, LA: 0.986 (0.975-0.998)
National, State, & Local Interaction	-			Pre, TX vs. LA[c], Local (<1.0): 0.948 (0.919-0.977) Post, TX vs. LA[c], Local (<1.0): 1.049 (1.019-1.079) Pre, TX vs. LA[c], Local (1.0–1.9): 0.378 (0.369-0.388)

				Post, TX vs. LA[c], Local (1.0–1.9): 0.419 (0.409-0.428) Pre, TX vs. LA[c], Local (2.0–3.4): 0.437 (0.429-0.445) Post, TX vs. LA[c], Local (2.0–3.4): 0.483 (0.476-0.491) Pre, TX vs. LA[c], Local (≥3.5): 0.655 (0.646-0.664) Post, TX vs. LA[c], Local (≥3.5): 0.724 (0.718-0.731)
State & Local Interaction	State (Texas vs. Louisiana[c]) * Local (Number of DATA-certified physicians per 100,000 population [1.0 – 1.9 vs. < 1.0[c]])	-0.918 (0.018)[b]	2565.7	TX, Local (1.0–1.9 vs. <1.0[c]): 1.079 (1.055-0.104) LA, Local (1.0–1.9 vs. <1.0[c]): 2.702 (2.629-2.777)
	State (Texas vs. Louisiana[c]) * Local (Number of DATA-certified physicians per 100,000 population [2.0 – 3.4 vs. < 1.0[c]])	-0.774 (0.016)[b]	2238.7	TX, Local (2.0–3.4 vs. <1.0[c]): 1.415 (1.395-1.435) LA, Local (2.0–3.4 vs. <1.0[c]): 3.069 (2.981-3.158)
	State (Texas vs. Louisiana[e]) * Local (Number of DATA-certified physicians per 100,000 population [≥ 3.5 vs. < 1.0[c]])	-0.370 (0.015)[b]	622.8	TX, Local (≥3.5 vs. <1.0[c]): 2.246 (2.217-2.276) LA, Local (≥3.5 vs. <1.0[c]): 3.252 (3.168-3.337)
Prescriber History	Prescribed buprenorphine as opioid addiction/dependence treatment previously (Yes vs. No[c])	2.235 (0.019)	13541.6	9.348 (9.003-9.707)

	Prescribed HCPs previously (Yes vs. No[c])	-1.927 (0.009)[b]	43448.5	0.146 (0.143-0.148)
	Prescribed C-II opioids previously (Yes vs. No[c])	-0.148 (0.006)[b]	574.4	0.862 (0.852-0.873)
	Prescribed acetaminophen/codeine previously (Yes vs. No[c])	0.179 (0.005)[b]	1284.0	1.196 (1.184-1.208)
	Prescribed tramadol previously (Yes vs. No[c])	-0.683 (0.006)[b]	15244.9	0.505 (0.500-0.511)
	Prescribed other opioids previously (Yes vs. No[c])	-0.205 (0.005)[b]	1411.1	0.815 (0.806-0.823)
Patient History	Received buprenorphine as opioid addiction/dependence treatment previously (Yes vs. No[c])	-4.418 (0.008)[b]	284498.1	0.012 (0.012-0.012)
	Received HCPs previously (Yes vs. No[c])	3.106 (0.007)[b]	199732.6	22.324 (22.022-22.630)
	Received C-II opioids previously (Yes vs. No[c])	2.763 (0.011)[b]	60030.6	15.854 (15.507-16.208)
	Received acetaminophen/codeine previously (Yes vs. No[c])	3.145 (0.012)[b]	71129.1	23.214 (22.684-23.757)
	Received tramadol previously (Yes vs. No[c])	2.562 (0.009)[b]	87194.8	12.963 (12.744-13.185)
	Received other opioids previously (Yes vs. No[c])	0.187 (0.012)[b]	246.7	1.206 (1.178-1.234)
Patient Age	< 24 years (vs. 45 – 54 years[c])	0.556 (0.007)[b]	5893.6	1.744 (1.719-1.769)
	25 – 34 years (vs. 45 – 54 years[c])	1.745 (0.004)[b]	201893.9	5.726 (5.682-5.770)
	35 – 44 years (vs. 45 – 54 years[c])	1.131 (0.004)[b]	83309.6	3.098 (3.074-3.122)
	55 – 64 years (vs. 45 – 54 years[c])	-0.951 (0.005)[b]	30246.1	0.387 (0.382-0.391)
	≥ 65 years (vs. 45 – 54 years[c])	-2.748 (0.011)[b]	61751.5	6.037 (5.902-6174)
Time	Week Number	0.001 (0.0001)[b]	73.2	1.001 (1.001-1.001)

[a]Modeling use of buprenorphine as opioid addiction treatment (Yes vs. No[c])

[b] $p<0.0001$
[c] Category reference
[d] $p=0.0188$
[e] $p=0.0006$
Abbreviations: SE=standard error; OR=odds ratio; CI=confidence interval; HCP=hydrocodone combination product; TX=Texas; LA=Louisiana; DATA=Drug Addiction Treatment Act
Notes: Logistic model c-statistic=0.917; "Local" category defined as physician density (number of physicians per 100,000 population)

Discussion

Given the current state of epidemic levels associated with prescription opioid analgesic abuse, interventions should continue to be developed to improve patient care. Additionally, interventions should be implemented at multiple levels of influence. At the core of these multiple levels, the patient suffering from opioid addiction/dependence and those in his/her immediate sphere of influence (e.g., spouse, family, friends, physician) have the potential to help the patient the most. However, environmental influences have the potential to foster behavioral change. The aim of this study was to assess the impact of multiple levels of influence on the use of buprenorphine as opioid addiction/dependence treatment.

At the national level, an increase of buprenorphine use was shown in Texas (OR=1.091, 95% CI=1.078-1.105) and a decrease of buprenorphine use in Louisiana (OR=0.986, 95% CI=0.975-0.998) following HCP rescheduling. HCP rescheduling as an intervention, while not aimed at improving opioid addiction/dependence treatment, was impactful toward restricting HCP use. Since HCPs had been the most prescribed drugs in the US from 2008 to 2012 (IMS Health, 2013), this regulation change had the potential to have far-reaching effects, including impacting buprenorphine use. Despite the intention to restrict HCPs, a national intervention was shown to have an impact on opioid addiction/dependence treatment. Additionally, this impact was independent of the effect of time, which accounts for general trends and shifts across the population, or any of the other variables in the model. These findings show the potential influence that a national regulation aimed at improving buprenorphine use could potentially have.

At the state level, for each local level, Texas was associated with a lower likelihood of buprenorphine use than Louisiana, before HCP rescheduling. After HCP rescheduling, Texas was associated with less likelihood of buprenorphine use than Louisiana for each local area (ranging from 5.2% reduction to 42.2% reduction), except <1.0, which was associated with only a slight increase in likelihood (OR=1.049, 95% CI=1.019-1.079) versus the same local area in Louisiana. This variation across states and between similar local areas, underscores that differences exist between these two states.

At the local level, each local area, both in Texas and Louisiana, were associated with an increased likelihood of buprenorphine use for each subsequent increase in DATA-certified physician density category, from lowest to highest. In other words, as the number of DATA-certified physicians per 100,000 increased, so did the likelihood of buprenorphine use. This may indicate that future interventions aimed at increasing the number of available DATA-certified physicians (or increasing their patient limits) could lead to increased use of buprenorphine as opioid addiction/dependence treatment. A proposal to increase the limit of patients who can be treated by DATA-certified physicians is currently under debate in congress (Harris, 2016).

Further, local differences may help to identify areas for future interventions targeted at different local areas. The inclusion of patient age was helpful to compare with other studies which have found opioid abuse and drug overdose mortality for these same age categories to be elevated (Haynes et al., 2016; Leonard J. Paulozzi et al., 2011).

Prescription opioid analgesic abuse is inextricably linked to the use of prescription opioid analgesics. One intervention which holds particular promise is the use of buprenorphine

as opioid addiction/dependence treatment on an outpatient basis. As a nation, it is important to identify potential targets for future interventions at meaningful levels of influence.

Applying a social ecological model for this study identified potential areas to target future interventions. It also identified potential governmental levels at which interventions can be implemented. Additionally, the model assessed the impact of different interventions (e.g., national intervention of rescheduling HCPs). This model accounts for all of the collective characteristics found within each level (national, state, and local).

The findings of the study should be considered with the following limitations. Patient attributes (e.g., diagnosis, racial and ethnic background, socio-economic status) were limited in both PDMP datasets. Therefore, controlling for these patient attributes was not possible. Data from Louisiana was not able to be attributed to a particular parish, limiting the ability to generalize the concept of the "local area" to be county- or parish-specific. These results cannot be considered generalizable to other states.

Conclusion

Application of a social ecological model has utility in assessing the impact of interventions and identifying future targets for interventions at feasible levels of external influence (national, state, and local). Prescription opioid analgesic addiction/dependence is a national concern which necessitates the use of efficiently targeted interventions to treat persons suffering from its effects. Future studies are warranted to more closely identify targets for future interventions to improve patient care for persons suffering from opioid addiction/dependence.

CHAPTER 6: EXECUTIVE SUMMARY

Millions of Americans suffer from pain, which can be treated with a variety of therapies. Prescription opioid analgesics are among the most widely used treatments for pain. The appropriate use of prescription opioid analgesics can be effective as a part of a pain management strategy.

However, a certain degree of risk of abuse, addiction, and dependence is inherently associated with prescription opioid analgesic use. This risk cannot be predicted nor eradicated. Interventions aimed at restricting the use of opioid analgesics have been implemented, the latest of which was rescheduling HCPs from schedule III to schedule II (C-II). This federal intervention affected prescribing patterns across all states, though to varying degrees of which are yet to be determined. This study assessed the trends of HCP use over time, comparing the two neighboring states of Texas and Louisiana. These states have different prescribing policies for C-IIs, as well as other differing inherent characteristics influencing prescription opioid analgesic use. These differences were evident with the changes in prescribing trends for HCPs and other types of prescription opioid analgesics.

Additionally, this study applied a social ecological model to assess the impact of multiple levels of influence on the treatment of opioid addiction/dependence using buprenorphine. The model showed utility in assessing the impact of the population-level influences at the national, state, and local levels. Interventions targeting a specific level of influence may improve patient care through its subsequent effectiveness.

APPENDIX

Appendix A. Data Sources

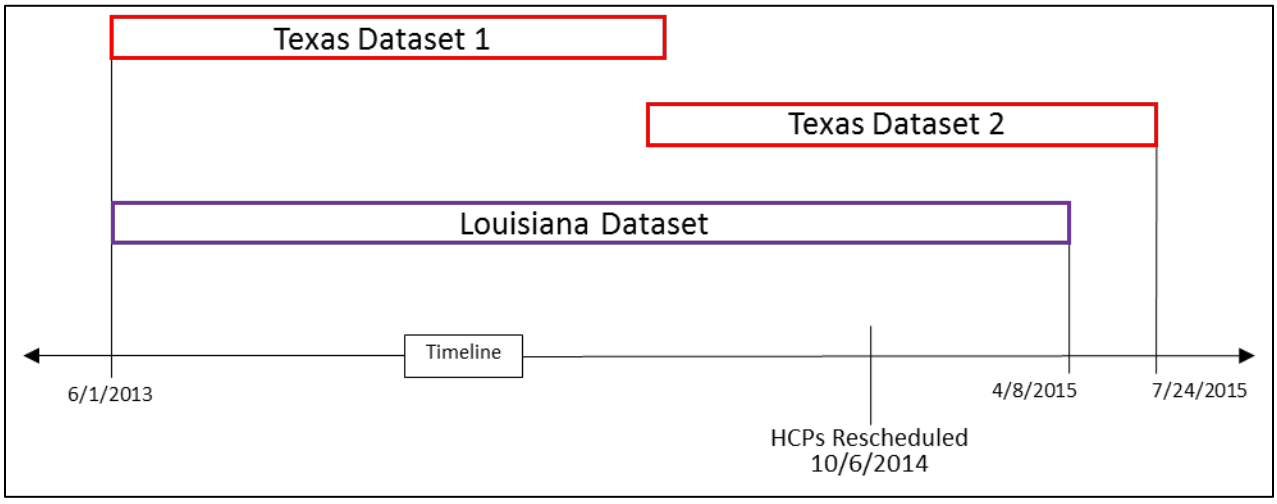
Data Description	Source
De-identified prescription level data for all controlled prescription drugs dispensed from community pharmacies within the state of Texas (no inpatient data)	Texas Department of Public Safety
De-identified prescription level data for all controlled prescription drugs dispensed from community pharmacies within the state of Louisiana (no inpatient data)	Louisiana Board of Pharmacy
NDC codes, other drug information (e.g., strength, morphine milligram equivalent conversion factor, drug class)	Centers for Disease Control and Prevention (CDC)
NDC codes, other drug information (e.g., controlled drug schedule, strength, form, drug class)	US Food & Drug Administration (FDA)
NDC codes, other drug information (e.g., strength, route, form)	Multiple online sources
Buprenorphine providers by Zip (Texas & Louisiana)	SAMHSA
Texas Physician and Physician Assistant data	Texas Medical Board[a]
Louisiana Physician and Physician Assistant data	Louisiana State Board of Medical Examiners[a]
Texas PDMP Registrants (Pharmacist and Prescriber)	Texas Department of Public Safety
Texas Public Health Region	Texas Department of State Health Services
Louisiana Public Health Region	State of Louisiana Department of Health & Hospitals
State, County, City, Zip data	US Census Bureau
County demographics – Texas	Texas Association of Counties
Zip code by county	US Zip Codes.org
Population data	US Census Bureau

Characteristics by zip code (e.g., RUCA codes, urban and rural designations, travel distances and times to urban areas)	University of Washington WWAMI Rural Health Research Center
Mean income and population by zip code	University of Michigan Population Studies Center (Institute for Social Research)

[a]Fee charged for this data

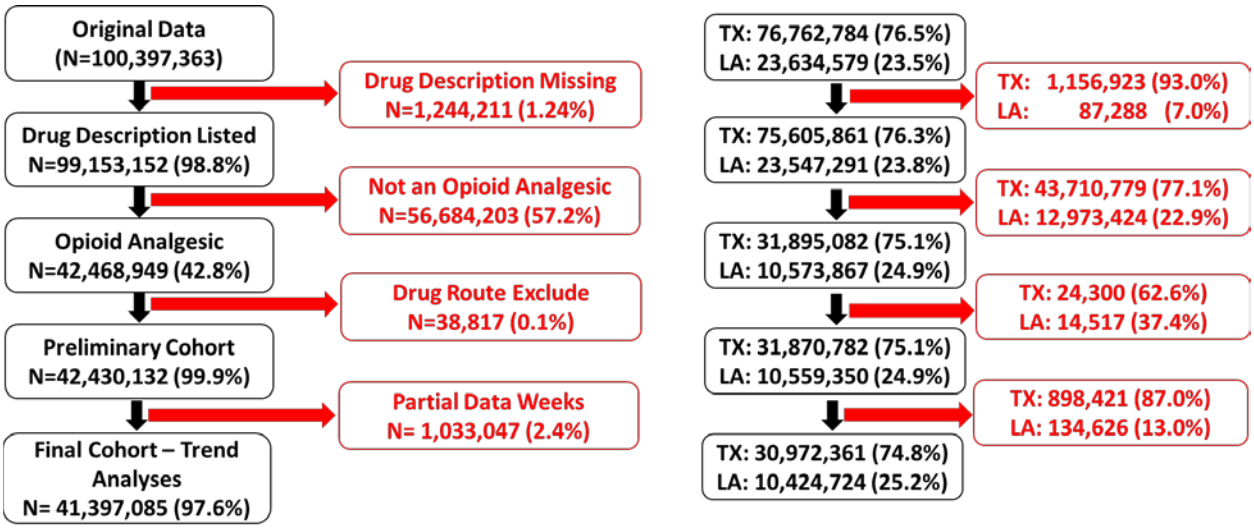
Abbreviations: NDC=National Drug Code; SAMHSA=Substance Abuse and Mental Health Services Administration; PDMP=prescription drug monitoring program; RUCA=Rural Urban Commuting Area; WWAMI=Washington, Wyoming, Alaska, Montana, and Idaho (a collaborative group of universities from these states)

Appendix B. Prescription Drug Monitoring Program Datasets and Timeline

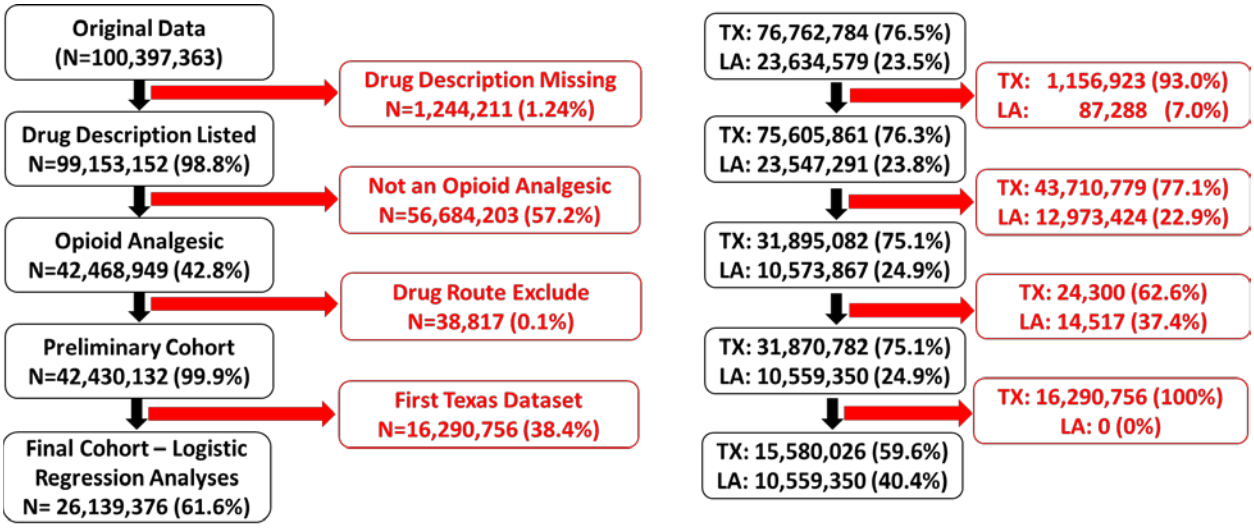


Note: No duplicate observations between any of the three datasets

Appendix C. Final Cohort Identification – Trend Analysis



Appendix D. Final Cohort Identification – Logistic Regression Analysis

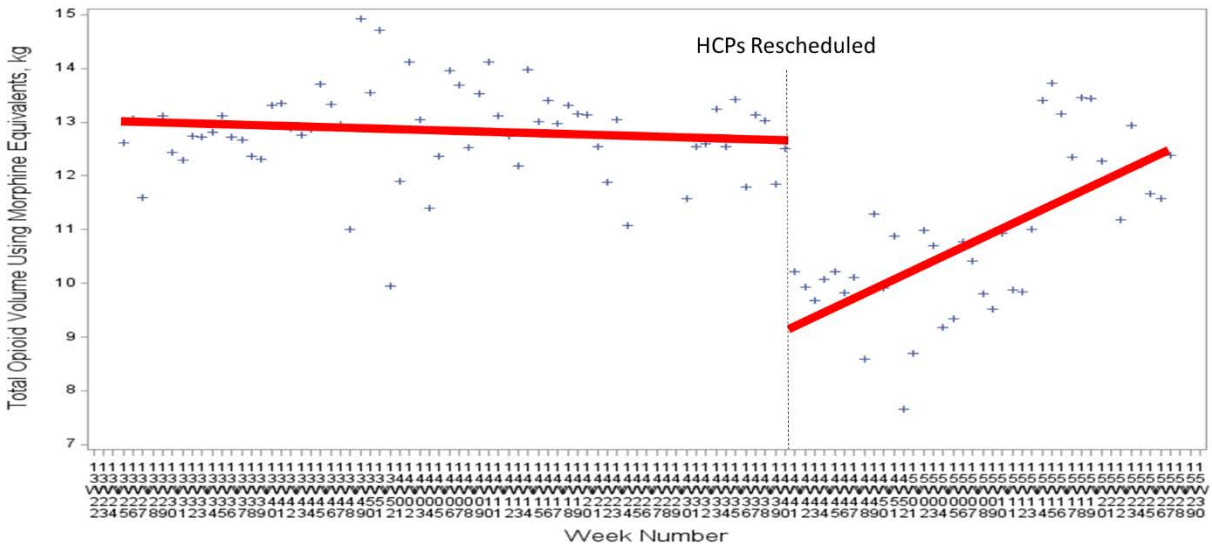


Appendix E. General Population by State

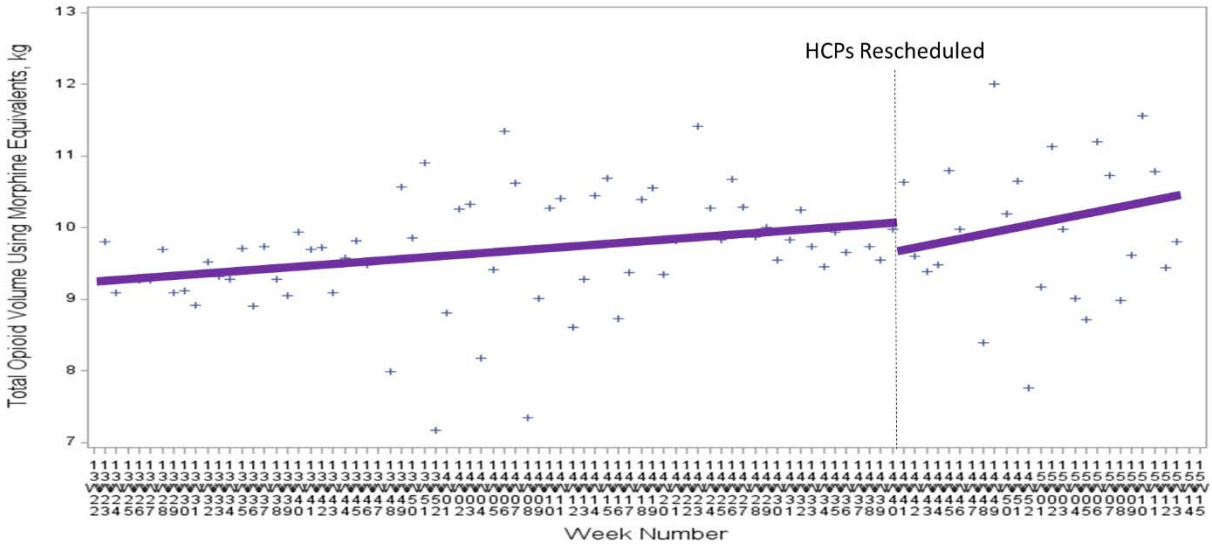
Description	Texas, N (% of both states)	Louisiana, N (% of both states)
General Population (from US Census 2013 estimates)	26,448,193 (85.11)	4,625,470 (14.89)

Source: (US Census Bureau, 2015)

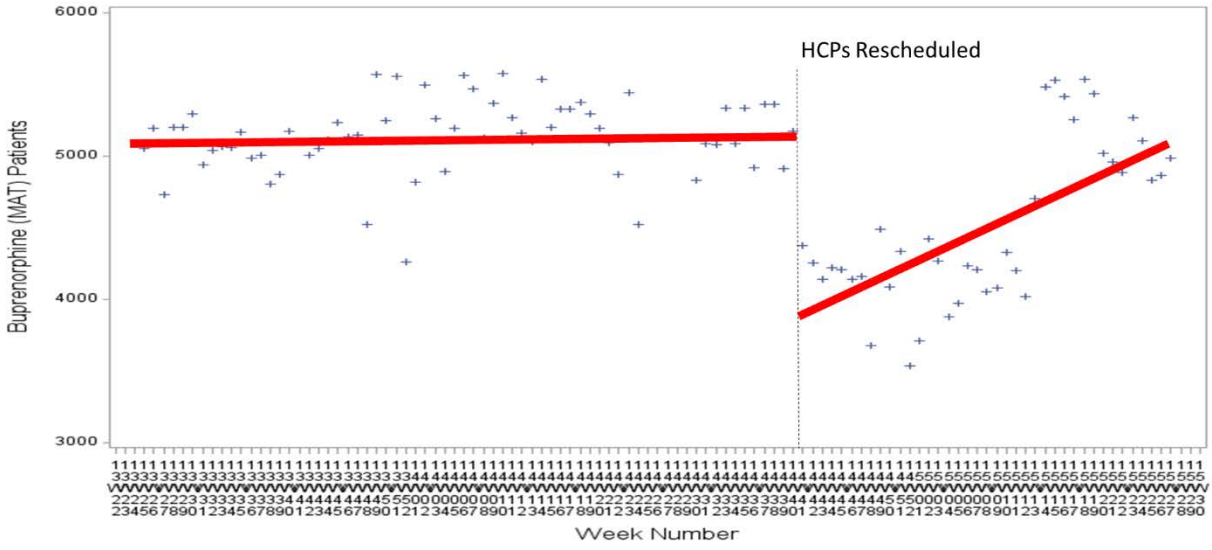
Appendix F. Trend Plot for Buprenorphine as Opioid Addiction Treatment in Texas



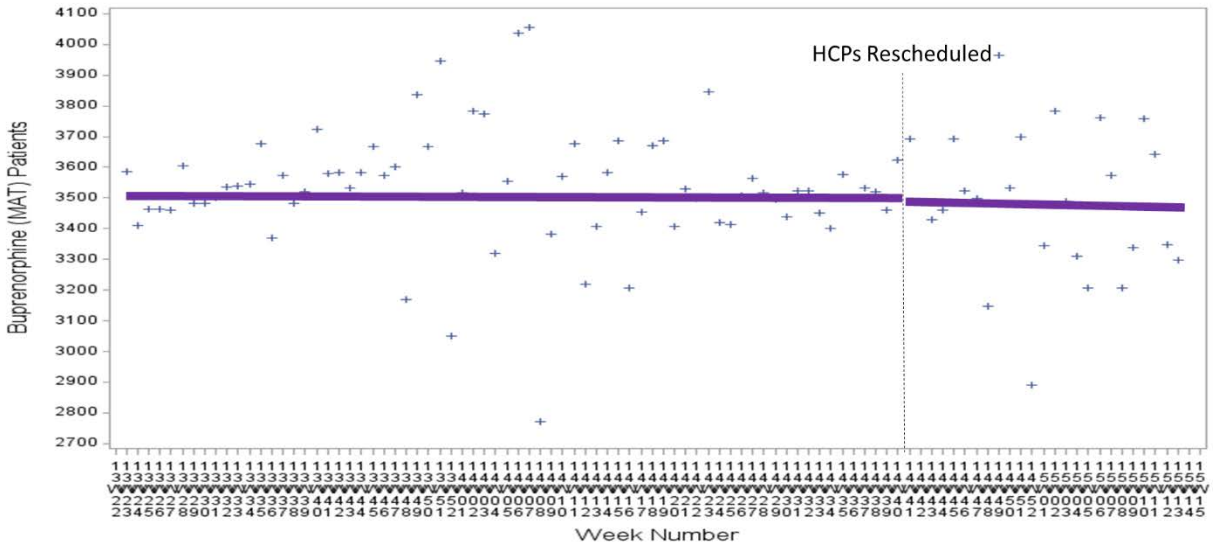
Appendix G. Trend Plot for Buprenorphine as Opioid Addiction Treatment in Louisiana



Appendix H. Trend Plot for Patients Using Buprenorphine as Opioid Addiction/Dependence Treatment - Texas



Appendix I. Trend Plot for Patients Using Buprenorphine as Opioid Addiction/Dependence Treatment - Louisiana



Appendix J. Number of Patients by Opioid Analgesic Type

Opioid Type	Texas, N (Col%, Row%)	Louisiana, N (Col%, Row%)
HCP	3,641,811 (53.10, 60.27)	2,400,236 (64.31, 39.73)
C-II	576,280 (8.40, 40.74)	838,155 (22.46, 59.26)
APAP/codeine	1,832,628 (26.72, 88.17)	245,842 (6.59, 11.83)
Tramadol	4,944,696 (72.09, 63.03)	2,900,723 (77.71, 36.97)
Buprenorphine (as opioid addiction treatment)	52,280 (0.76, 45.66)	62,224 (1.67, 54.34)
Total	6,858,942 (100, 64.76)	3,732,532 (100, 35.24)

Abbreviations: HCP=hydrocodone combination product; APAP=acetaminophen

Appendix K. Number of Prescribers by Opioid Analgesic Type for Logistic Regression Analyses

Opioid Type	Texas, N (Col%, Row%)	Louisiana, N (Col%, Row%)
HCP	67,055 (73.92, 66.74)	33,423 (69.00, 33.26)
C-II	20,502 (22.60, 53.65)	17,709 (36.56, 46.35)
APAP/codeine	58,598 (64.59, 82.43)	12,487 (25.78, 17.57)
Tramadol	64,334 (70.92, 72.53)	24,368 (50.31, 27.47)
Buprenorphine (as opioid addiction treatment)	2,199 (2.42, 48.80)	2,307 (4.76, 51.20)
Total	90,718 (100, 65.19)	48,437 (100, 34.81)

Abbreviations: HCP=hydrocodone combination product; APAP=acetaminophen

Appendix L. Number of Pharmacies by Opioid Type for Logistic Regression Analyses

Opioid Type	Texas, N (Col%, Row%)	Louisiana, N (Col%, Row%)
HCP	5,011 (98.16, 73.70)	1,788 (79.29, 26.30)
C-II	4,601 (90.13, 75.03)	1,531 (67.89, 24.97)
APAP/codeine	4,927 (96.51, 78.74)	1,330 (58.98, 21.26)
Tramadol	4,932 (96.61, 76.48)	1,517 (67.27, 23.52)
Buprenorphine (as opioid addiction treatment)	3,183 (62.35, 76.00)	1,005 (44.57, 24.00)
Total	5,105 (100, 69.36)	2,255 (100, 30.64)

Abbreviations: HCP=hydrocodone combination product; APAP=acetaminophen

Appendix M. Estimates of Total Opioid Volume per Week for Buprenorphine as Opioid Addiction/Dependence Treatment in Morphine Equivalents, kg

Drug Category	State	Volume at Week 1, MME	Rate of Change During Pre-Intervention Period, MME/Week	Immediate Volume Increase or Decrease At Time of Intervention, MME	Rate of Change During Post-Intervention Period, MME/Week
Buprenorphine	**Texas**	13.01 *	-0.006	-3.385 *	0.081 *
	Louisiana	9.31 *	0.009	-0.029	0.017

*p<0.05
Abbreviations: MKE=morphine kilogram equivalent

Appendix N. Estimates of Number of Patients per Week using Buprenorphine as Opioid Addiction/Dependence Treatment in Morphine Equivalents, kg

Drug Category	State	Number of Patients at Week 1	Rate of Change During Pre-Intervention Period, Patients/Week	Immediate Increase or Decrease At Time of Intervention, Number of Patients	Rate of Change During Post-Intervention Period, Patients/Week
Buprenorphine	**Texas**	5099 *	0.71	-1270 *	30.36 *
	Louisiana	3522 *	0.15	-3.9	-2.26

*p<0.05
Abbreviations: MKE=morphine kilogram equivalent

Appendix O. Number of Patients using Buprenorphine as Opioid Addiction/Dependence Treatment by Age

Description	Categories	Texas, N (Col%, Row%)	Louisiana, N (Col%, Row%)
Age	Under 18	19 (0.04, 54.29)	16 (0.03, 45.71)
	18 – 24	3,049 (6.67, 47.96)	3,308 (5.93, 52.04)
	25 – 34	16,212 (35.44, 41.04)	23,289 (41.72, 58.96)
	35 – 44	13,090 (28.62, 43.75)	16,828 (30.15, 56.25)
	45 – 54	7,657 (16.74, 48.22)	8,222 (14.73, 51.78)
	55 – 64	4,757 (10.40, 57.16)	3,565 (6.39, 42.84)
	Over 65	958 (2.09, 61.97)	588 (1.05, 38.03)
	Total	45,742 (100, 45.04)	55,816 (100, 54.96)

Appendix P. Manuscript 3

Assessing the Impact of Rescheduling Hydrocodone Combination Products On Opioid Analgesic Use: A Trend Analysis

Abstract

Background: Factors from multiple levels of external influence impact the use of medication therapy, including federal interventions, state policies, local environment, physician prescribing patterns, pharmacy characteristics, patient behavior, and other factors. The use of opioid analgesics, specifically hydrocodone combination products (HCPs) which had been the most prescribed drugs in the US until 2012, is also influenced by these factors. A federal intervention was implemented in October 2014 when HCPs were rescheduled from C-III to the more restrictive C-II in October 2014. The objective of this study was to assess the impact of HCP rescheduling on prescription opioid analgesic use.

Methods: A retrospective cohort design was employed using data from the Texas and Louisiana prescription drug monitoring programs. This data contains prescription level information for all controlled substances (including opioid analgesics) dispensed from community pharmacies from June 1, 2013 to April 8, 2015. Opioid analgesics were grouped into four categories: 1) HCPs; 2) C-II opioid analgesics (other than HCPs); 3) acetaminophen/codeine; and 4) tramadol. Segmented regression of interrupted time series was used to assess trends across the four categories.

Results: At the start of the study period, Louisiana used a greater amount of HCPs, C-II opioid analgesics, and acetaminophen/codeine on a per capita basis versus Texas. The immediate effect of rescheduling resulted in a decrease of HCPs in both states (41.1 morphine kilogram equivalents [MKE] for Texas and 3.1 MKE for Louisiana) and a significant increase of acetaminophen/codeine in both states (6.8 MKE for Texas and 0.3 MKE for Louisiana), and an increase of tramadol dispensing in Texas (14.6 MKE).

Conclusion: Rescheduling HCPs significantly impacted opioid analgesic use in both states. Supplemental regulations on prescribing C-IIs found in Texas (including the requirement of physicians to use state-supplied C-II prescription pads) were likely influential in reducing HCP dispensing. Additionally, switching to less effective opioid analgesics was found in both states. Future research is warranted to assess the impact on patient care, including patient pain relief and prescription opioid analgesic abuse.

Introduction

Pain affects millions of Americans and is a significant health concern. The 2012 National Health Interview Survey estimated that over the previous three months, 126.1 million of adults had at least some pain, 25.5 million (11.1%) had pain on a daily basis, and 23.4 million (10.3%) had “a lot” of pain during their last pain experience (Nahin, 2015). A study by Gaskin and Richard estimated the prevalence of chronic pain in the US was 100 million, and cost between $560 to $635 billion in 2010 (Gaskin & Richard, 2012).

Physicians often prescribe opioid analgesics for the treatment of pain. Opioid prescribing trends in the US had been on the rise since the 1990s. From 1997 to 2007, retail sales (in terms of grams of medication sold) of hydrocodone increased by 280%, oxycodone increased by 866%, and codeine decreased by 25% (Manchikanti, Fellows, et al., 2010). The US used 99% of the world's hydrocodone supply in 2012 (International Narcotics Control Board, 2013). From 2008 to 2012, HCPs topped the list as the most prescribed drugs in the US from 2008 to 2012 (IMS Health, 2013).

Additionally, mortality associated with prescription opioid analgesic abuse has reached epidemic levels (Leonard J. Paulozzi et al., 2011). From 1999 to 2011, deaths from prescription analgesic used increased by four times (Levi et al., 2015). In 2013, deaths from drug overdoses surpassed that of motor vehicle crashes to become the leading cause of injury deaths. Approximately 36% of drug overdose deaths were associated with prescription analgesics (Levi et al., 2015).

In an effort to curb the problem, the Drug Enforcement Administration (DEA) rescheduled HCPs from schedule III (C-III) to schedule II (C-II) in October 2014 (Federal Register, 2014b). By design, the differences in regulations between schedule II and schedule III are significant. Additional restrictions affect all levels of the supply chain: manufacturing, distributing, prescribing, and dispensing (US Congress, 1970). One significant difference in regulations between C-II and C-III is that prescriptions cannot be refilled for C-IIs. Additionally, variation in supplemental regulations exist between states regarding C-IIs, which could affect use. For example, Texas is the only state which requires prescribers to use serialized

prescription pads when prescribing C-IIs (Texas State Board of Pharmacy, 2014). The neighboring state of Louisiana has no similar supplemental regulation. Further, nurse practitioners (NPs) are not allowed to prescribe C-IIs in Texas (in most outpatient settings), but they are allowed to prescribe C-IIs in Louisiana (Stokowski, 2015). Therefore, the impact of rescheduling HCPs could impact HCP use differently across states.

Since HCP rescheduling could affect prescribing trends of HCPs, use of other alternative opioid analgesics could also be affected. Additionally, patient care in terms of pain management could be affected. The objective of this study was to assess the impact of rescheduling HCPs across the states of Texas and Louisiana on four major categories of opioid analgesics: 1) HCPs; 2) C-IIs (other than HCPs); 3) codeine/acetaminophen; and 4) tramadol.

Methods

A retrospective cohort study was conducted using de-identified data from the Texas and Louisiana prescription drug monitoring programs (PDMPs). These databases contain prescription-level data for each C-II to C-V medication dispensed from community pharmacies classified as outpatient. State regulations allow administrators of the PDMP data at the state of Texas (Prescription Access in Texas [PAT], operated by the Texas Department of Public Safety) and the state of Louisiana (Prescription Monitoring Program [PMP], operated by the Louisiana Board of Pharmacy) to allow access to a limited number of researchers to assess epidemiological trends using the de-identified data.

Key variables in the dataset included the drug name, National Drug Code (NDC), drug strength, quantity supplied, and date dispensed. Transactions were included if the drug prescribed was listed in Table 2.2, and grouped by opioid category. Note that tramadol was categorized as a synthetic opioid. Additionally, only opioid analgesics were included. Buprenorphine used as opioid addiction/dependence treatment was excluded. Since the focus of this study was opioid analgesics, opioids combined with other drugs not typically indicated primarily for pain were excluded (e.g., cough and cold syrups containing opioids) (Leonard J. Paulozzi et al., 2015). Only transactions with the five key variables listed previously were included. Due to the nature of the PDMP data received, dispensing occurring during the weeks either at the beginning or end of a dataset (two datasets from Texas and one dataset from Louisiana) found to be significantly low in volume due to incomplete data capture were excluded and counted as missing data. This was done in an effort to avoid skewing the results from the known complete weeks.

Morphine milligram equivalents (MMEs) were calculated for each transaction using the formula below:

MME = (MME drug specific conversion factor) * (drug strength) * (quantity supplied)

The MME drug specific conversion factor was obtained from the Centers for Disease Control and Prevention (Centers for Disease Control and Prevention, 2015b). This factor is only intended for analytic purposes and not for clinical use. The sum of the MMEs for all prescriptions for each week served as a single time point for each opioid analgesic category.

Time series analysis was performed by using segmented regression of interrupted time series to assess prescribing trends (Wagner, Soumerai, Zhang, & Ross-Degnan, 2002). This type of analysis is considered a strong quasi-experimental design used to evaluate longitudinal effects of an intervention implemented at a single point in time. Recommendations for this analysis include a minimum of 12 observations before the intervention and 12 observations after the intervention to assess the trend. Observations must be at evenly spaced intervals in order to accurately assess trends. Data were assessed on a weekly intervals. The command "PROC AUTOREG" in SAS version 9.3 (SAS Institute Inc., Cary, NC) was used to quantify trends and assess statistical significance.

Results

Prescriptions within the four opioid analgesic categories for both states totaled 40,785,707 (75.6% from Texas, 24.4% Louisiana), spanning the dates: June 1, 2013 to June 21, 2014 (Texas dataset 1); June 2, 2014 to July 24, 2015 (Texas dataset 2); and June 1, 2013 to April 8, 2015 (Louisiana dataset). The original datasets from Texas spanned 71 weeks pre-rescheduling and 42 weeks post-rescheduling. Eleven weeks from Texas were incomplete and subsequently excluded and counted as missing data (weeks 22 to 24 of 2013, weeks 25 to 29 of 2014, and weeks 28 to 30 of 2015), resulting in 63 weeks pre-rescheduling and 39 weeks post-rescheduling. The original dataset from Louisiana spanned 61 weeks pre-rescheduling and 39 weeks post-rescheduling. Three weeks from Louisiana were incomplete and subsequently excluded and counted as missing data (week 22 of 2013 and weeks 14 to 15 of 2015), resulting

in 70 weeks pre-rescheduling and 25 weeks post-rescheduling. The final number of prescriptions used for the analysis totaled 39,789,306 (75.3% from Texas, 24.7% from Louisiana).

On a per capita basis, Louisiana consumed 29% more HCPs, 134% more C-II opioid analgesics, and 36% more acetaminophen/codeine than in Texas at the start of the study period (Table P.1). Prescribing rates for HCPs was 478.2 per 1,000 for Texas and 695.0 per 1,000 for Louisiana for the one year period from July 1, 2013 to June 30, 2014. Prescribing rates for codeine/acetaminophen was 24.2 per 1,000 for Texas and 34.6 per 1,000 for Louisiana for the one year period from July 1, 2013 to June 30, 2014.

The rate of change in terms of morphine kilogram equivalent (MKE) during the pre-rescheduling period resulted in a decreasing rate for HCPs and C-IIs in both states (-0.047 MKE/week and -0.120 MKE/week, respectively for Texas and -0.034 MKE/week and -0.031 MKE/week, respectively for Louisiana) (Table P.2).

The immediate impact of rescheduling resulted in a 41.10 MKE decrease of HCPs in Texas and a 3.14 MKE decrease of HCPs in Louisiana. On a per capita basis, the immediate impact of rescheduling HCPs translated to a greater relative reduction in HCP use in Texas versus Louisiana of 129%. The immediate impact of rescheduling resulted in an increase in Texas for both acetaminophen/codeine (6.82 MKE) and tramadol (14.62 MKE), and an increase in Louisiana for acetaminophen/codeine (0.26 MKE). On a per capita basis, the immediate impact of rescheduling HCPs translated to a greater relative increase in acetaminophen/codeine use in Texas versus Louisiana of 354%.

The rate of change in terms of MKE during the post-rescheduling period resulted in an increased rate of acetaminophen/codeine in Texas (0.119 MKE/week). Refer to Table P.2 and Figures P.1 to P.8 for the trends of volumes across both states for each of the four opioid analgesic categories.

Table P.1. Parameter Estimates from the Segmented Regression Model Assessing Opioid Use in Morphine Milligram Equivalents (MMEs) per Day per 100 Capita

Drug Category	State	Volume at Week 1, MME	Rate of Change During Pre-Intervention Period, MME/Day	Immediate Volume Increase or Decrease At Time of Intervention, MME	Rate of Change During Post-Intervention Period, MME/Day
Hydrocodone Combination Products	**Texas**	69.21*	-0.03*	-22.20*	0.02
	Louisiana	89.36*	-0.11*	-9.71*	0.09
Schedule II Opioid Analgesics	**Texas**	61.09*	-0.06*	2.86	-0.03
	Louisiana	143.23*	-0.09*	-0.34	0.10
Acetaminophen with Codeine	**Texas**	1.01*	0.00	3.68*	0.06*
	Louisiana	1.38*	0.00	0.81*	0.01
Tramadol	**Texas**	-20.76	0.34	7.90*	0.13
	Louisiana	17.19*	0.05	0.29	0.03

*$p<0.05$

Abbreviations: MME=morphine milligram equivalent

Table P.2. Parameter Estimates from the Segmented Regression Model Assessing Opioid Use in Morphine Kilogram Equivalents (MKEs) per Week

Drug Category	State	Volume at Week 1, MKE	Rate of Change During Pre-Intervention Period, MKE/Week	Immediate Volume Increase or Decrease At Time of Intervention, MKE	Rate of Change During Post-Intervention Period, MKE/Week
Hydrocodone Combination Products	**Texas**	128.12*	-0.047*	-41.10*	0.033
	Louisiana	28.93*	-0.034*	-3.14*	0.031
Schedule II Opioid Analgesics	**Texas**	113.10*	-0.120*	5.30	-0.051
	Louisiana	46.37*	-0.031*	-0.11	0.032
Acetaminophen with Codeine	**Texas**	1.86*	0.009	6.82*	0.119*
	Louisiana	0.45*	-0.001	0.26*	0.002
Tramadol	**Texas**	-38.44	0.622	14.62*	0.241
	Louisiana	5.57*	0.017	0.09	0.010

*$p<0.05$

Abbreviations: MKE=morphine kilogram equivalents

Figure P.1. Total Weekly Opioid Volume of Hydrocodone Combination Products in Texas Using Morphine Equivalents, kg

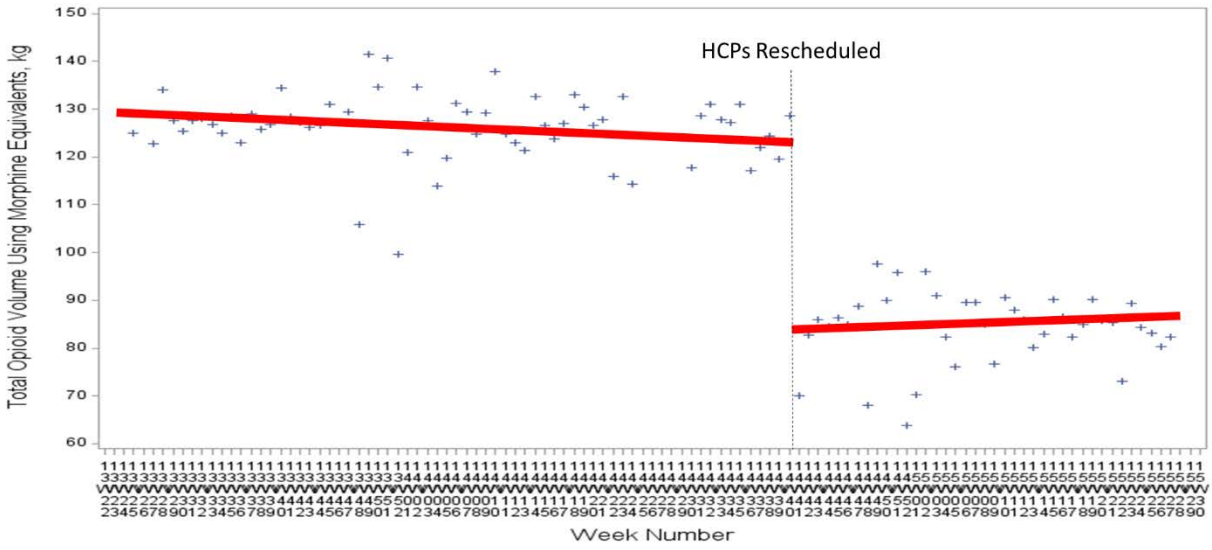


Figure P.2. Total Weekly Opioid Volume of Hydrocodone Combination Products in Louisiana Using Morphine Equivalents, kg

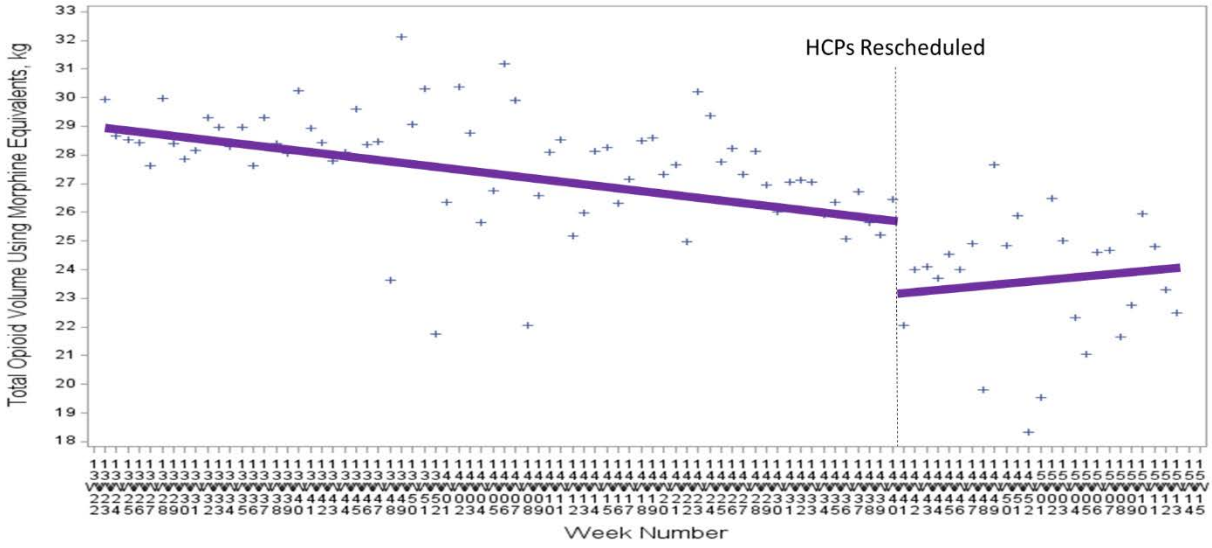


Figure P.3. Total Weekly Opioid Volume of Schedule II Opioid Analgesics in Texas Using Morphine Equivalents, kg

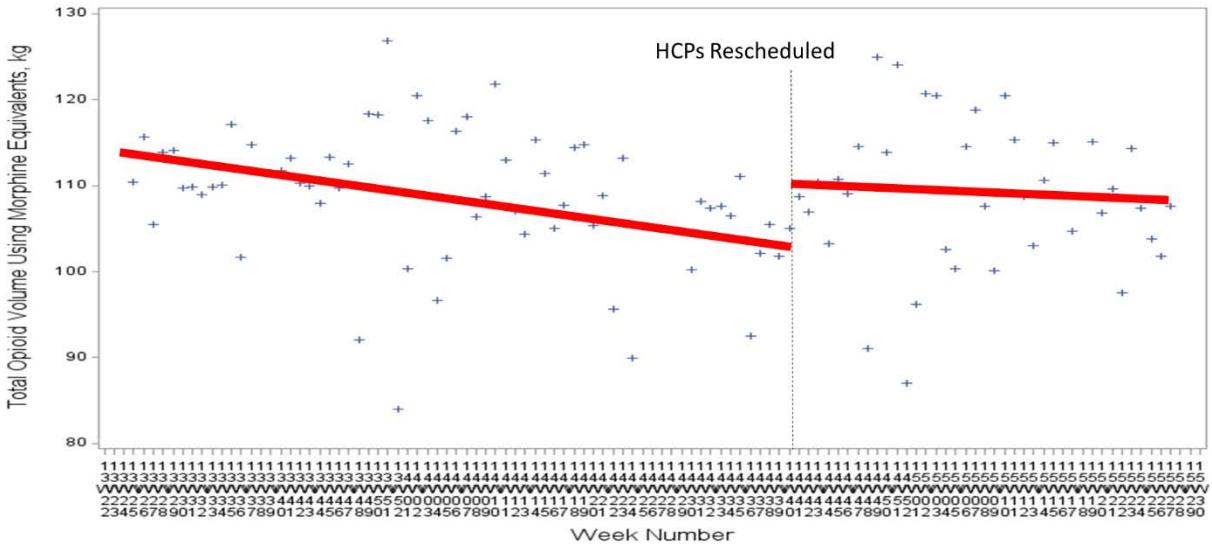


Figure P.4. Total Weekly Opioid Volume of Schedule II Opioid Analgesics in Louisiana Using Morphine Equivalents, kg

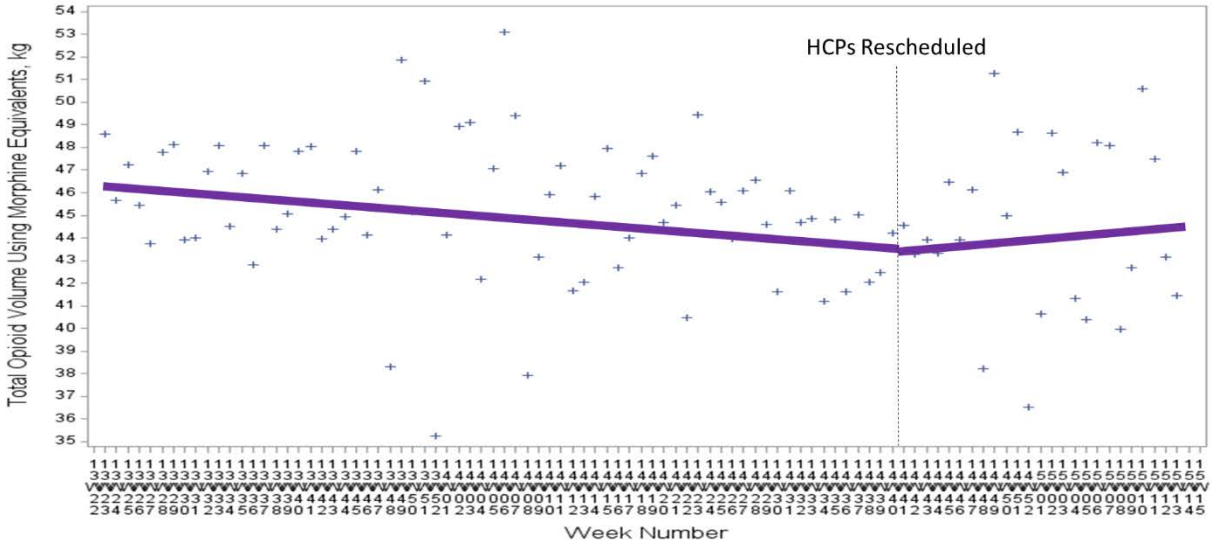


Figure P.5. Total Weekly Opioid Volume of Acetaminophen with Codeine in Texas Using Morphine Equivalents, kg

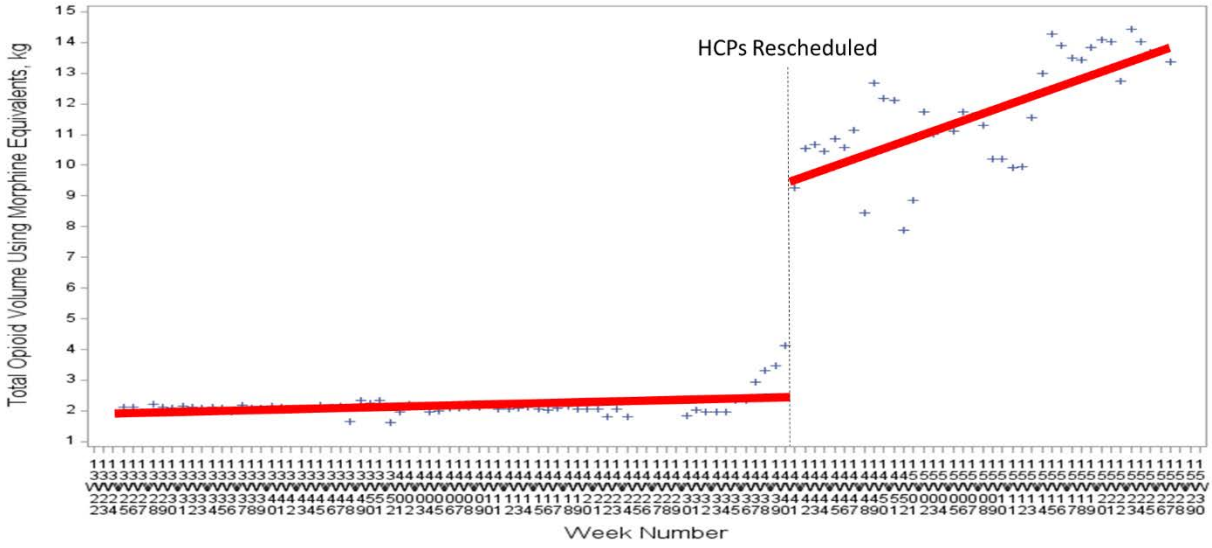


Figure P.6. Total Weekly Opioid Volume of Acetaminophen with Codeine in Louisiana Using Morphine Equivalents, kg

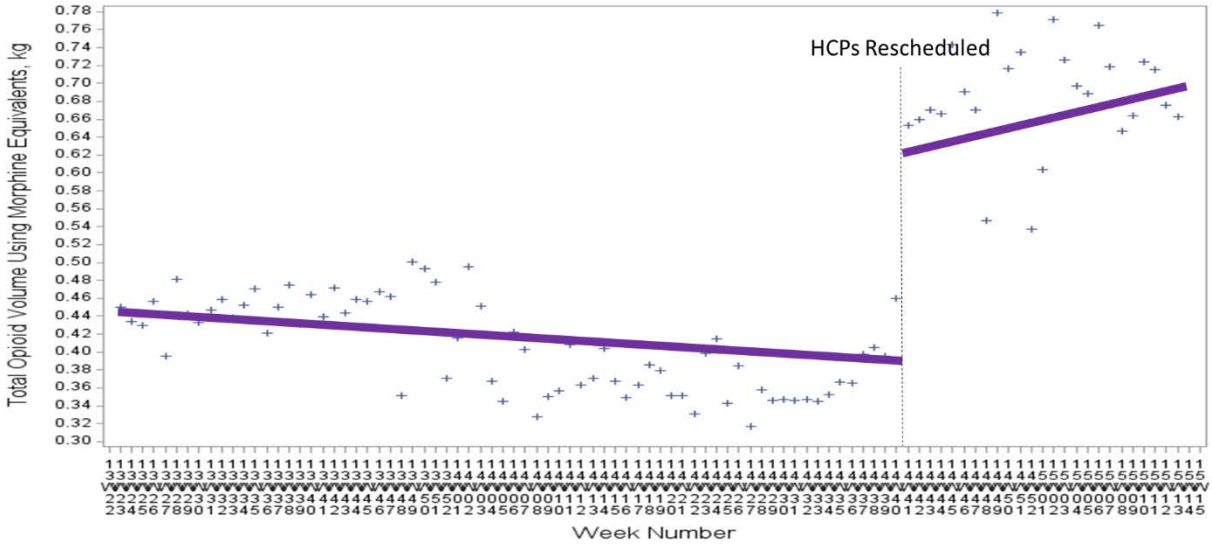


Figure P.7. Total Weekly Opioid Volume of Tramadol in Texas Using Morphine Equivalents, kg

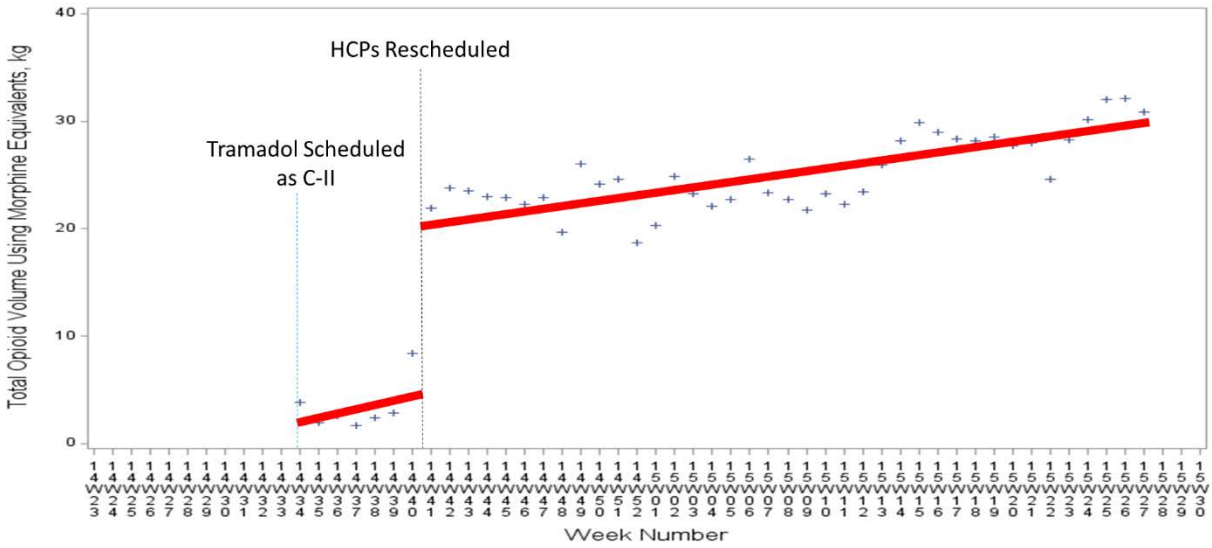
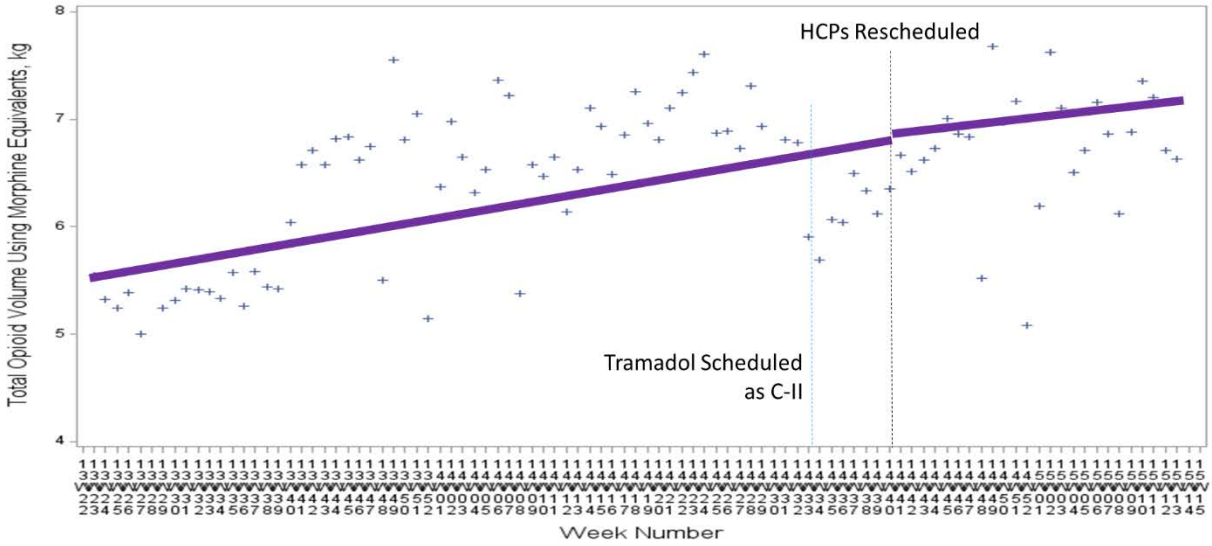


Figure P.8. Total Weekly Opioid Volume of Tramadol in Louisiana Using Morphine Equivalents, kg



Discussion

These changes highlight the impact of the federal intervention of rescheduling HCPs from C-III to C-II on opioid analgesic use in two states with different supplemental regulations concerning scheduled opioid analgesics prescribing. HCP use was initially greater per capita for Louisiana than Texas and decreased by less than half than that of Texas. This is likely attributable to the combination of C-II pad requirements for Texas and NPs not allowed to prescribe C-IIs in Texas. The reduction of HCP use in Texas was significant, as expected due to the additional restrictions in regulations found in Texas versus Louisiana. Louisiana also experienced a statistically significant reduction in HCP use, though the relative reduction was much greater (129%) for Texas.

Acetaminophen/codeine use increased significantly for both states, though Texas increased by over four times that of Louisiana at the time of rescheduling. This indicates that the collective pain for these states which was previously covered by HCPs was switched to acetaminophen/codeine. Additionally, tramadol served as a substitute for HCPs in Texas, by increasing significantly at the time of rescheduling. Further research into how this switching impacted patient care is warranted.

These findings are similar to the 2015 CDC study by Paulozzi et al. with respect to prescribing rates for the state of Louisiana (Leonard J. Paulozzi et al., 2015). That study found that Louisiana prescribing rates for hydrocodone SA to be 659.6/1,000 state residents and 45.1/1,000 state residents for codeine for the year 2013. This is comparable to this study's findings of 695.0/1,000 state residents for HCPs and 34.7/1,000 state residents for

acetaminophen/codeine for a one year period from July 1, 2013 to June 30, 2014. Slight differences can be attributed to different timeframes and variation in defining these two specific opioid analgesics.

Conclusion

HCP use was affected by the rescheduling intervention. States with differences in C-II prescribing regulations were affected differently. Additionally, switching to less effective opioid analgesics was found. Future research is warranted to assess the impact to patient care, including patient pain relief and prescription opioid analgesic abuse.

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