ABSTRACT

Title of Dissertation:	ESSAYS ON REGULATING PAIN AND PLEASURE
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Psychoactive substances play an important role in modern society. They can be of therapeutic value, but their abuse by individuals remains an important policy challenge. Changes in technology and medicine, coupled with evolving norms surrounding the use of psychoactives, have altered much of the drug policy landscape in the last two decades. Currently, the opioid overdose crisis is one of the most challenging public health problems facing state and local jurisdictions. Excessive supply of prescription medications and the arrival of new synthetic opioids, often designed to circumvent regulatory control, have been linked to a tens of thousands of fatal overdoses in the United States in recent years. Advances in chemistry and trade contribute to the recent increase in number of new psychoactive substances (NPS) that mimic controlled drugs, overwhelming many

regulatory systems. At the same time, an increasing number states in the US have started to relax access to cannabis for medical and recreational purposes.

The following three essays explore questions related to contemporary drug policy. Chapter 2 quantitatively assesses the relationship between the design of prescription drug monitoring programs (PMPs) and opioid overdose-related outcomes. The analysis departs from a dichotomous specification found in much of the literature and shows that robustness of policy design is negatively associated with prescription opioid overdose-related outcomes.

Chapter 3 provides a comprehensive and theoretical analysis of how jurisdictions across the globe have approached new psychoactive substances (NPS). It includes a conceptual framework for regulating new substances, assesses the market drivers behind NPS, and offers some considerations regarding policy evaluations going forward.

Chapter 4 applies some of the analytical considerations in Chapter 3 to empirically assess the relationship between cannabis and its synthetic analogs. Using two years of data for all fifty states, I quantitatively explore the relationship between legal access to medical cannabis and exposure to cannabimimetics, showing that there may be a substitution effect. I end with a summary chapter of policy implications and avenues for future research.

ESSAYS ON REGULATING PAIN AND PLEASURE

by

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Dedication

To my sister, Larissa Pardo.

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List of Abbreviations

AAPCC – American Association of Poison Control Centers
ACMD – Advisory Council on the Misuse of Drugs
AMA – American Medical Association
APIS – Alcohol Policy Information System
BZP – Benzylpiperazine
CB1 – Cannabinoid Receptor Type 1
CBD – Cannabidiol
CDC – Centers for Disease Control and Prevention
CESAR – Center for Substance Abuse Research
CFR – Code of Federal Regulations
CND – Commission on Narcotic Drugs
CSA – Controlled Substances Act
DAWN – Drug Abuse Warning Network
DEA – Drug Enforcement Administration
DMT – N,N-Dimethyltryptamine
EACD – Expert Advisory Commission on Drugs
ED – Emergency Department
EMCDDA – European Monitoring Centre for Drugs and Drug Addiction
EU – European Union
FDA – Food and Drug Administration
FTC – Federal Trade Commission
GAO – Government Accountability Office
GPSR – General Product Safety Regulations
HCUP – Healthcare Cost and Utilization Project
ICD – International Statistical Classification of Diseases and Related Health Problems
INCB – International Narcotics Control Board
IND – Investigational New Drug
LSD – Lysergic acid diethylamide
MDA – Misuse of Drugs Act
MDMA -- 3,4-Methylenedioxymethamphetamine, commonly known as ecstasy
MDPV – Methylenedioxypyrovalerone
NAMSDL – National Alliance for Model State Drug Laws
NCHS – National Center for Health Statistics
NCSL – National Conference of State Legislatures
NDEWS – National Drug Early Warning System
NFLIS – National Forensic Laboratory Information System
NPS – New Psychoactive Substance
ONDCP – Office of National Drug Control Policy
OPR – Opioid Pain Reliever
PDAPS – Prescription Drug Abuse Policy System
PIED -- Performance or Image Enhancing Drugs
PMP/PDMP – Prescription Drug Monitoring Program
PSA – Psychoactive Substances Act
SAMHSA – Substance Abuse and Mental Health Services Administration
SCRA – Synthetic Cannabinoid Receptor Agonists

SID – State Inpatient Databases
SITSA -- Stop the Importation and Trafficking of Synthetic Analogues Act
THC – Tetrahydrocannabinol
UNODC – United Nations Office on Drugs and Crime
WONDER – Wide-ranging Online Data for Epidemiologic Research

1 Introduction

1.1 Scope

The distinct and familiar states of pain and pleasure are two powerful stimuli that mold human experience. These concepts are often found in religion, philosophy, law, and economics. Recent advances in science and technology have provided insights into the psychological and neurological mechanisms of pain and pleasure. The purpose of this research is not to add to the literature on quantifying or describing pain or pleasure. Biologists, psychologists, and neurologists have labored for decades to understand their mechanics and purposes.

Rather, research in this dissertation assesses the potential and actual policies aimed at regulating pain relief and access to pleasure as defined by recreational drug use. In this context, I am focused on *substances* (principally intoxicants) and not behaviors (like gambling, video games or other vices/time sinks). This dissertation discusses several classes of psychoactives: opioids, cannabis, and new psychoactive substances (generally cannabimimetics and cathinones, but also synthetic opioids). Many of these substances, which can be used for therapeutic purposes (such as the opioid class of drugs), cause pleasurable altered states of mind in addition to harm (acute toxicity, overdose, addiction, impairment, etc.). Therefore, policy design must navigate between the benefits and risks of use of psychoactives.

1.2 Definition of pain and pain relief

Doctors and psychologists have long sought to treat a patient's condition or reduce pain (i.e. pain relief). Defining pain may seem simple enough. Who hasn't experienced some

form of pain in their lives? Here I draw on the work of influential psychiatrist and thinker Thomas Szasz who suggests that we are limited in understanding such experiences due to what he says is our "primitive" linguistic expression of either pain or pleasure. In this case, we have few words to describe the many different types of pain or pleasure relevant to the human experience. Szasz divides each experience into two categories: organic and psychogenic (Szasz 1988). The former relates to the body while the latter relates to the mind. For example, a broken arm causes organic sensations of severe discomfort (pain) that cause an individual to seek medical treatment and relief.

This classical understanding of organic pain can be reinterpreted to understand psychogenic pain, though the anatomical and biological processes may differ. Mental anguish, such as anxiety or depression, can cause disturbing and emotional states of mind. According to Szasz's read of Sir Francis Walshe, the famed British neurologist of the mid-20th century, psychogenic pain is understood not through the biological interpretations of primary sensations by the body but rather "complex states of mind" and "emotionally toned ideas" (Walshe 1953; Szasz 1988). Here Szasz extends the psychoanalytic approach of psychogenic pain where an affect, such as anxiety or depression, is understood to be the ego's reaction to danger or loss.

Pain serves a biological purpose in avoiding harm. This is especially the case for physical pain (the body quickly moves the hand away from a hot stove). Szasz extends this understanding to psychogenic pain. This applies to psychoactives. For some drug users, psychogenic sources of pain, such as stress or anxiety, are often motivating factors that contribute to drug use and the development of addiction (Sinha 2008). This is acutely relevant to those suffering substance use disorder. Withdrawal can cause physical pain and

discomfort as well as elevated stress and anxiety (Harris and Gewirtz 2004; J. R. Hughes, Higgins, and Bickel 1994; Kosten and O'Connor 2003). Individuals whose drug use could be classified as chronic and compulsive are reported to suffer from increased levels of anxiety and suggest that withdrawal is a strong negative motivating factor to continue drug use simply to avoid both organic and psychogenic pain associated with detoxification (Lejuez et al. 2006; Baker et al. 2004).

Pain is subjective; modern medicine cannot accurately detect or measure it. Apart from the most obvious signs of trauma, practitioners often rely, almost entirely, on the patient's word. Treatment for different conditions depends, in part, on the source of pain. Szasz suggests that acute pain is usually due to injury or illness (e.g. somatic or organic). However, Szasz, writing half a century ago, suggests that chronic pain "is often a sign that the sufferer wishes to occupy the sick role" (e.g. psychogenic) (Szasz 1988, xlii). Szasz, speaking from the view of a psychiatrist, argues that both patient and physician "collude" to accept such pain as the source of some bodily illness. He does not dismiss the real possibility of chronic pain (e.g. rheumatism), but asserts that a patient may (un)knowingly deceive the doctor by pointing to somatic pain when in fact the origin of the pain is psychological. Medical practitioners first try to rule out physical sources before examining the possibility that a patient may be suffering psychogenic pain. This should not be new to prescribers and health practitioners who often guard against such deception sometimes in the form today of "doctor shopping".

Szasz's critique of the medical community's view of chronic pain, which is aimed at pain control, may seem harsh. Nevertheless his writing is prescient. Starting in the 1990s, industry and professional groups began an awareness campaign to encourage medical

practitioners to view pain as the "fifth vital sign" alongside pulse, temperature, respiratory rate and blood pressure, encouraging practitioners to assess patient pain levels (Anson 2016). By 2016, the American Medical Association (AMA) voted to drop pain as a vital sign as it is impossible to measure and, according to the AMA, played a role in creating the opioid epidemic (S. Johnson 2016). How medical practitioners address pain is important; improper treatment can worsen an individual's prognosis and result in undesirable outcomes (overdoses, substance use disorder, etc.). The AMA now recognizes the mistake of unnecessary pharmacological therapies for a multitude of diagnoses related to pain, especially chronic pain, which may or may not have been psychogenic in nature or could have been managed more effectively with alternative, non-opioid therapies.

1.3 Definition of pleasure

Szasz's framework is also helpful in understanding pleasure. The ego views pain as loss and conversely it views pleasure as gain (Szasz 1988). Hunger pangs are alleviated with the addition of food, which is pleasing. In this case, pleasure is a signaling of satisfaction and reaffirmed by evolutionary reward mechanisms. Use of substances, especially by those that suffer substance use disorder, fit this understanding of pleasure. Many psychoactive substances reinforce our innate neural reward mechanisms (Koob 1992). For some, the use of psychoactives for reward-seeking behavior (i.e., pleasure) can become habit forming (Wise 1996). Paradoxically, compulsive drug using behavior may transform from seeking pleasure to avoiding pain as the desire to use drugs for recreational purposes competes with other affects (e.g. anxiety to avoid withdrawal or to achieve some baseline state) (Dennis 2017).

However, unlike pain, which communicates an immediate call to action by an external observer, pleasure does not elicit such a similar response. Therefore, society often understands pain better than it does pleasure. Szasz notes that with unwanted pain both the individual and the observer act to alleviate such pain. However, the opposite is the case with pleasure, which calls for no immediate action, except when action is needed to sustain the pleasurable state (Szasz 1988). This is an important distinction which impedes our understanding of how others can take pleasure in what may appear to observers to be self-destructive or artificial. The typical response to understanding problematic drug use is to ascribe such behavior to predispositions (either environmental or genetic). Szasz notes that "this fact may also account at least in part for the paucity of scientific (psychological, physiological, or philosophical) studies of pleasure" (Szasz 1988, 204). In the field of drug policy, pleasure is often overlooked or excluded for similar subjective reasons, sometimes reducing it to physiological or sensory effects in individual drug users (Duff 2008; D. Moore 2008; Race 2017).

Policy-oriented research often focuses on drug using behaviors through a lens of pathological outcomes. Research on drug-related harms are important, observable, and relatively straightforward: number of drug treatment admissions, drug overdoses, emergency department episodes, calls to poison control centers, etc. Yet, understanding the pleasure motivations and outcomes related to drug use offers insights that are otherwise overlooked. For example, Howard Becker first examined some of the hedonic motivations for using cannabis (Becker 1953). His insights over sixty years ago, such as learning to use in ways that will result in the desired effects and then associating those effects with pleasure, are still relevant today. Drug use can sometimes enhance pleasure of other stimuli

and activities, such as music, food, sex, or social engagements. I maintain that many underlying pleasurable motivators of drug use can and should inform policy decisions.

The person-specific nature of pleasure complicates much of this understanding. It is often harder for the observer to comprehend the source or nature of pleasure than it is pain. In many societies, pleasure must be validated. Here Szasz makes one of the most interesting contributions to understanding pleasure and drug use. He argues that there are four vantage points from which the observer views and either validates or invalidates the source of pleasure. I have reproduced the table below (Table 1.1).

In this case, Szasz argues that observers often view other's drug use as a socially undesirable or artificial source of pleasure, making it difficult to validate. The individual using the drug may be unable to articulate his pleasure, but he experiences pleasure nonetheless. Szasz faults our cultural sensitivities toward pleasurable experiences, which he argues are complicated and arbitrary value judgements. He states that "we regard the habitual ingestion of some substances as perfectly acceptable modes of enjoyment; others are outlawed, their use is labeled 'addiction,' their users are prosecuted, jailed or 'treated'" (Szasz 1988, 250). Society's evolving perception toward the use of cannabis supports Szasz in this regard. Changes in our understanding of the consequences of cannabis use have shaped social attitudes toward the drug. No longer is cannabis use seen as deviant and it is increasingly accepted as a recreational intoxicant.

However, society's disapproval of recreational drug use (apart from alcohol and tobacco) is related to other relevant factors besides lack of understanding. The degree of intoxication and disinhibition from substances may pose legitimate risk to the safety and wellbeing to

the individual and society. Yet, there are shades of nuance. Western cultures generally accept the intoxicative pleasure of ethanol while maintaining rules to reduce the drug's intoxicative harm (Babor 2010a).

Table 1.1: Validation of Pleasure

Position of observer	Validation	Conclusion regarding experience
Can see source of satisfaction and considers it legitimate in nature and appropriate in intensity.	Validation is possible; satisfying object is either outside of the self or the observer can adequately identify himself with the experience	Real pleasure. Complete agreement between observer and experiencing ego as to the appropriateness and intensity of affect (e.g. normal sexual orgasm or pleasure from possession or accomplishment.)
Can see the source of the satisfaction and considers it legitimate but exaggerated because of the specific relationship between ego and object	Validation is possible; observer identifies with the experiencing ego but maintains a position of greater discrimination and noninvolvement.	Pleasure is regarded as real but exaggerated (e.g., being in love or infatuation). Partial agreement between observer and experiencing ego.
Can see the source of the satisfaction, considers it illegitimate, and may exaggerate its intensity over what is actually experienced by the observed ego.	Validation is possible but seriously hindered by complex process of identification and its repudiation and by unconscious ethical preconceptions.	Pleasure is regarded as real and appropriate in the circumstances but as pathological and socially undesirable (perverted, sadistic or due to addiction). Partial agreement between observer and experiencing ego.
Cannot see the sources of satisfaction or judges it unsatisfying, unreal or infantile.	Validation is not possible; the observer is unaware or repudiates knowledge of the source of the pleasure.	Illusion, hypomania, mania. There is complete disagreement between observer and experiencing ego. The pleasure is regarded as essentially pathological (e.g., Freud's view of religion).

Source: Szasz (1988), Table IV, 228-229.

Using Szasz's definitions and framework to understand pain and pleasure give us insight into some of the motivations behind drug use. Szasz states that pain and pleasure "emerge with an analysis of human experience in terms of two fundamental conceptions" (Szasz 1988, 238). These concepts are 1) how the body functions in its relationship with the ego; and 2) psychological development. In closing, Szasz argues that:

> These considerations should make it apparent why the psychological approach to bodily feelings (pain, pleasure, etc.) is relevant and necessary. In other words, if instead of dwelling on the body as a physical machine we focus on man and his relationships with himself and others, then the psychological method of observation and description is essential. (Szasz 1988, 243)

I end this section by noting that pain and pleasure are important drivers behind drug use. Use of drugs, and especially substance use disorder, is a complex psychological and social phenomenon. Individuals will often go great lengths to obtain drugs. Those individuals may be healthy or suffering from a diagnosable condition, such as a substance use disorder. Nevertheless, that fact does not negate the pain (or pleasure) experienced in the absence (or use) of psychoactive drugs.

1.4 Contemporary drug policy

Humans have used psychoactive substances through much of civilization, perhaps contributing to our own evolution (Hill and Newlin 2002). Drugs, or more accurately psychoactive substances, often have medicinal properties that treat or alleviate unwanted symptoms, such as pain. However, many of these substances have the potential to induce altered states of mind that are also pleasing to the user. This reaffirms elements of a pain-pleasure continuum described by some philosophers (Bentham 1907; Spinoza 2012). But sometimes what cures us may also ail us. Use of these substances presents risk of harm to the user and those around him, including but not limited to toxic effects (organ and tissue damage), psychological maladies (dependence), disinhibition and intoxication, and even death by overdose (Babor et al. 2010).

Balancing the need for the therapeutic effects of psychoactives against their risk of harm was the original intent of modern drug policy enshrined by the international drug control

regime since the beginning of the 20th century. Recognizing the utility of psychoactives but also the harm caused by drug addiction and overdose, the UN Single Convention on Narcotic Drugs of 1961 obliges a signatory country to prohibit the supply and use of drugs outside of medicinal or scientific purposes to protect the "public health and welfare" of its citizens. Yet, contemporary drug policy has taken many forms across countries and over time with some countries prioritizing law enforcement and supply-side efforts while others have sought to reduce demand or the attendant harms of unauthorized drug use (MacCoun and Reuter 2001; Babor et al. 2010). For the purposes of this research, I limit my scope of drug policy to substances that are controlled or subject to control (i.e. prohibition) by national and international laws that apply to psychoactives. Though important, this precludes me from examining in great detail policies that govern access to permitted psychoactives for non-medical use (e.g., caffeine, alcohol and tobacco). Some of these substances have received a great deal of attention and research in policy and academic circles. Rather, my focus remains on use of psychoactives that are less understood or whose use is proscribed.

Drug policy, like many other artifacts of the modern era, is a subset of social and health policy that seeks to minimize the harms associated with the supply and use of mind-altering substances (M. Kleiman 1992; Babor et al. 2010). Drug policy can be divided into two overarching sub-branches that can impede or complement each other: laws and programs (M. Kleiman 1992). Laws, or the statutory underpinnings of drug policy, dictate the control elements surrounding psychoactive substances (taxes, regulations, and prohibitions). Kleiman states that laws determine what substances may be sold, to whom, when and at what price. Laws can and have included prohibitory regimes that proscribe the supply or

use of certain substances deemed by society to be unfit for human consumption. Laws are generally implemented through programmatic efforts. This is especially true for drug policy which, unlike other policy realms, must respond to dynamic markets and a basket of evolving social tastes, attitudes, and problems. Kleiman has identified several programmatic efforts, including law enforcement and what he calls "persuasion, help and control" programs, otherwise known as demand reduction programs.

Rather than discuss in detail the frustration with the many shortcomings of US drug policy of the last fifty years (e.g., excessive state intrusion into the lives of drug users, incarceration, failed and invasive source-country efforts, human and civil rights abuses, etc.), this research addresses considerations of pain and pleasure as they relate to drug policy.

Throughout much of Western history, at least since the era of colonialization, psychoactives were primarily used medicinally. Courtwright notes that during early global commerce of psychoactives, "drugs typically began their careers as expensive and rarefied medicines, touted for a variety of human and animal ailments" (Courtwright 2009, 3–4). Courtwright goes on to note that only once the psychoactive and pleasurable effects gained popular acceptance and commensurate levels of consumption did the drug's political and legal status change (Courtwright 2009). Some of these legal changes included prohibition (e.g., heroin) or further regulation to improve the health and safety of drug users and those around him (e.g., alcohol). He cites chocolate, coffee, tobacco and alcohol as legitimate sources of drug-induced pleasure that developed out of early medicinal use that were later commodified. With the advent of better pain relievers during the last century, alcohol has long ceased to serve any practical medicinal application (Courtwright 2009; Babor 2010a).

Modern drug policy, under the guise of medicine and health, has continued such practice of prioritizing therapy over pleasure. Though attitudes are changing with regard to use of cannabis, the drug was first accepted as a source of pain relief for those suffering terminal illness before its transformation into a socially acceptable source of intoxicative pleasure (Ferraiolo 2007; Khatapoush and Hallfors 2004).

Since the passage of the Harrison Act of 1914 in the United States, laws have prohibited the supply and use of most psychoactive substances outside of medically supervised treatment. The use of the prescription system relies on the medical profession to act as a responsible gatekeeper for psychopharmaceuticals. This system of controls, enshrined in US law, is today embedded in the international drug control regime via the UN Single Convention on Narcotic Drugs of 1961 which commits signatories to "require medical prescriptions for the supply or dispensation of drugs to individuals" (UN Single Convention Article 320(2b)).

The framework of US drug policy, at least at the federal level, has sought to limit supply and use of psychoactive substances through prohibition (with the notable exceptions of alcohol and tobacco). In the case of drugs considered therapeutic, individuals may only lawfully access substances to treat some sort of medical condition. Lawful access to pain relief for anything more serious than a headache or moderate muscle stiffness, for many Americans, requires obtaining a prescription from a prescriber to treat some diagnosable condition, which is then filled at a pharmacy by a licensed dispensing agent. The goal of this restricted access is to ensure that substances of known risk are utilized for their therapeutic purposes, protecting public health by preventing misuse and abuse. This

includes a proscription on the use of these substances for non-therapeutic means, i.e. recreationally, as a source of pleasure.

Yet drug policy is more than a legal system to access medicines via doctors and pharmacists. The set of drug issues that are sometimes bundled into the contemporary "drug problem" comprise complex social and economic matters, including security and violence, class and race, and public health. Unbundling these issues is complex. However, noting the complexity of issues frames the scope of the research proposed here. It is necessary to discuss briefly four developments in contemporary US drug policy. Not all of these issues are relevant to the scope of this dissertation, but should be mentioned given their importance today.

The first such development includes shifts in drug demand and what many authorities view as "emerging drug threats" and drug policy priorities. Until the last few years the US has experienced a substantial decrease in use of cocaine, the drug of principal concern since the 1980s, since about the mid-2000s and a growing acceptance and consumption of cannabis (Kilmer et al. 2014). This coincided with a slow but marked increase in the use of opioid pain relievers, largely to treat acute and chronic pain (Paulozzi, Budnitz, and Xi 2006; Adams, Bledsoe, and Armstrong 2016; Seppala and Rose 2010). In the last few years the US has seen an alarming rise in the prevalence of heroin and other non-controlled opioids, such as new synthetic opioids and illicitly manufactured fentanyl (Mars et al. 2014; Compton, Jones, and Baldwin 2016).

Major shifts in use of traditional drugs went largely unnoticed by much of the general public until about 2010. However, the slow but alarming rise in prescription opioids for

pain relief has drawn much recent attention (R. Rudd et al. 2016). Today, overdose deaths attributed to opioid pain relievers (OPR) and other illicit opioids surpass homicides, firearm deaths, and motor vehicle accidents (NCHS 2015). Overdoses stemming from improper use of these drugs has been categorized as a major public health problem (ONDCP 2011; US Surgeon General 2016).

The second major development is the emergence of an entire set of substances that are uncontrolled: new psychoactive substances (NPS). Many of these substances are research chemicals or designed by entrepreneurial chemists to skirt existing drug controls. The concern regarding newly developed drugs that have not been tested or used by humans is that their psychoactive effects and harms are unknown. NPS has been a problem facing Europe for the last fifteen years, and US authorities have reported use of cannabimimetics, including synthetic cannabinoids such as *Spice* or *K2* (King 2014a; L. Johnson et al. 2016). However, the principal threat posed by NPS has been the arrival of uncontrolled synthetic opioids, such as fentanyl analogs. These opioids are often sold as heroin and are now a large contributing factor in the rise of fatal overdoses in the US (Gladden 2016).

The third development facing contemporary US drug policy has to do with the legalization of cannabis at the sub-national level. The current changes in state laws regarding the regulation of cannabis in the United States are in conflict with federal laws that prohibit the use of cannabis outside of approved medical and scientific purposes. Nonetheless, the growing social and legal acceptance of cannabis is evidence of a shift in the general public's attitude, recognizing the use of this drug for purposes of pleasure as well as pain relief. Today, nine states and the District of Columbia have legalized cannabis for recreational (non-medical) purposes for adults over 21 years. In addition, 28 states, the

District of Columbia, and Puerto Rico allow for patients to access some form of medical cannabis that contains tetrahydrocannabinol (THC), the principal intoxicating chemical. Another 15 states allow for no/low THC or high cannabidiol (CBD) formulations of products derived from the plant. Polling shows that the public is overwhelming in favor of use of cannabis for "medical purposes if prescribed by a doctor." No one firm has tracked public opinion of medical cannabis over decades, but a collection of national surveys from ProCon report that since 1998 support for medical marijuana has ranged from 60 to 85% of Americans. In a recent poll by Quinnipiac, 89% of respondents support medical marijuana (Gass 2016).

The fourth development relates to the social costs incurred by policies aimed at reducing drug use—what many might refer to as "the war on drugs." Drug enforcement policies aimed at prohibiting the unauthorized production, distribution, and use of psychoactive substances has been criticized by social commentators of different political leanings as well as the general public (Alexander 2012; McWhorter 2014; Block and Obioha 2012; Western and Wildeman 2009; Hart 2014). Other scholars criticizing contemporary drug enforcement point to problems of racial injustice and deteriorating community-police relationships as well as such efforts being expensive and ineffective (Reuter 2013; J. Caulkins and Reuter 2016). The US is often criticized for having the world's highest incarceration rate. Of the roughly 1.5 million convicted prisoners, approximately 300,000 are for drug law offenses (J. Caulkins and Reuter 2016; Carson and Anderson 2016). However, this number excludes the share of drug law violators held in jails.

It bears mentioning why these issues selected over other contemporary drug issues. Opioid overdose deaths have reached alarming levels. Even more worrying is the fact that a

proportion of prescription drug users migrate toward use of street opioids like heroin and fentanyl (Compton, Jones, and Baldwin 2016; Mars et al. 2014; Cicero, Ellis, and Surratt 2012; Ciccarone 2017). NPS has been categorized as a serious challenge to contemporary drug policy and the existing set of drug controls (A. Winstock and Wilkins 2011; INCB 2013). At the same time, the legalization of cannabis for non-medical or non-scientific purposes (i.e., recreational use) is nothing short of historic as such moves are in clear violation with the spirit and letter of international agreements and federal law. Punitive drug policies that alienate the community and ensnare substantial portions of young people and minorities are starting to be relaxed in hopes of shifting the discourse away from punishment toward support of those with problematic drug use. How the United States approaches these issues will be of great importance in shaping the future of drug policy.

1.5 Research Motivation

Much of contemporary drug policy, the scholarly literature, and the public discourse fail to consider access to pleasure. The conversation over pain relief exists, but until recently has emphasized opioid pain relievers to manage chronic non-cancer pain (Paulozzi, Budnitz, and Xi 2006; Adams, Bledsoe, and Armstrong 2016; Seppala and Rose 2010). The evidence supporting such treatment has since been questioned (Fields 2011; Chou et al. 2015; Chaparro et al. 2014).

After two decades of over promotion and over prescription, the US faces a serious opioid overdose epidemic (Paulozzi, Budnitz, and Xi 2006; "CDC Grand Rounds: Prescription Drug Overdoses — a U.S. Epidemic" 2012; US Surgeon General 2016). Further, attempts to restrict access and reduce oversupply of these prescription drugs may have displaced

some users to street opioid markets (R. Rudd et al. 2016; Compton, Jones, and Baldwin 2016; Cicero TJ et al. 2014; Alpert, Powell, and Pacula 2017).

Since the mid-1990s, states have started to relax their cannabis laws to allow patients to access medical cannabis to treat certain ailments, including chronic pain. Recent literature suggests that cannabinoids may be effective in alleviating some chronic pain (Whiting et al. 2015; Lynch and Ware 2015; National Academies of Sciences, Engineering, and Medicine 2017). Other research suggests that there may even be a substitution effect between cannabis and opioids at the population level (Powell, Pacula, and Jacobson 2015; Smart 2015; Powell, Pacula, and Jacobson 2018; Bradford and Bradford 2017).

Cannabis, though long viewed as an outlet for hedonic drug pleasure, seems to aid in alleviating pain. Cannabis's therapeutic values are of increasing interest from both a science and policy perspective. The Drug Enforcement Administration and the National Institute on Drug Abuse have indicated their intentions to loosen restrictions on researching cannabis's therapeutic values. Yet, these recent efforts have been blocked by the Justice Department under Attorney General Sessions (Zapotosky and Barrett 2017). Nonetheless, the drug is still used by a majority of individuals for non-medical ends, principally as a source of or enhancement to pleasure (J. P. Caulkins, Kilmer, and Kleiman 2016). Cannabis intoxication is a desirable state for many who use the drug. Its prohibition may entice some portion of would be cannabis users to seek out legal or uncontrolled alternatives (Reuter and Pardo 2016a).

The literature on New Psychoactive Substances (NPS) focuses mostly on technical aspects regarding the chemical composition or potential psychoactive qualities of such drugs.

Qualitative research in Europe has studied user populations, modes of administration, and reasons behind use of such drugs (Measham et al. 2010; Measham, Moore, and Østergaard 2011; K. Moore Dargan, Paul I., Wood, and Measham 2013), but the policy options aimed at reducing harms of NPS remains grounded on the prohibition paradigm of control (Reuter and Pardo 2016a; Stevens et al. 2015; Stevens and Measham 2014). Limited by their choices, a growing number of governments have adopted broad and expansive laws aimed at prohibiting NPS (Reuter 2011; Reuter and Pardo 2016a; Home Office 2014; Kavanagh and Power 2014). However, very little consideration has been given to pleasure, which I maintain is a substantial driver of certain NPS use.

In that vein, the literature underscores the substitutive qualities of some NPS for traditional drugs (K. Moore Dargan, Paul I., Wood, and Measham 2013; Reuter and Pardo 2016a). Poor quality cocaine and ecstasy in the UK may have encouraged some drug users to seek out cathinone-derived substances that mimic the effects of known stimulants or entactogens (Measham et al. 2010; K. Moore Dargan, Paul I., Wood, and Measham 2013; King 2014a, 2014b). However, outside of the ethnographic literature little empirical research has been done on NPS user populations in the US. For example, little assessment has been made as to the potential impacts that certain regulatory approaches may have on the whole basket of drugs and drug use. Are cannabis and synthetic cannabinoid receptor agonists (SCRAs) substitutes? Does tightening or loosening controls on one type of drug impact consumption of the other?

The challenges posed by opioid overdoses, as a result of prescription drug misuse, and the use of synthetic cannabinoids represent some of the most important drug policy issues in

the US today. Further, the lack of consideration toward motivating factors such as pain relief and access to pleasure make this research even more important.

1.6 Organization of the dissertation

This dissertation explores the policy mechanisms and options used to control access to pain relief and pleasure (typified here as recreational drug use). Pain and pleasure are two distinct determinants that explain use of substances I have identified as being on the forefront of contemporary drug policy in the United States. I have framed this study around three research questions:

1. Does monitoring access to prescription opioid analgesics reduce opioid-related overdose deaths and emergency department episodes?
2. What are the options and considerations toward regulating novel drug-induced pleasures?
3. What is the relationship of legal access to cannabis on consumption of synthetic cannabinoids?

The answers to these research questions are explored in the following three essays, which detail the scope, methods, goals, and outcomes of several policy interventions that regulate pain relief and drug-induced pleasure.

This first chapter has introduced the concepts of pain relief and the recreational use of drugs as a source of pleasure. I have identified the major challenges of contemporary drug policy, framed the scope of the dissertation, and detailed the organization and motivation for the research.

The first essay (Chapter 2) quantitatively examines the relationship between one policy intervention—prescription drug monitoring programs—aimed at regulating access to opioid pain relievers and certain health-related outcomes such as drug overdose and emergency department use. Data on overdose deaths are collected from the CDC's Wide-ranging Online Data for Epidemiologic Research database (WONDER). Data on emergency department discharges come from the State Inpatient Databases (SID) from the Department of Health and Human Services' Agency for Healthcare Research and Quality. Legal data compiled by the Prescription Drug Abuse Policy System (PDAPS) and the National Alliance for Model State Drug Laws (NAMSDL) are used to measure the main explanatory variable of interest, prescription drug monitoring programs (PMPs).

For prescription overdose deaths, all data span from 1999 to 2015 and include all 50 states and the District of Columbia for a total of 867 observations. Heroin overdose deaths are reported less frequently. For emergency department discharges, data are incomplete, but SID includes emergency discharge figures for 37 states from 1999-2014, with some states completely missing. For this outcome variable, data include 468 prescription opioid observations and 376 heroin observations. Data for the explanatory variables and other covariates are complete for this series and come from the US Census Bureau's Current Population Survey.

A fixed effects approach is used to control for state-level effects. I calculate robust standard errors by clustering within each state to correct for heteroscedasticity and serial correlation for within-group estimators. This essay approaches PMP analysis in a novel fashion. I do not treat these policy interventions as dichotomous variables, but rather measure their strength across states and over time. This approach has yet to be considered in most of the

literature to date. In fact, until early 2016 researchers included PMPs as a binary variable in models. This essay shows that PMPs vary across states and over time and that evaluations should consider such variation.

The second essay (Chapter 3) is an analytical piece on the actual and potential policies that govern the regulation of new psychoactive substances (NPS). Different governments across the globe have attempted to regulate NPS, using existing legal and programmatic mechanisms or drafting new laws. This essay builds on earlier collaborative work done with Dr. Peter Reuter (Reuter and Pardo 2016a, 2016b) assessing these recent control efforts and their policy-analytic goals with consideration to regulating non-medical, non-scientific drug use (i.e., recreational drug use). This essay forms the analytical foundation for the consideration and design of regulatory policies that govern access to drug-induced pleasures.

This chapter comprises a comparative legal analysis and review of the sparse literature on NPS regulation, including what governments are currently doing to regulate substances of unknown harm. It then uses a logic model developed out of the foundations of drug policy literature (MacCoun and Reuter 2001) to assess the appropriate goals and challenges of regulating these substances. Lastly it conceptualizes the market drivers behind the NPS phenomenon, including who uses, why, and what reasons exist behind supply of non-controlled drugs. This essay assess the problem from a more conceptual perspective, giving policymakers a broad view of the phenomenon, its drivers, policy tradeoffs, and the regulatory challenges posed by NPS.

The third essay (Chapter 4) applies some of the analytical framework developed in Chapter 3 to study the use of certain NPS in the United States as a source of pleasure but perhaps also for pain relief purposes. This quantitative essay assess the impacts of reducing barriers to cannabis on use of synthetic cannabinoid receptor agonists (SCRAs). There is little research on the population-level relationship between cannabis and SCRAs. This essay is perhaps one of the first assessments of such relationship.

I hypothesize in this chapter that states that allow easy access to medical cannabis have lower per capita adverse health outcomes linked to synthetic cannabinoids. Cannabis intoxication is a pleasurable experience for many cannabis users. However, restrictions on the drug, including drug testing, limited access, criminal sanctions or loss of employment/social benefits, may induce some portion of the cannabis-using population to seek out legal alternatives, such as synthetic cannabinoids. Increasingly, synthetic cannabinoids are linked to a whole host of acute negative health outcomes, including death; outcomes that are worse than those associated typically with cannabis.

Data for this chapter come from a variety of sources. Emergency room data are preferred; unfortunately the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD) does not code for SCRAs. However, poison control centers do collect information on SCRA exposure. Therefore, my dependent variable is the number of calls to poison control centers for SCRA exposure. This data come from the American Association of Poison Control Centers (AAPCC), National Poison Data System. From AAPCC I calculate aggregate exposure counts by state and year from 2015 to 2016, for a total of 102 observations. State-level explanatory variables on access to cannabis, including medical and recreational cannabis laws, come from a variety of legal sources,

including the National Conference of State Legislatures (NCSL) and the Alcohol Policy Information System (APIS), which maintains an information portal on cannabis policy and law. Measures of medical cannabis patient counts come from state registries, where available. The analysis also includes controls for state laws prohibiting SCRAs.

The final chapter (Chapter 5) links common themes and discusses some relevant overarching policy implications for regulating pain relief and access to drug-induced pleasure as well as outlines some areas for further research. Several of the chapters in this dissertation break new ground in areas of drug policy. Only more recently has research started to examine the regulatory mechanisms nested within a state's Prescription Drug Monitoring Program (Bao et al. 2016; L. Johnson et al. 2016; Pardo 2017). There is virtually no assessment as to measuring the substitution effect between SCRA and cannabis, with most of the SCRA literature focusing on epidemiological outcomes and individual adverse health effects (Debruyne and Le Boisselier 2015; Forrester et al. 2012; Gunderson et al. 2012, 2014). Research in Chapter 4 is perhaps the first empirical assessment of such a relationship.

2 Do More Robust Prescription Drug Monitoring Programs Reduce Opioid Overdose Deaths?[i]

2.1 Background

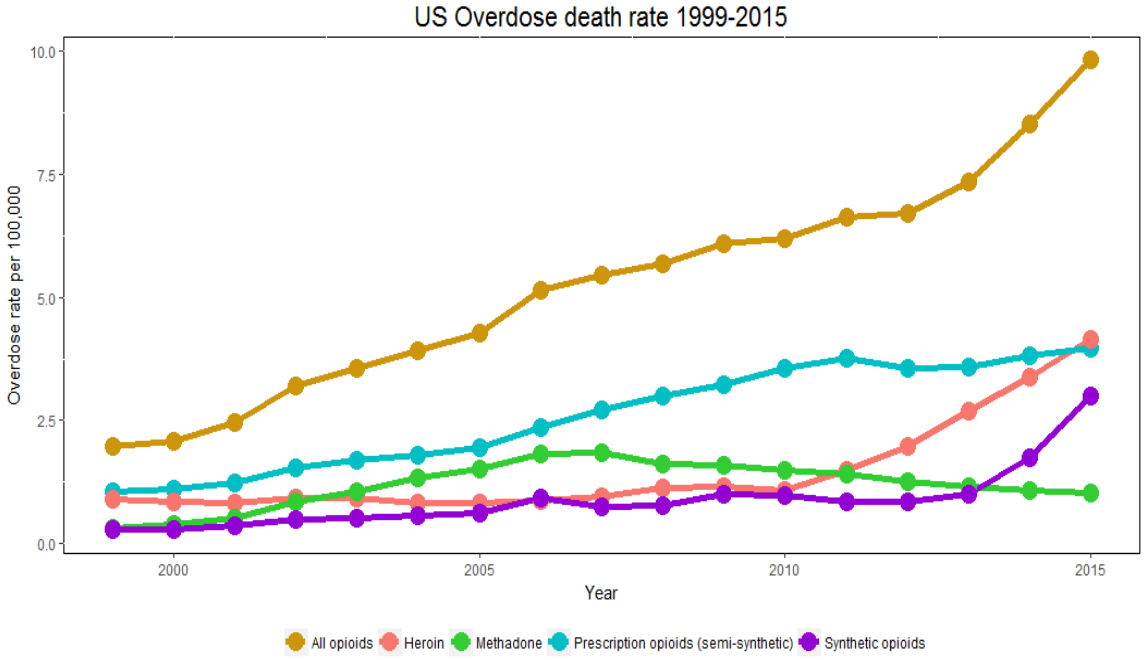
Drug overdoses deaths have more than tripled since 2000, with opioids involved in more than 60% of all overdose deaths (R. A. Rudd 2016). In 2015 there were 52,404 drug overdose deaths in the US, including 33,091 (63%) that involved an opioid (such as prescription analgesics or illicit narcotics such as heroin) (R. A. Rudd 2016). Opioid-involved deaths now far surpass homicides (15,696), are on par with firearm deaths (33,636) and are approaching motor vehicle deaths (38,300). Alarmingly, heroin overtook opioid pain reliever (OPR) deaths in 2015. Though heroin epidemics are nothing new to American drug policy scholars, the current epidemic is alarming because of the inclusion of powerful additives such as fentanyl and its analogs. CDC and DEA note that starting in 2013 the importation and distribution of fentanyl-laced heroin increased to unprecedented levels (Gladden 2016). The number of synthetic opioid overdose deaths more than tripled between 2012 and 2015 to more than 9,500 (CDC). See Figure 2.1.

This essay examines the relationship between one supply-side mechanism aimed at reducing over-prescription of opioid pain relievers and opioid overdose deaths. Policies aimed at reducing unnecessary prescribing and diversion via strict monitoring may achieve their stated goal, yet at the cost of displacing drug use behavior toward illicit sources. Here I examine how Prescription Drug Monitoring Programs (PMPs) impact indicators of

[i] Elements of this chapter come from a published paper Pardo, Bryce. 2017. "Do More Robust Prescription Drug Monitoring Programs Reduce Prescription Opioid Overdose?" Addiction, January doi:10.1111/add.13741.

morbidity and mortality, including OPR overdose deaths, heroin overdose deaths, and emergency department episodes for OPR and heroin.

Figure 2.1: US Overdose death rate 1999-2015



Globally, prescription opioid consumption varies by region though North America reports high prevalence of these substances (Fischer et al. 2014). In the United States, opioid pain reliever overdose deaths have increased 370% between 1999 and 2015. Through 2014, OPR fatal overdoses exceeded those of heroin or cocaine, and were linked to more than half of pharmaceutical overdose deaths ("CDC Grand Rounds: Prescription Drug Overdoses — a U.S. Epidemic" 2012; Jones CM, Mack KA, and Paulozzi LJ 2013). Synthetic opioid overdose deaths have been rising year over year since 2012.

How did prescription opioid overdoses become a problem? Starting in the 1990s, physicians, patients' rights groups, and pharmaceutical companies shifted the discussion around pain management therapies (Paulozzi, Budnitz, and Xi 2006; Adams, Bledsoe, and

Armstrong 2016; Seppala and Rose 2010). Many argue that excessive prescribing by physicians, doctor shopping, employee diversion, and inappropriate prescription by doctors in loosely regulated pain clinics known as "pill mills" contributed to oversupply of these drugs (Kennedy-Hendricks et al. 2016; Betses and Brennan 2013; Dhalla, Persaud, and Juurlink 2011). This oversupply arguably has contributed substantially to the current opioid overdose epidemic.

Safe access to prescription drugs has long been a concern for public health and safety officials. In order to prevent diversion and inappropriate prescribing, systems were put in place to monitor the writing and filling of prescriptions. One supplemental system is known as a prescription drug monitoring program (PMP or PDMP). PMPs are state-wide, electronic databases that help health practitioners and public safety officials reduce misuse and abuse of prescription drugs by collecting, analyzing, and distributing data on practitioner and patient prescription habits (Babor 2010b; C. S. Davis, Johnston, and Pierce 2015).

In 2014, the Congressional Research Service analyzed PMPs and found that each program varied in funding mechanism, information collection or Schedule[ii] monitoring (Finklea, Sacco, and Bagalman, 2014). The CRS report concluded that PMP evaluations are difficult, as many studies have not distinguished between proactive or reactive programs (the former sends unsolicited reports to prescribers about suspicious prescribing patterns),

[ii] Difference in Schedule monitoring could impact prescriber practices and outcomes of interest. For example, hydrocodone was a Schedule III narcotic until October 2014 when it was moved to Schedule II by the Drug Enforcement Administration. States that only monitor Schedule II drugs may encourage doctors to dispense unmonitored Schedule III drugs (Paulozzi, Kilbourne, and Desai 2011).

funding sources, oversight bodies or rules on gathering and maintaining information (Finklea, Sacco, and Bagalman, 2014).

Given such variation, debates in the literature persist (Paulozzi, Kilbourne, and Desai 2011; Haegerich et al. 2014; Pradel et al. 2009; Reifler et al. 2012; Delcher et al. 2016, 2015; Surratt et al. 2014; Gilson et al. 2012; Bao et al. 2016; Patrick et al. 2016). Simply, not all PMPs are the same and should not be evaluated assuming so (C. S. Davis, Johnston, and Pierce 2015; C. S. Davis, Pierce, and Dasgupta 2014). Recent research has started to tease out program differences, suggesting that design and mechanisms do correlate with overdose fatality (Patrick et al. 2016). This analysis aims to 1) estimate the relationship of PMP strength with opioid overdose deaths across states and over time; 2) estimate if displacement toward heroin occurred by assessing the relationship of PMP strength with heroin overdose deaths across states and over time; 3) estimate the relationship of PMP strength with emergency department episodes for heroin or OPR; and 4) gauge what level in PMP strength is associated with the greatest reduction outcomes measured. In this regard, I expand the literature on PMP evaluations by measuring program strength relative to each other and over time, rather than treating them as binary variables in models.

2.2 Data and methods

2.2.1 Design

Analytical factors complicate cross-program evaluations. Most of the literature is limited to examining prescriber practices within states (Clark et al. 2012; Gilson et al. 2012; Baehren et al. 2010; Delcher et al. 2015; Surratt et al. 2014; Bao et al. 2016). Others have attempted to tease out variations in PMP design and implementation, suggesting that

differences matter when it comes to types of Schedules monitored or reporting frequency (Paulozzi and Stier 2010; Patrick et al. 2016). Many evaluations lack variation in their samples or are limited when considering the difference in PMP strength relative to each other, often treating them in a binary fashion.

In order to analyze the association between PMPs and opioid overdose deaths I created a composite index variable, based on legal and regulatory data, to gauge PMP strength across states and over time. Such methods have been used in the public health field to evaluate the health outcomes of different policies (Chaloupka and Pacula 1998; Taber et al. 2015). Other scholars have suggested that such methodologies are empirically necessary to test policy effects of laws (Wagenaar and Burris 2013).

2.2.2 Data

2.2.2.1 Dependent variables

2.2.2.1.1 *Overdose deaths*

Age-adjusted opioid overdose deaths for all fifty states and the District of Columbia between 1999 to 2015 were obtained from multiple cause of death mortality counts reported by the CDC's Wide-ranging Online Data for Epidemiologic Research database (WONDER) (NCHS 2015). Death certificates are classified using the International Classification of Diseases, Tenth Revision (ICD-10). I queried WONDER for deaths certified by medical examiners with an underlying cause-of-death code of unintentional (X40–X44), suicide (X60–X64), homicide (X85), or undetermined intent (Y10–Y14), where drug-poisoning deaths involving opioids with a multiple cause-of-death code of

other opioids (T40.2), heroin (T40.1), methadone (T40.3), or other synthetic narcotics (T40.4).

In order to differentiate between prescription opioids (which are subject to PMP monitoring) from illicit opioids, I aggregate the overdose counts for other opioids (T40.2) by state and year. This gives me a measure for the number of overdose deaths related to OPR. I do not include methadone (T40.3) as federal regulations (42 CFR Part 2) prohibit reporting dispensed methadone to PDMPs as, by law, they are not prescribed but administered (Brandeis University 2015). I also exclude synthetic opioids (T40.4) from the analysis as the recent rise in deaths attributed to this class of opioids is driven primarily from illicit fentanyl that has become mixed into the street heroin market (Gladden 2016; Peterson 2016). At this time, it is difficult to reliably determine if an overdose attributed to a synthetic opioid, such as fentanyl, was due to prescription drug abuse or abuse of illicitly manufactured fentanyl or other synthetic analogs. Therefore, it is inherently tricky to reliably estimate any association between PMPs and overdose deaths that include counts for synthetic opioids with the public aggregated death count data from CDC. An earlier analysis of OPR death rates included both T40.2 and T40.4 (Pardo 2017). Because death rates for synthetic opioids have more than tripled in the last three years while prescription rates have remained the same, some have concluded that the majority of synthetic opioid overdose deaths must be due to illicit sources of fentanyl (Gladden 2016), which are not subject to PMP monitoring. Therefore, our analysis below only considers deaths coded as T40.2 to be OPR, which excludes both illicitly-sourced and prescription synthetic opioids, such as fentanyl and tramadol.

Due to privacy concerns, the CDC does not release the number of deaths in a state when there are less than 10 categorized deaths, censoring 33 observations from less populated states for other opioids (T40.2). I conservatively estimated the number of deaths at 5 (rounded mean of $\sum_0^9$) for each of the missing observations to keep a highly balanced panel. According to the CDC, the number of OPR overdoses in New Jersey for 2009 were improperly coded, resulting in a low number. Therefore, I imputed a mean based on the OPR overdose deaths in 2008 and 2010. The final data set included 51 jurisdictions with 17 time periods (n=51, T=17) for a total of N=867 observations.

Heroin overdoses (T40.1) have been fewer than those attributed to OPR. CDC data suppresses hundreds of observations, predominantly from state-years prior to 2010. In this case, I have a total of 469 observations. I opt not to estimate death rates as done for OPR since this could introduce a substantial amount of measurement error given that heroin overdose deaths are fewer than OPR throughout most of the series. However, recent data from CDC suggests that consumers are unknowingly using fentanyl (Gladden 2016; R. A. Rudd 2016; Peterson 2016). In addition to total number of heroin overdoses reported by CDC, I conservatively estimate a count of heroin overdoses that also include synthetic opioid deaths to account for illicit fentanyl in the supply of street heroin; I call this "heroin and fentanyl-laced heroin".

I should note an important caveat regarding overdose deaths. CDC notes that deaths involving more than one type of opioid are sometimes not distinguishable in reported data from medical examiners and that these death categories may not be mutually exclusive (R. A. Rudd 2016). This is likely to be true for heroin and fentanyl, especially at the beginning of the most recent fentanyl epidemic that started around 2012. Without the full death

certificate count, I am unable to precisely calculate the true count of heroin and illicitly-sourced fentanyl. I have included this analysis for the time being, but future work with full death certificate data will improve any findings here.

2.2.2.1.2 *Emergency department discharges*

Data on emergency department discharges come from the State Inpatient Databases (SID) from the Department of Health and Human Services' Agency for Healthcare Research and Quality. SID is one database tool developed by the Healthcare Cost and Utilization Project (HCUP) and captures hospital inpatient stays for states that report to HCUP. For emergency department discharges, data are incomplete, but SID includes emergency discharge counts for 37 states from 1999-2014, with some states completely missing. Depending on which type of drug poisoning, number of observations range from 376 to 468.

I queried the SID database using the HCUPnet online tool to search for total number of emergency department discharges, according to relevant ICD-9-CM diagnoses codes. The principal measure of emergency department discharges for poisonings are: opium (alkaloids) (965.00), heroin (965.01), and other opiates and related narcotics (965.09). The ICD codes for acute opioid poisonings have been considered incomplete or unclear by some researchers for not being able to disaggregate adverse public health events related to opioids (Reardon et al. 2016). In this case, ED discharges for opium (alkaloids) (965.00) and other opiates (965.09) may both be due to OPR subject to PMPs. Presumably opium (alkaloids) (965.00) includes natural alkaloids such as morphine, codeine and thebaine. And "other opiates" (965.09) captures ED discharges related to semi-synthetic opioids such

as oxycodone and hydrocodone. I consider poisonings for "other opiates" as well as poisonings for heroin in the analyses below under the assumption that coding for either event measures an exposure to an OPR that is subject to PMP monitoring or a displacement effect from OPR to heroin.

2.2.2.2 Independent variables

I utilized legal data compiled by the Prescription Drug Abuse Policy System (PDAPS) and the National Alliance for Model State Drug Laws (NAMSDL), which maintain data on state laws to measure my main explanatory variable of interest while also controlling for other factors that are associated with OPR overdose or PMP administration (NAMSDL 2012, 2014; PDAPS 2016). Other controls include access to naloxone, Good Samaritan laws, pain clinic management laws, and access to medical marijuana dispensaries. These are discussed in greater detail in the following sections.

Legal information allowed me to score PMPs by state and year (Table 2.1). This technique has advantages. First, it helps avoid problems of multicollinearity in regressions, something that Patrick et al. (2016) did not address, impeding authors from evaluating the full scope of PMP strength. Second, it allows me to measure PMP rigor, which is innovative and departs from the binary evaluation found in much of the literature. Lastly, the inclusion of administering agency is something not considered thus far in the literature.

I assessed eleven different rules and design mechanisms by state from 1999-2015 (PDAPS 2016). Brandeis University's PDMP Center of Excellence 2012 report on expert-determined best practices regulatory standards and a literature review conducted by Haegerich et al. (2014) assessed the limited research on PMPs and the regulatory

mechanisms that impact prescribing practices (Clark et al. 2012; Haegerich et al. 2014). In order to create an unweighted Score, I counted the number of regulatory mechanisms for each state-year. This was used as a baseline in models to measure the unweighted strength of PMPs.

However, the literature notes that some regulatory mechanisms are associated with changes in prescriber practices, suggesting that a weighted score may be more appropriate. I assigned weights to mechanisms that have an empirical or analytical basis in changing prescriber practices or reducing OPR overdose deaths. Absent studies, other regulatory mechanisms were weighted given expert opinion of potential reductions in OPR overdoses (e.g., when prescribers are required to check PMP before writing a prescription). Overall, I weighted five mechanisms according to the evidence or analytical discussion suggesting their impact on prescribing practices and overdoses; the remainder were assigned equal weights of 1. To ensure robustness of results I also conducted an unweighted sensitivity analyses using the baseline, unweighted score. Scores were obtained by summing the total weights by state for each year with a maximum possible score of 23. Table 2.1 describes each regulatory mechanism and weights in greater detail.

This weighting scheme is arguably more precise than a dichotomous specification. Likewise, treating each regulatory mechanism with equal weight is likely to be imprecise. Allowing law enforcement access to PMPs is unlikely to have the same impact on prescriber practices than if doctors are mandated by law to utilize PMPs. Regardless of weighting scheme, the evaluation of the collection PMP mechanisms provides additional level of detail that much of the literature has overlooked until recently. Recent articles have included additional regulatory mechanisms into econometric models, showing that such

regulatory details correlate with fewer prescription opioid overdoses (Bao et al. 2016; Clark et al. 2012).

Alternative weighting approaches could be considered. As mentioned above, I remove weighting entirely as well as remove certain regulatory components from the weighting score. Inclusion of additional continuous variables could improve measurement of PMP strength. For example, instead of a categorical variable for funding mechanism, the inclusion of PMP budgets or intake fees could strengthen the measure on financial resources that allow such a program to operate. Similarly, number or quality of staff could add additional dimensions to PMP rigor. The inclusion of additional regulatory mechanisms can also improve measures. For example, whether or not a PMP monitors and alerts for non-opioid analgesics, including those that are not scheduled such as some gabapentinoids, or benzodiazepines that interact dangerously with opioids (Jones and McAninch 2015; Jann, Kennedy, and Lopez 2014; Evoy, Morrison, and Saklad 2017).

These are merely alternatives of how to improve precision. Any composite measure of a broad policy can be enhanced. The index here is just one step toward improving policy measures given the gaps in the literature to date. Utilizing some composite measure of policy allows for improved assessment within a state, over time. This is something that cannot be done when assessing PMPs in a binary fashion. Likewise, weighting achieves some degree of policy nuance that may get lost when weighting is removed.

Table 2.1: Point Allocation to Rules to Create Score Variable

	Statutory regulation or best practice	*Outcomes listed from literature*	*Type (number of studies)*	*Weight*
1	Monitor more than Schedule II drugs (Schedules III, IV or V)	Reduced doctor shopping, decreased inappropriate OPR use	Time series and descriptive/before-after (13)	3
2	PDMP permitted or required (i.e. proactive) to identify suspicious prescribing, dispensing or purchasing activity	Decreased prescription sales	Observational with controls (4)	4
3	Access for law enforcement and prosecutors	None	None	1
4	Access for Physicians, Pharmacists, NP/PA, Dentists, Chiropractors	None	None	1
5	Reporting frequency	Decreased doctor shopping, increase use of program by prescribers.	Observational with controls (2)	Baseline <month, >week -2 if not required -1 for monthly 0 for less than a month, greater than a week 1 for weekly 2 for daily 3 for live system
6	Prescribers required to check PMP before prescribing to a patient	None	None, but Haegerich et al.(Haegerich et al. 2014) and Davis et al.(C. S. Davis, Pierce, and Dasgupta 2014) mention it.	4
7	PMP permitted to share data with other states	None	None, but Brandeis best practices report mentions	1
8	Law requires program evaluation	None	None	1
9	PMP has oversight board	None	None	1
10	Data retention	None	None	1
11	Funding mechanism	None	None, but Brandeis best practices report mentions	0 no funding 1 grants or gifts 2 charging fees 3 appropriated

In order to isolate the operational effects of a PMP on opioid overdose deaths, I assigned a score to state-years when a rule was in place in a state's regulatory regime for more than

five months during a calendar year and not when enabling legislation was passed. This is something that not always explicitly addressed in the literature.

Across the country, PMPs are administered by a variety of agencies, such as health departments or state law enforcement agencies. Each of these agencies has different policy goals, organizational structures, and bureaucratic cultures (C. S. Davis, Johnston, and Pierce 2015). To my knowledge, there has not been any empirical evaluation of the effects associated with type of administering agency, but research suggests that such differences complicate evaluations (Finklea, Sacco, and Bagalman, 2014; C. S. Davis, Pierce, and Dasgupta 2014). Data from PDAPS allowed me to create a categorical variable for administering agency to evaluate PMPs while controlling for the type of administering agency.

I also measured possible confounders, such as access to naloxone (Doe-Simkins et al. 2009; Straus, Ghitza, and Tai 2013), Good Samaritan laws (Banta-Green et al. 2013), pain clinic management laws (Kennedy-Hendricks et al. 2016) and access to medical marijuana dispensaries (Smart 2015; Powell, Pacula, and Jacobson 2015) which have been found to negatively correlate or reduce OPR overdose. I treat these variables dichotomously because many of these policies are new and the variation among them is relatively small compared to variation in PMPs. Further, few states had them in place throughout our series (for example, less than 13% of state-years had naloxone laws in place).

I also included demographic measures, including median household income by state, proportion of adults over 25 with a high school education, and proportion of the population that is white from the 2010 Census, by state and year (US Census Bureau 2015a, 2015b,

2015c). Intercensal estimates were calculated for proportion white for years 2000-2010; I assigned proportion white for 2010 for years 2011-2015. Prior literature has suggested these covariates may be related to opioid use and overdose (Paulozzi, Kilbourne, and Desai 2011).

Because overadjustment bias is a concern, I refrained from including data on OPR prescription rates. Mechanistically, I assume that opioid prescriptions have an effect on OPR overdose (Paulozzi and Ryan 2006). Yet, prescriptions are likely affected by policies often captured by PMPs. Similar to other analyses, I am attempting to isolate the causal mechanism that PMPs have on OPR overdose deaths via changes in prescribing practices (Patrick et al. 2016). Therefore the inclusion of prescription data would incur overadjustment and bias estimates toward the null (Schisterman, Cole, and Platt 2009; VanderWeele 2009).

2.2.3 Statistical Analysis

2.2.3.1 Overdose deaths

A two-way fixed effects approach was used to control for state-level and time-dependent effects. I calculated robust standard errors by clustering within each state to correct for heteroscedasticity and serial correlation for within-group estimators (Arellano 1987; Paulozzi, Kilbourne, and Desai 2011). Because the unit of analysis is states and I have sampled all 50 states and DC, two-way fixed effects allows us to control for market-wide unobservables like drug reformulations, including the sale of tamper-resistant oxycodone, and state-level time-invariant unobservables, like statewide social attitudes toward pain

management. Analysis was conducted in Stata 13.1 using the *xtreg* procedure with fixed effects.

I log-transformed age-adjusted death rate to normalize the distribution and aid with interpretation. The model included our primary predictor, PMP score, along with a vector of possible confounders, X_{it} (naloxone, Good Samaritan laws, pain clinic laws, and medical marijuana dispensaries), a year dummy, a vector of demographic controls (Z_{it}), and state-specific idiosyncratic effects (u_i):

$$\ln(death\ rate_{it}) = \beta_0 + \beta_1 Score_{it} + \omega X_{it} + \delta Year_t + \gamma Z_{it} + u_i + \epsilon_{it}$$

In order to analyze a possible regulatory tipping point, I collapsed score into 4 different classes (scores 1-7=1; scores 8-10=2; scores 11-13=3; scores 14-21=4) to determine if there was greater association at different levels of PMP strength. This roughly approximates the quartile values of the scored variable, though scores cluster in the middle around 8 to 13, suggesting a certain combination of rules may exist. I ran similar models with the inclusion of a categorical variable to control for the type of agency administering the PMP.

I also conducted several sensitivity analyses to ensure robustness of estimates by removing certain regulatory mechanisms that are supported by few or no empirical evidence from the index variable *Score*, including funding and reporting frequency. Likewise, I removed the weighting scheme entirely and treated each regulatory mechanism equally to further test robustness of our approach. Lastly, I ran a similar model with each of the 11 regulatory components as separate covariates to identify which may be associated with reduced OPR overdose deaths.

2.2.3.2 Emergency department discharges

I used the same model specification to test for emergency department discharges by state and year. Data on ED discharges is not as complete as data on fatal overdoses. In this case, I have observations for 37 states. First, I calculated the rate of ED discharges per 100,000 inhabitants by year. The distribution for ED discharge rates is similar to that of overdose deaths. Both are right-skewed and were log-normalized. Here I am interested to see if PMP strength had a similar effect on drug-involved poisonings, controlling for the same list of confounding variables above.

2.3 Results

2.3.1 Descriptive Statistics

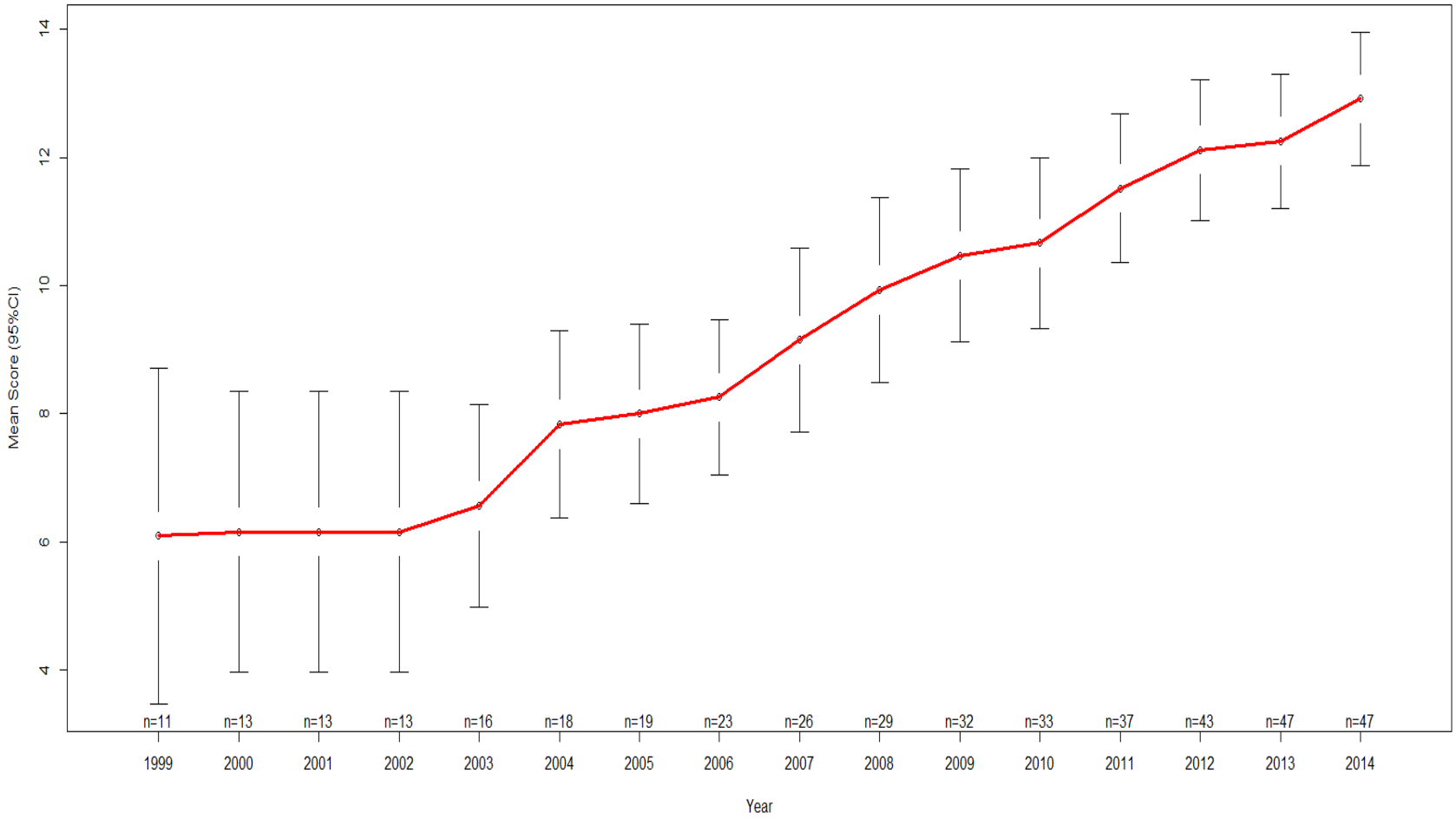
The dependent variable, log of age-adjusted OPR death rate per 100,000 inhabitants, has a minimum of -2.35, a maximum of 3.23 and a mean of 0.75. Our dependent variable of log of age-adjusted heroin death rate per 100,000 inhabitants has a minimum of -2.30, a maximum of 2.59 and a mean of 0.41. Log of ED discharge rates for OPR ranged from -0.096 to 2.56 with a mean of 1.61. Log of ED discharge rates for heroin ranged from -1.53 to 2.07 with a mean of 0.43. See Table 2.2 for a quick reference. I note that the average rates for ED discharges are higher than for overdose deaths.

Table 2.2: Descriptive statistics for dependent variables

Variable	Minimum	Maximum	Mean	Std. Dev.	N
Log of OPR death rate	-2.35	3.23	0.75	0.86	867
Log of heroin death rate	-2.30	2.59	0.41	0.84	469
Log of OPR ED discharge rates	-0.096	2.56	1.61	0.51	468
Log of Heroin ED discharge rates	-1.53	2.07	0.43	0.78	376

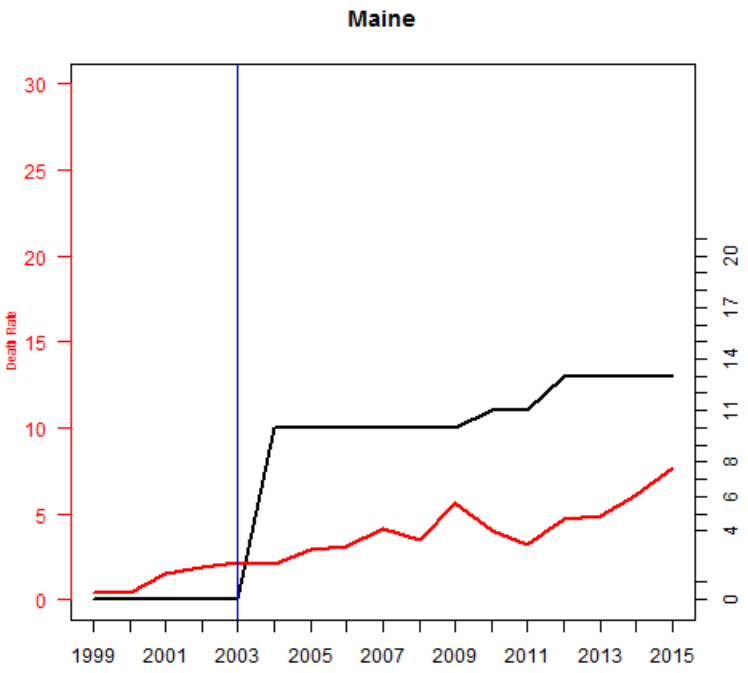
I report descriptive statistics for all independent variables in Tables 2.3 and 2.4. However, I first report some statistics of the main explanatory variable, the PMP index score. The total number of PMPs and their scores have changed over time. The score has a minimum value of 0, maximum value of 21, and a mean of 5.61 with a standard deviation of 6 for all observations. For state-years with an operating PMP (n=468), the score ranges from 1 to 21 with an average of 10.39. Figure 2.2 shows the mean score and variation over time for operational PMPs across the country. Additional state PMP scores are plotted in Figures 2.3 to 2.6 for several states, showing PMP adoption and variation in score over time. Nationally, since 1999, the number and strength of PMPs in place has increased. This is important to consider. Most analyses up to this point have evaluated whether or not a PMP is operational, ignoring the variation across state and over time.

Figure 2.2: Score of Prescription Monitoring Programs, National Average



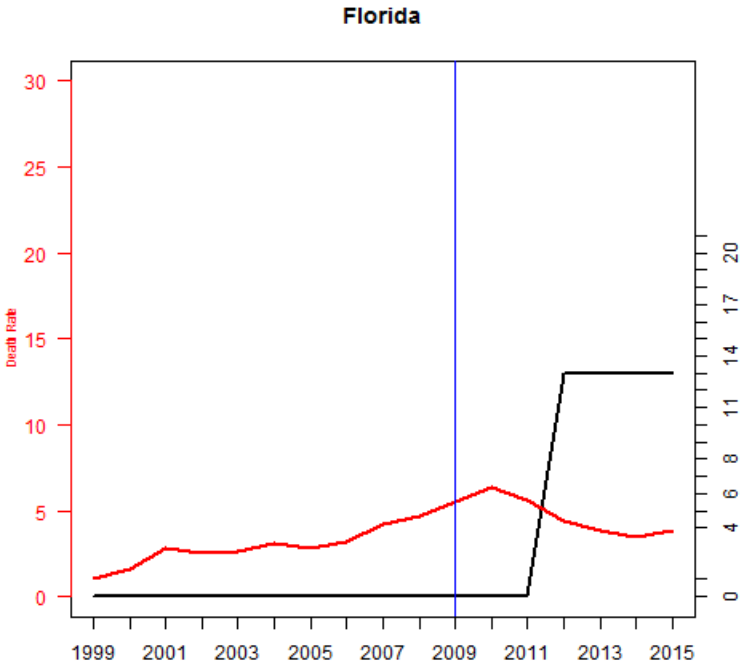
Note: Number of states with operational PMPs denoted by n.

Figure 2.3: Score of Prescription Monitoring Programs, Maine



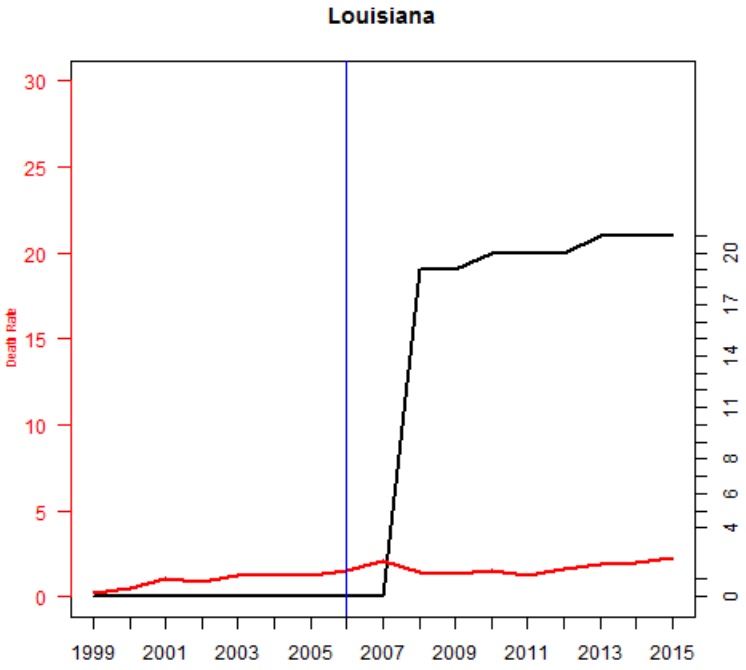
Note: Red line plots opioid overdose deaths; black line plots PMP score; blue vertical line indicates year of legal adoption of PMP

Figure 2.4: Score of Prescription Monitoring Programs, Florida



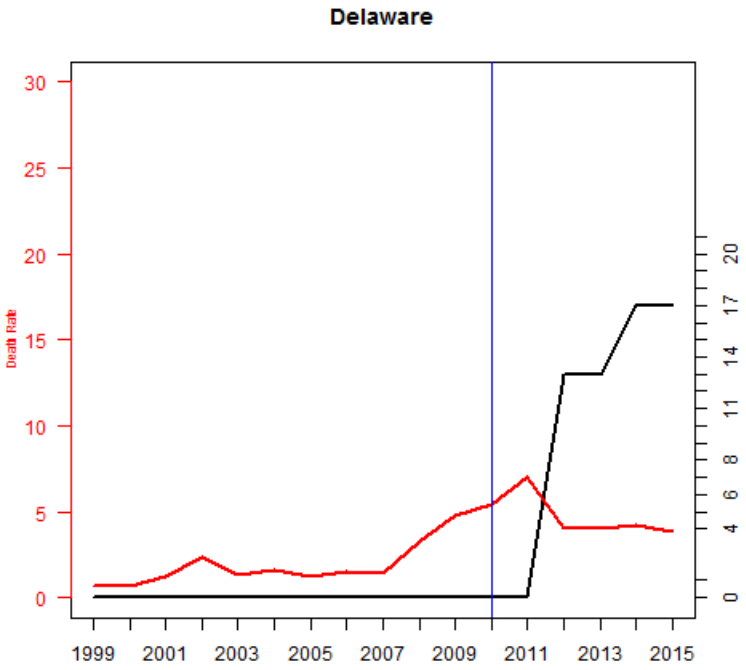
Note: Red line plots opioid overdose deaths; black line plots PMP score; blue vertical line indicates year of legal adoption of PMP

Figure 2.5: Score of Prescription Monitoring Programs, Louisiana



Note: Red line plots opioid overdose deaths; black line plots PMP score; blue vertical line indicates year of legal adoption of PMP

Figure 2.6: Score of Prescription Monitoring Programs, Delaware



Note: Red line plots opioid overdose deaths; black line plots PMP score; blue vertical line indicates year of legal adoption of PMP

Tables 2.3 to 2.6 report descriptive statistics and correlation coefficients between the four outcome variables and each of the variables in the dataset, including the 11 different regulatory mechanisms that make up the composite index score. Those with a coefficient above 0.3 include whether or not the PMP monitors Schedule 3 drugs, permitted or required to identify suspicious activity, allows access to law enforcement or prescribers, has greater reporting frequency, and retains prescription information. Issues of simultaneity likely contribute to the moderate and positive correlation with overdoses; states suffering from increased overdoses are probably adopting such rules. Additionally, these six components are also moderately correlated with each other with a minimum correlation coefficient of 0.58. However, using a fixed effects approach resolves issue of endogeneity due to issues of simultaneity.

I do report similar correlation coefficients for heroin overdose death rates and the eleven different PMP regulatory mechanisms. In this case, I note that only reporting frequency and interstate sharing are correlated with heroin overdose death rates with a correlation coefficient greater than 0.3.

Some of the variables are moderately correlated with prescription opioid ED discharge rates. This includes a positive correlation on certain PMP mechanisms, including access by physicians, frequency reporting, and retention length. The scored index variable was slightly correlated at 0.35. I report fewer correlations for heroin ED discharges. In this case naloxone and Good Samaritan laws are positively correlated with heroin ED discharges (correlation coefficient of 0.40).

Table 2.3: Descriptive Statistics for OPR overdose deaths for states with and without PMPs

		All Observations n=867		No PMP n=399		PMP Operational n=468		Correlation with OPR overdose rates
	variable	mean	sd	mean	sd	mean	sd	PMP operational
1	*Score*	5.60	6.01	--	--	10.39	4.15	0.4
2	*Schedule 3*	0.55	0.5	--	--	0.88	0.33	0.39
3	*Disclosure*	0.36	0.48	--	--	0.58	0.49	0.3
4	*Access by police*	0.57	0.5	--	--	0.89	0.31	0.37
5	*Access by prescribers*	0.53	0.5	--	--	0.83	0.37	0.41
6	*Frequency*	1.35	1.36	--	--	2.24	1.05	0.39
7	*Prescribe*	0.03	0.17	--	--	0.056	0.23	0.15
8	*Share*	0.16	0.37	--	--	0.3	0.46	0.15
9	*Evaluation*	0.17	0.37	--	--	0.20	0.40	0.18
10	*Oversight*	0.25	0.43	--	--	0.37	0.48	0.1
11	*Retention time*	2.63	2.3	--	--	4.07	1.48	0.32
12	*Funding*	0.84	1.13	--	--	1.36	1.17	0.25
13	*Naloxone*	0.13	0.34	0.035	0.18	0.218	0.41	0.22
14	*Samaritan*	0.10	0.30	0.025	0.16	0.167	0.37	0.19
15	*Pain clinic laws*	0.04	0.20	0.0025	0.05	0.077	0.27	0.16
16	*MMJ Dispensary*	0.11	0.31	0.033	0.18	0.173	0.38	0.16
17	*White*	80.8	13.6	80.9	13.3	80.6	13.8	0.13
18	*Income*	55766.3	8571.82	57184.7	9118.4	54557.06	7887.3	-0.18
19	*Education*	81.39	20.45	86.31	8.257	77.20	26.06	-0.16

Note: Variables 2 to 12 were collapsed into our index variable, Score. See Table 2.1 for description of variables.

Table 2.4: Descriptive Statistics for heroin overdose deaths for states with and without PMPs

		All Observations n=469		No PMP n=171		PMP Operational n=298		Correlation with heroin overdose rates
	variable	mean	sd	mean	sd	mean	sd	PMP operational
1	*Score*	6.36	5.97	--	--	10.01	4.41	0.36
2	*Schedule 3*	0.62	0.48	--	--	0.86	0.35	0.28
3	*Disclosure*	0.34	0.47	--	--	0.47	0.5	0.26
4	*Access by police*	0.65	0.48	--	--	0.88	0.33	0.25
5	*Access by prescribers*	0.62	0.49	--	--	0.85	0.36	0.27
6	*Frequency*	1.59	1.34	--	--	2.23	1.03	0.34
7	*Prescribe*	0.04	0.21	--	--	0.07	0.26	0.21
8	*Share*	0.21	0.41	--	--	0.33	0.47	0.34
9	*Evaluation*	0.19	0.39	--	--	0.22	0.41	0.28
10	*Oversight*	0.3	0.46	--	--	0.39	0.49	0.25
11	*Retention time*	3.04	2.24	--	--	4.12	1.49	0.18
12	*Funding*	0.94	1.17	--	--	1.35	1.19	0.13
13	*Naloxone*	0.25	0.43	0.08	0.27	0.34	0.48	0.46
14	*Samaritan*	0.18	0.38	0.03	0.17	0.26	0.44	0.45
15	*Pain clinic laws*	0.07	0.26	0.01	0.08	0.11	0.32	0.21
16	*MMJ Dispensary*	0.18	0.38	0.06	0.24	0.24	0.43	0.25
17	*White*	81.08	8.84	81.02	10.42	81.11	7.8	0.04
18	*Income*	57333.88	8406.12	60145.74	8324.98	55720.36	8032.02	0.04
19	*Education*	86.42	3.17	87.09	2.56	86.03	3.42	-0.41

Note: Variables 2 to 12 were collapsed into our index variable, Score. See Table 2.1 for description of variables.

Table 2.5: Descriptive Statistics for OPR ED discharges for states with and without PMPs

		All Observations n=468		No PMP n=201		PMP Operational n=267		Correlation with OPR ED discharge rates
	variable	mean	sd	mean	sd	mean	sd	PMP operational
1	*Score*	6.06	5.85	--	--	10.61	3.39	0.35
2	*Schedule 3*	0.63	0.48	--	--	0.95	0.22	0.35
3	*Disclosure*	0.4	0.49	--	--	0.6	0.49	0.21
4	*Access by police*	0.62	0.48	--	--	0.91	0.29	0.32
5	*Access by prescribers*	0.6	0.49	--	--	0.9	0.3	0.41
6	*Frequency*	1.43	1.36	--	--	2.28	1.06	0.42
7	*Prescribe*	0.02	0.13	--	--	0.03	0.17	0.2
8	*Share*	0.18	0.38	--	--	0.3	0.46	0.19
9	*Evaluation*	0.2	0.4	--	--	0.22	0.41	0.16
10	*Oversight*	0.24	0.43	--	--	0.31	0.47	0.14
11	*Retention time*	2.82	2.21	--	--	3.9	1.51	0.37
12	*Funding*	0.85	1.13	--	--	1.34	1.2	0.21
13	*Naloxone*	0.12	0.33	0.01	0.1	0.21	0.41	0.03
14	*Samaritan*	0.09	0.29	0.01	0.12	0.15	0.35	0.06
15	*Pain clinic laws*	0.03	0.18	0	0.07	0.05	0.22	0.15
16	*MMJ Dispensary*	0.14	0.35	0.03	0.18	0.22	0.42	0.15
17	*White*	82.21	13.26	84.77	8.19	80.29	15.8	0.23
18	*Income*	55871.09	7894.91	57311	8015.04	54787.12	7640.73	-0.47
19	*Education*	86.58	3.53	87.28	3.17	86.06	3.71	-0.08

Note: Variables 2 to 12 were collapsed into our index variable, Score. See Table 2.1 for description of variables.

Table 2.6: Descriptive Statistics for heroin ED discharges for states with and without PMPs

		All Observations n=376		No PMP n=152		PMP Operational n=224		Correlation with heroin ED discharge rates
	variable	mean	sd	mean	sd	mean	sd	PMP operational
1	*Score*	6.09	5.67	--	--	10.22	3.4	0.18
2	*Schedule 3*	0.64	0.48	--	--	0.95	0.23	0.15
3	*Disclosure*	0.37	0.48	--	--	0.54	0.5	0.13
4	*Access by police*	0.64	0.48	--	--	0.91	0.29	0.22
5	*Access by prescribers*	0.6	0.49	--	--	0.88	0.33	0.07
6	*Frequency*	1.43	1.35	--	--	2.2	1.09	0.19
7	*Prescribe*	0.02	0.14	--	--	0.04	0.19	-0.03
8	*Share*	0.19	0.39	--	--	0.31	0.46	0.23
9	*Evaluation*	0.21	0.41	--	--	0.23	0.42	0.19
10	*Oversight*	0.25	0.44	--	--	0.33	0.47	0.28
11	*Retention time*	2.84	2.23	--	--	3.93	1.53	0.15
12	*Funding*	0.82	1.12	--	--	1.25	1.19	0.08
13	*Naloxone*	0.15	0.36	0.01	0.11	0.25	0.43	0.40
14	*Samaritan*	0.11	0.32	0.02	0.14	0.17	0.38	0.40
15	*Pain clinic laws*	0.04	0.2	0.01	0.08	0.06	0.24	0.03
16	*MMJ Dispensary*	0.18	0.38	0.05	0.21	0.26	0.44	0.17
17	*White*	83.17	8.49	83.95	8.23	82.64	8.64	-0.01
18	*Income*	56486.15	8192.33	59810.22	8248.88	54230.54	7358.23	0.23
19	*Education*	86.35	3.4	87.53	2.81	85.55	3.54	0.19

Note: Variables 2 to 12 were collapsed into our index variable, Score. See Table 2.1 for description of variables.

For the OPR data set (n=897), the majority of PMPs are administered by professional or licensing authorities (26%, n=223), followed by departments of health (23%, n=196), then law enforcement agencies (9%, n=79), then attorneys general offices (4%, n=34), then consumer protection agencies (1%, n=10) and finally by other agencies (0.9%, n=8). West Virginia, though it had a PMP in place according to the law, did not have an administering authority for 2003 due to legal confusion (Crosse 2004).

In terms of other covariates, for states with operational PMPs approximately 22% (n=102) had laws in place to allow access to naloxone, while only 17% (n=78) had passed Good Samaritan laws. Only 8% (n=36) of state-years with operational PMPs had laws in place to regulate pain clinics and 17% (n=81) had legally protected and operational medical marijuana dispensaries.

Table 2.7 compares the differences in overdose death rates and other control variables between states with and without operational PMPs at the beginning, middle, and end of the time series. I conducted a T-test to compare the average overdose rates to determine if differences existed between states with and without operational PMPs for each of the variables considered. As shown, age-adjusted overdose death rates have risen for both groups for both heroin and OPR. Heroin overdose death rates are not significantly different across states or over time. For 2007 and 2015 I do report a significant difference for OPR death rates, with PMP operational states reporting higher overdose death rates. Again, I suspect issues of simultaneity.

Table 2.7: Comparison of states with and without operational PMPs, overdose death rates selected years

	No PMP	PMP Operational	Overall	T-score of overdose rates between No PMP/PMP
	mean	mean	mean	
1999				
Number of states	40	11		
OPR overdose rate	0.82	1.66	1	-1.65 (p=0.12)
Heroin overdose rate[a]	1.06	1.43	1.17	-0.83 (p=0.43)
PMP Score	--	6.09	1.31	
Naloxone	--	--	--	
Good Samaritan	--	--	--	
Pain Clinic Laws	--	--	--	
MMJ Dispensary	--	--	--	
White	82.82	0.09	0.02	0.54 (p=0.60)
Income	57301.68	79.55	82.12	0.05 (p=0.96)
Education	85.93	57184.91	57276.49	1.8* (p=0.09)
2007				
Number of states	25	26		
OPR overdose rate	2.36	3.58	2.98	-2.06** (p<0.05)
Heroin overdose rate[a]	1.54	1.08	1.27	1.35 (p=0.21)
PMP Score	--	9.15	4.67	
Naloxone	0.04	0.08	0.06	-0.55 (p=0.58)
Good Samaritan	--	0.04	0.02	
Pain Clinic Laws	--	--	--	
MMJ Dispensary	--	0.08	0.04	
White	80.38	80.72	80.55	-0.09 (p=0.93)
Income	59459.28	55840.5	57614.41	1.56 (p=0.13)
Education	87.16	84.88	86	2.35** (p=0.02)
2015				
Number of states	3	48		
OPR overdose rate	2.9	4.82	4.71	-2.40* (p=0.064)
Heroin overdose rate[a]	7.6	4.77	4.9	1.21 (p=0.42)
PMP Score	--	12.98	12.22	
Naloxone	0.33	0.56	0.55	-0.67 (p=0.57)
Good Samaritan	0.33	0.48	0.47	-0.43 (p=0.71)
Pain Clinic Laws	--	0.21	0.2	
MMJ Dispensary	0.33	0.35	0.35	-0.06 (p=0.96)
White	72.07	80.43	79.94	-0.54 (p=0.64)
Income	63247	56621.6	57011.33	1.8 (p=0.18)
Education	89.47	88.19	88.26	1.58 (p=0.19)

[a]Fewer observations due to censoring
*** Significant at the 1 percent level. ** Significant at the 5 percent level. * Significant at the 10 percent level.

In Table 2.8 below I compare rates of OPR and heroin ED discharge rates between states with and without operational PMPs for selected years. I report no significant difference across years among states with or without PMPs except for levels of education in 2007.

Table 2.8: Comparison of states with and without operational PMPs, emergency department discharge rates selected years

	No PMP	PMP Operational	Overall	T-score of overdose rates between No PMP/PMP
	mean	mean	mean	
1999				
Number of states	10	4		
OPR ER discharge rate	112.3	229.25	145.71	-0.75 (p=0.50)
Heroin ER discharge rate[a]	116.13	232.25	154.83	-0.93 (p=0.42)
PMP Score	--	7	2	
Naloxone	--	--	--	
Good Samaritan	--	--	--	
Pain Clinic Laws	--	--	--	
MMJ Dispensary	--	0.25	0.07	
White	85.74	67.98	80.66	1.18 (p=0.32)
Income	59158.7	61960.5	59959.21	-0.96 (p=0.36)
Education	87.19	85.45	86.69	0.73 (p=0.50)
2007				
Number of states	16	16		
OPR ER discharge rate	329.38	391.88	360.63	-0.51 (p=0.61)
Heroin ER discharge rate[a]	109.55	122.82	116.18	-0.29 (p=0.78)
PMP Score	--	9.25	4.63	
Naloxone	--	0.06	0.03	-0.55 (p=0.58)
Good Samaritan	--	--	--	
Pain Clinic Laws	--	--	--	
MMJ Dispensary	--	0.13	0.06	
White	83.88	80.59	82.23	0.70 (p=0.49)
Income	58603.19	56668.75	57635.97	0.69 (p=0.50)
Education	87.24	84.82	86.03	1.93* (p=0.06)
2014				
Number of states	2	33		
OPR ER discharge rate	324.5	413.24	408.17	-0.37 (p=0.77)
Heroin ER discharge rate[a]	299	232.03	234.13	--
PMP Score	--	13	12.26	
Naloxone	--	0.61	0.57	
Good Samaritan	--	0.48	0.46	
Pain Clinic Laws	--	0.15	0.14	
MMJ Dispensary	--	0.36	0.34	
White	87.2	81.52	81.84	1.78 (p=0.26)
Income	56815	54742.91	54861.31	1.38 (p=0.18)
Education	89.25	87.7	87.79	1.14 (p=0.41)

[a]Fewer observations due to censoring. T-test cannot be calculated for heroin in 2014 because only 1 state without a PMP reported heroin ER discharges.

*** Significant at the 1 percent level. ** Significant at the 5 percent level. * Significant at the 10 percent level.

2.3.2 Regression Results

2.3.2.1 Overdose deaths

2.3.2.1.1 *Prescription opioids*

The first aim is to estimate the relationship of PMP strength with OPR overdose deaths. Models I and II show that PMP strength, as measured by the score variable, is negatively correlated with OPR overdose deaths. Another aim of this analysis is to measure what level in PMP strength is associated with the greatest reduction in OPR overdose. Models III and IV suggest that PMPs that score in the third quartile are associated with the greatest reduction in OPR overdose deaths. All estimates and standard errors in Table 2.9 are reported using robust standard errors, clustered at the state-level. Here I briefly interpret the findings of our main explanatory variables of interest.

In Model I the coefficient for score is significantly associated with a 1% reduction in the OPR overdose death rate for each point assigned to a state's PMP score. When holding everything else constant, a one point increase in the average PMP score for 2014 is associated with approximately 200 additional lives saved nationwide for that year. Model II suggests that a one point increase in score is significantly associated with a 2% reduction OPR overdose death rate. This translates to approximately 400 additional lives saved nationwide in 2014. I calculate that a 1 point increase in PMP strength at time of adoption comes to, on average, between 1,700 and 3,400 lives saved between 1999 and 2014.

In Model III, when scoring on quartiles, I report a statistically significant negative association with OPR overdose deaths for scores in the third quartiles as compared to states without operational PMPs. Here, PMPs with scores in the third quartile are associated with

about a 19% reduction in OPR overdose death rate. States that scored in the fourth quartile show no significant association and have a smaller magnitude than those in the third quartile. It would appear that there are diminishing regulatory returns as the significance drops when moving to quartile 4 from quartile 3. However, these coefficients are not significantly different when using an F-test to test whether or not they are different from each other. When compared to states without operational PMPs, those that scored in the third quartile are associated with saving, on average, 3500 lives nationwide in 2014, holding everything else constant. Model IV reports similar results. The magnitude increases slightly for PMPs that score in the third quartile. In this specification, PMPs with scores in the third and fourth quartile are significantly associated with a 21% reduction in OPR overdose death rate when compared to a state with no PMP and controlling for administering agency.

In addition to comparing coefficients of quartile score from the referent of no operational PMP, I compute the marginal effect of moving from one quartile to the next in Models III and IV. In Model III each move from one quartile to the next is estimated to reduce overdose deaths by about 4 percent. When controlling for agency in Model IV, a move from one quartile to the next is estimated to reduce OPR overdose by six percent.

Models that include agency report to different agencies are negatively or positively associated with the log of OPR overdose death rate. Consumer protection agencies are significantly associated with an increase in overdoses in one model specified. When law enforcement administers the PMP models report a negative association on OPR overdoses. Law enforcement was significantly associated with a reduction in overdose deaths in models specified.

In models where I treat the score as a continuous variable, access to naloxone was associated with fewer OPR overdose deaths, though insignificant. Good Samaritan laws were positively associated with OPR overdose deaths, though insignificant as well. Controlling for demographic covariates had little impact on models. Coefficients for whether or not a state had a pain clinic law in place were negative but non-significant for all models specified. Coefficients on operational medical marijuana dispensaries are negative but not statistically significant for models considered.

I do not report the outputs from all of the sensitivity analyses where I altered the value of the *Score* variable. The removal of different rules or weighting from the score did little to change regression estimates or their significance, except for *Score* in Model I when reporting frequency was removed ($p=0.20$). Likewise, removing the weighting scheme increased estimate magnitude for *Score* (upwards of 80%), but direction remained negative. In Models III and IV, unweighted scores shifted significance to the fourth quartile, though magnitude slightly decreased while direction remained the same. See Table 2.14 for estimates of the unweighted sensitivity analysis. When running the model with each of the 11 regulatory components as covariates instead of a composite S*core*, I report that only reporting frequency is significant with reduced overdose deaths ($p<0.05$).

In terms of the progression from quartiles, about half (23) of state PMPs increase from one quartile to another (e.g., either from quartile 1 to quartile 2, or 3 to 4). Of those, six move up by two quartiles through the series (e.g., quartile 1 to 3 or 2 to 4). Throughout the entire time series, 17 states moved from a potential tipping point between quartiles 2 and 3, which is associated with the greatest reduction in OPR overdose deaths.

Table 2.9: Analysis of log of age-adjusted OPR overdose death rate, SEs calculated with state-level clustered robust standard errors.

Regressors	Model I† $\widehat{\boldsymbol{\beta}}$ (SE) N=867	Model II‡ $\widehat{\boldsymbol{\beta}}$ (SE) N=867	Model III† $\widehat{\boldsymbol{\beta}}$ (SE) N=867	Model IV‡ $\widehat{\boldsymbol{\beta}}$ (SE) N=867
Score (continuous)	-0.01* (.006)	-0.016** (0.01)		
Score[a] (class)				
1st quartile			-0.03 (0.11)	-0.04 (0.01)
2nd quartile			0.09 (0.08)	0.07 (0.07)
3rd quartile			-0.2** (0.1)	-0.23** (0.1)
4th quartile			-0.19 (0.12)	-0.23** (0.11)
Agency[b]				
Law Enforcement		-0.29*** (0.09)		-0.41*** (0.08)
Department of Health		0.09 (0.12)		0.05 (0.1)
Consumer Protection		0.21* (0.12)		0.09 (0.12)
Professional and licensing		0.15 (0.1)		0.08 (0.1)
Other		0.26 (0.17)		0.14 (0.13)
Naloxone	0.04 (0.13)	0.08 (0.12)	0.05 (0.12)	0.08 (0.12)
Good Samaritan Laws	0.04 (0.12)	0.02 (0.1)	0.01 (0.11)	0.003 (0.11)
Pain Clinic Laws	-0.04 (0.13)	-0.02 (0.13)	-0.06 (0.13)	-0.05 (0.13)
Med. Marijuana Dispensary	-0.15 (0.11)	-0.15 (0.11)	-0.17 (0.1)	-0.17 (0.1)
Education	0.04 (0.03)	0.04 (0.02)	0.04 (0.02)	0.04 (0.02)
White	-0.05 (0.05)	-0.06 (0.05)	-0.06 (0.04)	-0.07 (0.04)
Income (in thousands)	-0.009 (0.008)	-0.008 (0.007)	-0.008 (0.008)	-0.007 (0.008)
R^2 within	0.71	0.72	0.72	0.72
σ_u	1.01	1.05	1.10	1.14
σ_e	0.37	0.37	0.37	0.37
ρ	0.88	0.89	0.90	0.91

[a]Ref=no PMP; [b]Ref=no agency; Attorneys General offices were dropped from output because they were time invariant as California and Pennsylvania had AG-administered PMPs that predate our time series.
†Controlling for year, naloxone, Good Samaritan laws, pain clinic laws, medical marijuana dispensaries and demographic factors
‡Controlling for type of administering agency, year, naloxone, Good Samaritan laws, pain clinic laws, medical marijuana dispensaries and demographic factors.
Parameters are rounded to 2 significant digits. Year dummies omitted to save space in output.
*** Significant at the 1 percent level. ** Significant at the 5 percent level. * Significant at the 10 percent level.

2.3.2.1.2 *Heroin*

Given that OPR and heroin are both opioids, it is plausible that policies aimed at restricting access to prescription opioids may encourage some individuals to seek opioid substitutes found in the illicit market. The literature on the pathway from OPR to heroin suggests that some proportion of OPR users may move on to heroin, though the mechanisms are not well understood (Compton, Jones, and Baldwin 2016). Therefore, I run similar models to determine if there is a displacement effect toward heroin. Estimates are reported in Table 2.10. Here I interpret the main coefficient of interest on PMP score for models considered. I expect to see a positive sign on Score estimates.

In all models, PMP strength is not significantly associated with heroin overdose deaths. The magnitude of the estimates for all models considered is smaller than those for regressions of OPR death rates. The sign for Model I, when Score is a continuous variable, is positive. When I examine PMP strength by quartile (Models III and IV) the sign changes from quartiles 1 to 2 and from 3 to 4. Again, these coefficients are not significant. In this case, estimates do not suggest that there is a relationship between PMP strength and heroin overdose. This converges with some early literature on the relationship between PMPs and heroin use and initiation (Ali et al. 2017).

In terms of demographic covariates, percentage white is positively and significantly associated with overdose deaths. Income is negatively and significantly associated with overdose deaths for two of the models considered (Models I and III).

I do report a positive and significant relationship for access to naloxone in all models. In this case, naloxone is associated with a 30-36% increase in heroin overdose deaths.

Because the variable on naloxone is a binary indicator, measuring whether or not a state has such a law in place in a given year, it may not accurately reflect how much naloxone is distributed or used. Studies have shown that naloxone reverses opioid overdose when administered to an individual (Sarz Maxwell MD et al. 2006; Straus, Ghitza, and Tai 2013) and I am cautious when interpreting these findings.

Table 2.10: Analysis of log of age-adjusted heroin overdose death rate, SEs calculated with state-level clustered robust standard errors.

Regressors	Model I† $\widehat{\boldsymbol{\beta}}$ (SE) N=469	Model II‡ $\widehat{\boldsymbol{\beta}}$ (SE) N=469	Model III† $\widehat{\boldsymbol{\beta}}$ (SE) N=469	Model IV‡ $\widehat{\boldsymbol{\beta}}$ (SE) N=469
Score (continuous)	0.002 (0.012)	-0.001 (0.012)		
Score[a] (class)				
1st quartile			-0.04 (0.19)	-0.03 (0.18)
2nd quartile			0.04 (0.15)	0.07 (0.144)
3rd quartile			-0.11 (0.15)	-0.12 (0.14)
4th quartile			0.14 (0.21)	0.06 (0.21)
Agency[b]				
Law Enforcement		-0.49*** (0.15)		-0.55*** (0.15)
Department of Health		-0.24 (0.2)		-0.2 (0.19)
Consumer Protection		-0.34* (0.19)		-0.36* (0.2)
Professional and licensing		0.23* (01.3)		0.22 (0.13)
Other		0.05 (0.22)		-0.003 (0.2)
Naloxone	0.26* (0.139)	0.31** (0.14)	0.27** (0.13)	0.3** (0.12)
Good Samaritan Laws	0.01 (0.135)	0.02 (0.13)	0.03 (0.13)	0.03 (0.12)
Pain Clinic Laws	0.094 (0.27)	0.13 (0.24)	0.06 (0.26)	0.08 (0.23)
Med. Marijuana Dispensary	-0.089 (0.116)	-0.07 (0.11)	-0.14 (0.11)	-0.12 (0.1)
Education	0.006 (0.04)	0.02 (0.04)	0.01 (0.04)	0.02 (0.04)
White	0.397*** (0.1)	0.33*** (0.11)	0.4*** (0.11)	0.32*** (0.11)
Income (in thousands)	-0.02** 0.009	-0.015 (0.01)	-0.018** (0.009)	-0.015 (0.01)
R^2 within	0.73	0.74	0.73	0.75
σ_u	4.38	3.64	4.43	3.58
σ_e	0.38	0.37	0.38	0.37
ρ	0.99	0.99	0.99	0.99

[a]Ref=no PMP; [b]Ref=no agency; Attorneys General offices were dropped from output because they were time invariant as California and Pennsylvania had AG-administered PMPs that predate our time series.
†Controlling for year, naloxone, Good Samaritan laws, pain clinic laws, medical marijuana dispensaries and demographic factors
‡Controlling for type of administering agency, year, naloxone, Good Samaritan laws, pain clinic laws, medical marijuana dispensaries and demographic factors.
Parameters are rounded to 2 significant digits. Year dummies omitted to save space in output.
*** Significant at the 1 percent level. ** Significant at the 5 percent level. * Significant at the 10 percent level.

2.3.2.1.3 *Heroin and fentanyl-laced heroin*

The number of fentanyl-related overdose deaths has risen sharply since 2012. CDC and DEA note that starting around 2012/13 the importation and distribution of fentanyl-laced heroin increased sharply (Gladden 2016). As shown in Figure 2.1, the number of synthetic opioid overdose deaths more than tripled between 2012 and 2015 to more than 9,500, largely due to fentanyls (NCHS 2015). The illicit nature of the products sold in the illicit market means that users are often unaware that the powder they just purchased contains fentanyl.

Synthetic opioids continue to be sold in illicit opioid markets, mostly disguised as heroin (NDEWS 2016). It is too early to tell if the drug and its analogs will supplant heroin and prescription drugs as the dominant illicitly traded opioid in the United States. Yet according to one recent report, users may be seeking out fentanyl in some markets in New England (NDEWS 2016). As fentanyl continues to permeate the illicit market, I consider a separate outcome measure under the assumption that heroin-coded deaths may not capture the true nature of the problem as some might be attributed to illicit fentanyl. In addition to heroin-attributed overdose deaths, I measure the share of overdose deaths attributed to heroin and fentanyl-laced heroin. Not all deaths for synthetic opioids are attributable to illicit fentanyl, especially for years prior to 2012. I therefore deflate post-2012 deaths to account for the steady rate of overdoses for synthetic opioids not attributable to illicit fentanyl. Without the full CDC multiple cause of death data, I am unable to project fentanyl-related overdose deaths using demographic factors similarly to other recent studies (Ruhm 2017).

In order to measure the number of deaths attributed to fentanyl sold in the illicit market, I examine the average number of deaths for synthetic opioids between 1999 and 2005, which were fairly stable across states. During 2006 and 2007 there was a brief period where fentanyl entered the illicit heroin market (DEA 2006; NFLIS 2008). Since I am trying to deflate synthetic opioid overdose deaths to account for "natural" overdoses from synthetic opioids not attributed to illicit fentanyl (such as deaths attributed to tramadol or fentanyl patches), I calculate the six year average from 1999 to 2005. I then subtract out this average death count by state for years starting in 2013 to estimate a count of deaths attributed to illicit fentanyl. I then add these estimated fentanyl overdose deaths to heroin-attributed overdose deaths to obtain a total count for heroin and fentanyl-laced heroin.

This approach is problematic for various reasons. Namely, multiple cause of death counts provided by CDC are not exclusive. An individual death may be coded with both heroin and synthetic opioids. Ideally I would be able to isolate the individual synthetic deaths from the heroin deaths using the full multiple cause of death data. Nonetheless, this examination of heroin and fentanyl-laced heroin is a preliminary approach to assessing the hypothesis that prescription monitoring may have displaced users to illicit markets where heroin deaths may be subject to greater under-reporting.

I run the same models with these estimated death counts to determine if a displacement effect occurred with respect to heroin and fentanyl-laced heroin. Table 2.11 reports these estimates. I report no relationship between PMP strength and estimated per capita overdose counts of heroin and fentanyl-laced heroin. Models estimate a similar positive and significant relationship for access to naloxone and a similar negative relationship with income as was reported in Table 2.10. In Models II and IV, where I measure PMP by

quartile, I report a significant and substantial negative relationship with operational medical marijuana dispensaries.

Table 2.11: Analysis of log of age-adjusted estimated heroin/fentanyl overdose death rate, SEs calculated with state-level clustered robust standard errors.

	Model I†	Model II‡	Model III†	Model IV‡
	$\widehat{\boldsymbol{\beta}}$ (SE)	$\widehat{\boldsymbol{\beta}}$ (SE)	$\widehat{\boldsymbol{\beta}}$ (SE)	$\widehat{\boldsymbol{\beta}}$ (SE)
Regressors	**N=534**	**N=534**	**N=534**	**N=534**
Score (continuous)	0.003 (0.011)	-0.0007 (0.011)		
Score[a] (class)				
1st quartile			-0.03 (0.2)	-0.004 (0.19)
2nd quartile			0.11 (0.16)	0.15 (0.16)
3rd quartile			-0.077 (0.16)	-0.09 (0.15)
4th quartile			0.18 (0.21)	0.11 (0.22)
Agency[b]				
Law Enforcement		-0.71*** (0.19)		-0.82*** (0.19)
Department of Health		-0.29 (0.21)		-0.28 (0.2)
Consumer Protection		-0.47** (0.21)		-0.51** (0.23)
Professional and licensing		0.28* (0.16)		0.25 (0.15)
Other		-0.15 (0.30)		-0.23 (0.27)
Naloxone	0.28* (0.16)	0.35** (0.15)	0.28* (0.14)	0.34** (0.14)
Good Samaritan Laws	-0.05 (0.15)	-0.056 (0.14)	-0.02 (0.14)	-0.04 (0.13)
Pain Clinic Laws	0.25 (0.27)	0.29 (0.25)	0.19 (0.27)	0.22 (0.24)
Med. Marijuana Dispensary	-0.22 (0.15)	-0.18 (0.15)	-0.28* (0.14)	-0.25* (0.14)
Education	0.04 (0.06)	0.058 (0.05)	0.04 (0.05)	0.057 (0.05)
White	0.12 (0.11)	0.08 (0.11)	0.11 (0.11)	0.075 (0.1)
Income (in thousands)	-0.028** (0.013)	-0.024* (0.013)	-0.026** (0.012)	-0.023* (0.013)
R^2 within	0.76	0.78	0.76	0.78
σ_u	1.69	1.46	1.63	1.35
σ_e	0.44	0.43	0.44	0.43
ρ	0.94	0.92	0.93	0.91

[a]Ref=no PMP; [b]Ref=no agency; Attorneys General offices were dropped from output because they were time invariant as California and Pennsylvania had AG-administered PMPs that predate our time series.
†Controlling for year, naloxone, Good Samaritan laws, pain clinic laws, medical marijuana dispensaries and demographic factors
‡Controlling for type of administering agency, year, naloxone, Good Samaritan laws, pain clinic laws, medical marijuana dispensaries and demographic factors.
Parameters are rounded to 2 significant digits. Year dummies are omitted to save space in output.
*** Significant at the 1 percent level. ** Significant at the 5 percent level. * Significant at the 10 percent level.

2.3.2.2 Emergency department discharges

2.3.2.2.1 *Prescription opioids*

In order to measure the impact on morbidity that PMPs have, I report the association between PMP score and the log of the rate of ED discharges for OPR or heroin. Again, I have fewer observations than overdose death fatalities as some states do not report data to HCUP. This data set contains 468 observations from 35 states. In this case, I report a negative relationship with PMP and ED discharges for prescription opioids. In Models I and II, a one point increase in PMP score is associated with a less than 1% reduction in prescription opioid ED discharges. In Models II and IV, when controlling for administering agency, models report a significant negative relationship. In Model II, a one point increase in PMP score is associated with a less than one percent reduction in ED discharges for prescription opioids. In Models III and IV, I report that PMPs in the 4^{th} quartile are associated with approximately 11-12% fewer ED discharges for prescription opioids when compared to a state-year without a PMP.

Education, access to naloxone, and an operational medical marijuana dispensary are also negatively, and sometimes significantly, associated with fewer ED discharges for prescription opioids. In this case, an operational medical marijuana dispensary is associated with approximately 6% fewer ED discharges. These findings support findings reported in Table 2.9 that PMP strength is negatively associated with prescription opioid mortality and significant at the 10% level.

Table 2.12: Analysis of log of OPR ED discharge rates, SEs calculated with state-level clustered robust standard errors.

Regressors	Model I† $\widehat{\boldsymbol{\beta}}$ (SE) N=468	Model II‡ $\widehat{\boldsymbol{\beta}}$ (SE) N=468	Model III† $\widehat{\boldsymbol{\beta}}$ (SE) N=468	Model IV‡ $\widehat{\boldsymbol{\beta}}$ (SE) N=468
Score (continuous)	-0.007* (0.004)	-0.0078* (0.0039)		
Score[a] (class)				
1st quartile			0.043 (0.051)	0.042 (0.055)
2nd quartile			-0.039 (0.046)	-0.039 (0.047)
3rd quartile			-0.039 (0.042)	-0.039 (0.041)
4th quartile			-0.12* (0.069)	-0.13* (0.066)
Agency[b]				
Law Enforcement		-0.02 (0.037)		-0.047 (0.045)
Department of Health		-0.018 (0.056)		-0.041 (0.06)
Consumer Protection		-		-
Professional and licensing		0.068 (0.043)		0.04 (0.038)
Other		0.18*** (0.059)		0.15 (0.06)
Naloxone	-0.049 (0.045)	-0.04 (0.04)	-0.048 (0.041)	-0.044 (0.041)
Good Samaritan Laws	0.032 (0.029)	0.037 (0.027)	0.017 (0.013)	0.025 (0.029)
Pain Clinic Laws	-0.0026 (0.032)	0.026 (0.04)	0.056 (0.048)	0.081 (0.058)
Med. Marijuana Dispensary	-0.06* (0.033)	-0.064* (0.033)	-0.059 (0.035)	-0.06* (0.035)
Education	-0.018* (0.01)	-0.016 (0.011)	-0.02 (0.01)	-0.018* (0.01)
White	0.029 (0.029)	0.029 (0.03)	0.029 (0.029)	0.028 (0.03)
Income (in thousands)	-0.0021 (0.0029)	-0.0014 (0.003)	-0.0019 (0.0029)	-0.0013 (0.0029)
R^2 within	0.90	0.90	0.90	0.90
σ_u	0.34	0.35	0.35	0.34
σ_e	0.13	0.13	0.13	0.13
ρ	0.87	0.87	0.88	0.88

[a]Ref=no PMP; [b]Ref=no agency; Attorneys General offices were dropped from output because they were time invariant as California and Pennsylvania had AG-administered PMPs that predate our time series. No states in series had PMPs administered by Consumer Protection Agencies.

†Controlling for year, naloxone, Good Samaritan laws, pain clinic laws, medical marijuana dispensaries and demographic factors

‡Controlling for type of administering agency, year, naloxone, Good Samaritan laws, pain clinic laws, medical marijuana dispensaries and demographic factors.

Parameters are rounded to 2 significant digits. Year dummies are omitted to save space in output.

*** Significant at the 1 percent level. ** Significant at the 5 percent level. * Significant at the 10 percent level.

2.3.2.2.2 *Heroin*

I also evaluate potential displacement from prescription opioids to heroin by running a similar model but with log of the rate of ED discharges for heroin. Here, fewer states report ED discharges, with a total of 376 observations for 35 states. In all models considered I report no significant association with heroin ED discharges. The sign on our explanatory variable of PMP score is negative and positive depending on model considered. I do note that in Models III and IV, where PMP score is collapsed into quartiles, the magnitude and direction change. Generally the coefficients diminish in absolute value going from quartiles one to three and become positive in quartile four. Though estimates are not significant, I note the monotonicity of coefficient estimates for PMP score in Model III

Most covariates report no relation with the rate of heroin ED discharges. Proportion white is significantly associated with more ED discharges for heroin. In this case, a one percentage point increase in the proportion of white residents per state is associated with up to 21% more ED discharges for heroin.

The null results reported in Table 2.13 replicate results reported in Table 2.10. In Table 2.10 I report no association with PMP strength and heroin mortality. Here I report a similar null relationship with PMP strength and heroin morbidity. However, coefficients are smaller in magnitude and trend positively when examining PMP strength by quartile, suggesting more restrictive PMPs are non-significantly associated with greater heroin morbidity versus state-years without an operational PMP.

Table 2.13: Analysis of log of heroin ED discharge rates, SEs calculated with state-level clustered robust standard errors.

Regressors	Model I† $\widehat{\beta}$ (SE) N=376	Model II‡ $\widehat{\beta}$ (SE) N=376	Model III† $\widehat{\beta}$ (SE) N=376	Model IV‡ $\widehat{\beta}$ (SE) N=376
Score (continuous)	-0.002 (0.008)	-0.0004 (0.01)		
Score[a] (class)				
1st quartile			-0.14 (0.18)	-0.099 (0.178)
2nd quartile			-0.077 (0.11)	-0.018 (0.121)
3rd quartile			-0.053 (0.11)	-0.025 (0.118)
4th quartile			0.058 (0.14)	0.04 (0.144)
Agency[b]				
Law Enforcement		-0.36*** (0.087)		-0.32*** (0.11)
Department of Health		-0.28 (0.19)		-0.25 (0.18)
Consumer Protection		-		-
Professional and licensing		0.089 (0.13)		0.12 (0.13)
Other		-0.23 (0.19)		-0.2 (0.19)
Naloxone	0.038 (0.14)	0.056 (0.14)	0.036 (0.14)	0.059 (0.13)
Good Samaritan Laws	-0.14 (0.13)	-0.14 (0.12)	-0.11 (0.12)	-0.12 (0.11)
Pain Clinic Laws	0.14 (0.34)	0.24 (0.32)	0.045 (0.37)	0.17 (0.32)
Med. Marijuana Dispensary	0.002 (0.11)	0.066 (0.13)	0.011 (0.12)	0.06 (0.13)
Education	-0.022 (0.03)	-0.012 (0.032)	-0.02 (0.03)	-0.01 (0.03)
White	0.17* (0.09)	0.19** (0.085)	0.19** (0.09)	0.19** (0.089)
Income (in thousands)	-0.0053 (0.0081)	-0.0029 (0.0086)	-0.006 (0.0081)	-0.003 (0.0081)
R^2 within	0.65	0.67	0.65	0.67
σ_u	2.40	2.68	2.57	2.71
σ_e	0.30	0.29	0.30	0.29
ρ	0.98	0.99	0.99	0.99

[a]Ref=no PMP; [b]Ref=no agency; Attorneys General offices were dropped from output because they were time invariant as California and Pennsylvania had AG-administered PMPs that predate our time series. No states in series had PMPs administered by Consumer Protection Agencies.

†Controlling for year, naloxone, Good Samaritan laws, pain clinic laws, medical marijuana dispensaries and demographic factors

‡Controlling for type of administering agency, year, naloxone, Good Samaritan laws, pain clinic laws, medical marijuana dispensaries and demographic factors.

Parameters are rounded to 2 significant digits. Year dummies are omitted to save space in output.

*** Significant at the 1 percent level. ** Significant at the 5 percent level. * Significant at the 10 percent level.

2.4 Discussion

The majority of the literature ignores the variation in PMP strength. However, scoring shows that strength matters. An additional one point increase in the score of PMP is associated with a 1-2% reduction in OPR overdose death rate. When collapsing PMP score into quartiles, I report a stronger magnitude for PMPs in the third and fourth quartiles, upwards of 20%, when compared to state-years without a PMP. I evaluate the impact that PMP strength has on prescription opioid morbidity, in this case discharges from emergency departments. I report a similar negative relationship; PMP strength is associated with reductions in the rate of emergency department discharges for prescription opioids. There was no significant association between PMP strength and heroin-related outcomes.

Because our PMP score may not reflect the true value of PMP strength, I conducted several sensitivity analyses by removing regulatory mechanisms or score weights. When removing funding or reporting frequency from score, as well as dropping weights, I report modest changes in results. Coefficient estimates using the weighting scheme are slightly conservative in magnitude compared to the unweighted score. Reporting frequency is the only regulatory mechanism that is significantly associated with reduced OPR overdose deaths when treating each regulatory component as individual covariates. Arguably all components, along with the weighting scheme, show that differences matter. Recent research suggests that similar programmatic differences are negatively associated with OPR overdose deaths (Patrick et al. 2016). Analysis here suggests that such combinations matter. Coefficient estimates for the unweighted analysis are reported in Table 2.14. As shown, estimated effect size for coefficients is larger by upwards of 80 percent. Significance and direction remain the same for models when compared to the weighted

analysis. Again, the only difference is the significance on score when collapsed into quartiles. Using an unweighted analysis, quartile 4 is negatively associated with reductions in overdose deaths instead of quartile 3.

Comparing the weighted and unweighted analysis, I show that weighting the score produces more conservative estimates of effect size. Additionally, as argued earlier, weighting produces a more accurate measure of policy impact as some regulatory mechanisms of PMP design have a greater association with changes in prescriber practices.

The average PMP scores 10 on my summative weighted scale. Comparing a state with the average PMP to a state without an operational PMP suggests that, holding all else constant, the state with a PMP will have 10% fewer prescription opioid overdose deaths. In terms of overdose deaths averted, I calculate that in 2014 an additional 200 lives would have been saved had states adopted one additional point to their PMP design. This is just one point in time. I calculate that a 1 point increase in PMP strength at time of adoption comes to, on average and depending on administering agency, between 1,700 and 3,400 lives saved between 1999 and 2014.

Table 2.14: Analysis of log of age-adjusted OPR overdose death rate, Unweighted Score SEs calculated with state-level clustered robust standard errors.

Regressors	Model I† $\widehat{\beta}$ (SE) N=376	Model II‡ $\widehat{\beta}$ (SE) N=376	Model III† $\widehat{\beta}$ (SE) N=376	Model IV‡ $\widehat{\beta}$ (SE) N=376
Score (continuous)	-0.018* (.011)	-0.028*** (0.001)		
Score[a] (class)				
1st quartile			0.21 (0.19)	0.17 (0.18)
2nd quartile			-0.03 (0.08)	-0.04 (0.07)
3rd quartile			-0.007 (0.11)	-0.04 (0.1)
4th quartile			-0.18* (0.1)	-0.23** (0.09)
Agency[b]				
Law Enforcement		-0.30*** (0.07)		-0.37*** (0.09)
Department of Health		0.09 (0.12)		-0.25 (0.18)
Consumer Protection		0.21* (0.12)		-
Professional and licensing		0.16 (0.1)		0.12 (0.13)
Other		0.25 (0.18)		0.17 (0.15)
Naloxone	0.05 (0.13)	0.09 (0.12)	0.08 (0.12)	0.10 (0.12)
Good Samaritan Laws	0.04 (0.12)	0.02 (0.1)	0.01 (0.11)	0.0002 (0.1)
Pain Clinic Laws	-0.05 (0.13)	-0.03 (0.13)	-0.002 (0.13)	0.01 (0.13)
Med. Marijuana Dispensary	-0.15 (0.11)	-0.15 (0.11)	-0.16 (0.11)	-0.15 (0.11)
Education	0.04 (0.02)	0.04 (0.02)	0.04 (0.02)	0.04 (0.02)
White	-0.06 (0.05)	-0.06 (0.05)	-0.06 (0.04)	-0.06 (0.04)
Income (in thousands)	-0.008 (0.008)	-0.008 (0.008)	-0.008 (0.008)	-0.008 (0.008)
R^2 within	0.71	0.72	0.71	0.72
σ_u	1.02	1.06	1.05	1.09
σ_e	0.37	0.37	0.37	0.37
ρ	0.88	0.89	0.89	0.90

[a]Ref=no PMP; [b]Ref=no agency; Attorneys General offices were dropped from output because they were time invariant as California and Pennsylvania had AG-administered PMPs that predate our time series. No states in series had PMPs administered by Consumer Protection Agencies.

†Controlling for year, naloxone, Good Samaritan laws, pain clinic laws, medical marijuana dispensaries and demographic factors

‡Controlling for type of administering agency, year, naloxone, Good Samaritan laws, pain clinic laws, medical marijuana dispensaries and demographic factors.

Parameters are rounded to 2 significant digits. Year dummies are omitted to save space in output.

*** Significant at the 1 percent level. ** Significant at the 5 percent level. * Significant at the 10 percent level.

I also evaluate any potential displacement effect that PMPs may have in the wider opioid market. Today's discussion surrounding heroin abuse stems from the notion that

restrictions on prescription opioids has encouraged some proportion of opioid users to seek out substitutes in the illicit market (Alpert, Powell, and Pacula 2017; Cicero, Ellis, and Surratt 2012). In this case, models considered do not report any significant positive relationship with PMP strength and heroin morbidity or mortality. I would expect a significant and positive relationship if this were the case. The fixed effects models considered suggest no relationship between heroin morbidity and mortality and PMP strength. When examining heroin morbidity, I do report an upward monotonic relationship between PMP quartile strength and ED discharges for heroin (Model III). Yet these estimates are not significant.

Further examination into a PMP's minimal standards should be a research and policy priority. In 2016 Congress passed and the President signed the Comprehensive Addiction and Recovery Act to strengthen and evaluate PMPs. Such a law may help determine which regulatory mechanisms have the biggest impact on reducing overdose deaths. Analysis here is preliminary and suggests that work ought to be done to determine which combination of regulatory mechanisms have the greatest association with reducing OPR overdoses. An appropriate factor or latent class analysis could tease out such insights. This early research indicates that such policy mechanisms and differences matter when it comes to the effectiveness of prescription drug monitoring.

A latent class analysis or factor analysis would allow researchers to tease out the potential combinations or constellations of regulatory mechanisms that have the greatest association with reductions in OPR-related outcomes of interest. My attempt to find a tipping point in regulatory mechanisms through the means of collapsing score into quartiles is merely a preliminary evaluation of such regulatory combinations. Analysis using the index score in

this body of research only shows that regulatory differences across states and over time within a state does seem to matter. Yet a latent class or factor analysis will allow a researcher to determine *which* policy mechanisms or combinations therein do indeed matter most. It could be that a handful of PMP "classes" exist. Some may be "in name only" with some bare minimum of standards; others may be "reactive", having some level of impact investigating the most egregious prescribers; and some may be "proactive" in nature, working hard to deter doctor shopping or diversion. I only speculate here without having made the effort to evaluate these distinctions. This is one area of future research.

The type of administering agency might also be associated with reductions in overdose rates. Law enforcement administration of a PMP seems to have the greatest protective factor on OPR overdose. Two explanations may drive this. First, many of the earlier PMPs were law enforcement focused, perhaps making them more experienced than later PMPs. Second, stated goals of many PMPs are to reduce misuse or inappropriate use of prescription drugs, rather than promote patient health (C. S. Davis, Johnston, and Pierce 2015). Law enforcement priorities align closely with those stated goals.

Good Samaritan laws and naloxone expansion programs appear to have no significant association on OPR mortality or morbidity. This could be due in part to the fact that few of these laws existed throughout the time series. Further, differences in these laws exist, yet, due to lack of legal data, I fail to capture their relative differences in this analysis. Analyses have shown that these programs are associated with reduced OPR overdose deaths within a state (Doe-Simkins et al. 2009; Sumner et al. 2016; Doyon et al. 2016).

However, access to naloxone is significantly associated with more heroin overdoses. Regression outputs report an increase in illicit opioid overdose death rates, upwards of 30%. I am cautious to attribute a positive relationship with naloxone and increased heroin mortality. I suspect issues of simultaneity are biasing results. Given that this is a binary indicator, this may not be appropriately measuring the degree of access to naloxone. Some states have loosened restrictions, allowing individuals to obtain it over the counter; others have limited access to first responders. More work is needed to evaluate these policy differences.

Reductions in ED discharges for OPR are associated with the presence of medical marijuana dispensaries support a substitution effect as reported in recent research (Powell, Pacula, and Jacobson 2015; Smart 2015; Bradford and Bradford 2016). However, I caution against reading too much into this given the small number of state-years reporting operational medical marijuana dispensaries (9% of sample). More research in the coming years may help determine if such a relationship is meaningful.

The impact of strengthening PMPs might have unintended consequences. In the United States, some research suggested a displacement of use toward heroin (Mars et al. 2014; Cicero, Ellis, and Surratt 2012; Alpert, Powell, and Pacula 2017). Abrupt restrictions on the supply of OPR may encourage some drug users to seek substitutes in the illicit market, though it is unclear what proportion of OPR users migrate to heroin (Compton, Jones, and Baldwin 2016). It should be a concern for policymakers who wish to avoid a displacement toward illicit opioids. This early research suggests that such a significant and positive association is not readily apparent. Findings here do not report any significant relationship between PMP strength and increased morbidity or mortality of illicit street opioids. This

supports other early evaluations (Ali et al. 2017). Nonetheless, given that the heroin and fentanyl epidemic is fairly recent, such a relationship may not be readily established with existing data. Future research analyzing any potential displacement effect will need to consider a lagged effect that supply control policies on OPR may have. For example, supply restrictions related to effective PMP design may not shift total market supply of OPR due to existing stocks. Evaluating displacement to illicit markets will need to examine how PMP implementation relates with heroin overdose deaths in the same time period as well as in some point later in time, using suitable lags.

2.4.1 Limitations

Though PMP strength is negatively associated with OPR morbidity and mortality, this analysis has its limits. First, the use of a summative scale may not accurately capture the true robustness of a state's PMP. Second, this analysis lacks some key characteristics that comprise PMPs, including whether prescriber participation is obligatory or voluntary. To my knowledge, state-year data on the percentage of doctors that register with PMPs are not available. This may contribute to measurement error. Additionally, this specification does not control for spatial autocorrelation, as was done by Paulozzi, et al. (Paulozzi, Kilbourne, and Desai 2011), noting the epidemiological nature of drug abuse which is often spatially correlated.

Another major limitation is the fact that ICD codes may not be accurate. Coroners may not record the true cause of death. A recent and sharp increase in deaths (80% between 2013 and 2014) from synthetic opioids, other than methadone, coincided with law enforcement reports of increased supply of illicit or non-controlled fentanyl or fentanyl

analogs (R. Rudd et al. 2016). According to CDC, ICD codes fail to distinguish illicitly imported or non-controlled sources of this drug, which are not subject to PMP oversight, from prescribed synthetic opioids. This recent phenomenon may introduce bias as some deaths may be underreported (Ruhm 2017).

2.4.2 Strengths

Analyzing PMPs in a binary fashion ignores important differences in their design. Therefore, it behooves researchers to look at their relative strength over time rather than treating such policy interventions dichotomously. Research here confirms recent findings elsewhere (Patrick et al. 2016). Some PMPs are reactive or in-name-only, while others have much more stringent rules and require reporting and participation by prescribers. It is important to recognize that PMPs differ in design and implementation. This analysis underscores such differences. Stronger PMPs correlate with reduced OPR overdose deaths, giving policymakers additional guidance when designing PMP regulations.

PMPs are one policy tool, among many, that can help save lives. In combination with other public-health oriented policies and pain management therapies, strengthening PMPs may reduce OPR overdose deaths in the short term. Nonetheless, given the serious public health threat posed by the recent opioid epidemic, states must consider the full scope of interventions that include treating substance use disorder, promoting harm reduction, and preventing iatrogenic drug addiction through unnecessary oversupply of prescription pain relievers.

3 New psychoactive substances: options toward regulating new forms of drug-induced pleasure[3]

3.1 Introduction and scope

In recent years, the New Psychoactive Substances (NPS) phenomenon has garnered a substantial amount of attention in the field of drug policy. In some circles, NPS can include performance or image enhancing drugs (PIEDs) that are used to improve one's cognitive, sexual, or physical capacities or performance (Corazza, Chan, and Roman-Urrestarazu 2017). However, the focus here will be on *psychoactives* that typically mimic the effects of controlled substances often used for pleasure or to treat pain.

This chapter provides a detailed examination of the NPS phenomenon, its market drivers and policy responses. First, it frames the phenomenon according to the various market niches as well as pharmacological classes of NPS. It then discusses some of the normative and policy concerns surrounding the regulation or control of new intoxicants for which little is known. In Section 3.6 I examine regulatory approaches discussed elsewhere (Reuter and Pardo 2016a, 2016b) and include some new approaches. Final sections focus on considerations of control, exploring the tradeoffs among policy approaches and a logic model for controlling or regulating certain classes of NPS.

I examine how the NPS phenomenon compares and contrasts with "traditional" drug problems. Policymakers ought to consider differentiating responses to new substances. Framing the phenomenon by various market niches and factors that go into consumer

[3] Elements of this chapter come from two co-authored pieces: Reuter, Peter, and Bryce Pardo. 2016. "Can New Psychoactive Substances Be Regulated Effectively? An Assessment of the British Psychoactive Substances Bill." *Addiction*, May. Reuter, Peter, and Bryce Pardo. 2016. "New Psychoactive Substances: Is a Regulated Legal Market Feasible?" *International Journal of Drug Policy*, October.

choice can inform policy decisions. This chapter illuminates some of the various policies aimed at addressing the NPS phenomenon, underlying where they succeed and fail. Thinking about where NPS fit in the broader drug market serves as the conceptual foundation for the third essay (Chapter 4).

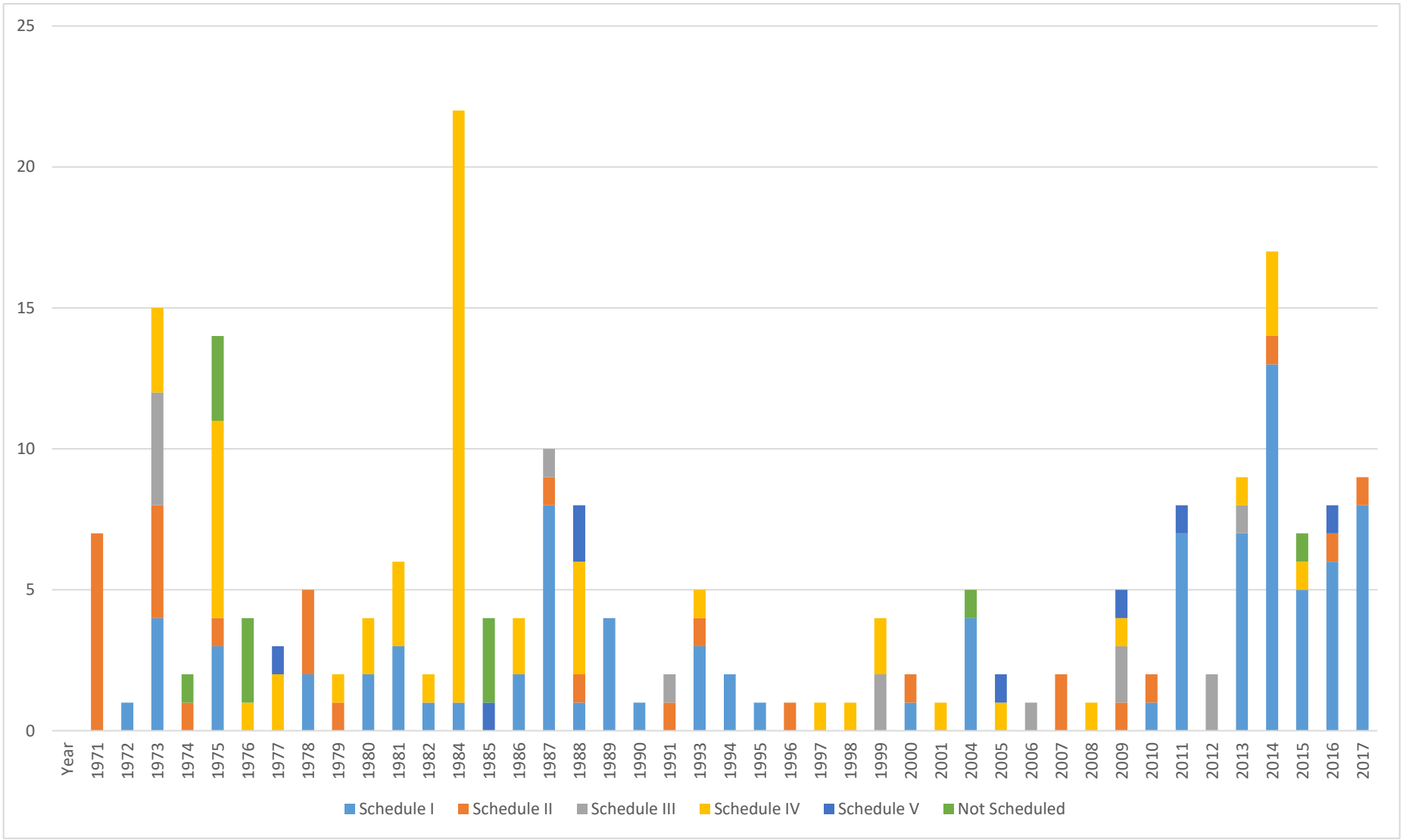
3.2 Background

NPS first emerged in Europe, where its use is still most prevalent. The European Union defines such substances as: "Narcotic or psychotropic drugs that are not scheduled under the United Nations 1961 or 1971 Conventions, but which may pose a threat to public health comparable to scheduled substances" (Council of Europe 2005). Over 60% of NPS seizures fall into just two categories (cannabimimetics and cathinones) (Evans-Brown et al. 2015; EMCDDA 2016d, 2017a). However, the proliferation of fentanyl analogs (new opioids) in North American drug markets is of great concern for public health and cannot be excluded from this analysis. Many NPS are manufactured by entrepreneurial chemists in China and very little is known about their pharmacology or harms (P. Griffiths et al. 2010; P. Griffiths, Evans-Brown, and Sedefov 2013). The majority of NPS so far mimic the effects of traditional drugs like, cocaine, MDMA, cannabis and heroin; many have never been used by humans before. These new substances fall under wide range of terms, including legal highs, synthetics, research chemicals, designer drugs, and party drugs. With the exclusion of new opioids, which are sold in illicit markets, most NPS are sold in convenience stores or head shops as alternatives to controlled substances. In many instances, these substances are explicitly labelled "not for human consumption" in an attempt to skirt existing narcotics and consumer safety laws.

Finding ways of circumventing drug prohibitions is not new (UNODC 1953). However, rapid advances in modern chemistry, communications and globalization, as well as growing wealth and changing mores with respect to drug-induced pleasures have magnified the problem, putting pressure on existing national and international drug control mechanisms (Dargan and Wood 2013). For example, the number of drugs on the list banned by international conventions has risen substantially. When the Single Convention passed in 1961 there were 85 controlled drugs, whereas by 2016 there were 253 under international control (International Narcotics Control Board 2016b, 2016a).

In comparison, NPS have been detected with greater frequency. Approximately 16 NPS were reported in 2005. Since then approximately 620—more than double the number of substances controlled internationally—are monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (Evans-Brown et al. 2015; EMCDDA 2016a, 2017a). The number of new substances is striking. More than 150 substances have been subject to scheduling decisions between 1971 and 2010 in the United States, about 4 per year. Since 2011, the Drug Enforcement Administration has scheduled an additional 60 substances, a more than doubling of the previous rate. The majority of these new substances (cathinones, cannabimimetics, and opioids) have been placed in the most restrictive Schedule. See Figure 3.1.

Figure 3.1: Number of Drugs Controlled by Schedule, 1971 - July 2017



Source: DEA (2017); years without scheduling decisions not shown.

Though the problem appears to be increasing rapidly, there is less to these numbers than meets the eye. Most NPS enter and exit the market quickly, gaining little or no market share. Many of these new substances are substitutes for each other; any one drug's success would drive most others out of the market. With a few exceptions, most of those substances turn out to have gained little acceptance among drug users at the time that they are detected. Others simply lose popularity, either because that particular experience is unattractive to new users or because of fears about adverse effects, usually reflecting actual experience of recreational users rather than government warnings[4]. In this respect, the market may be nearly self-regulating. This is particularly the case of the substances used for hedonic purposes (e.g., synthetic cannabinoids and cathinones that mimic cannabis or ecstasy) that experience frequent product turnover. For example, the JWH series of synthetic cannabinoids that came to be known as *Spice* and *K2* in 2010 and 2011 were quickly replaced by other synthetic cannabinoids, such as XLR11 or AB-FUBINACA, which were later replaced by MAB-CHMINACA and PB-22.[5]

This element of risk reduction and self-regulation may not be true for all NPS, however. Less is known about opioid NPS, but these synthetic opioids should be treated separately for reasons discussed later. According to several accounts, fentanyl and its analogs are often mixed with and sold as heroin or prescription opioids (Mcelroy 2016). The potency of these new synthetic opioids make them an attractive alternative for suppliers. Early research suggests most users are not drawn to these heroin substitutes (Ciccarone,

[4] For example, in 2011, the first year Monitoring the Future started inquiring, 11.4% of US high school seniors reported use of synthetic cannabis in the previous 12 months. At the time, this made synthetic cannabis the second most widely used class of drug after cannabis (excluding alcohol and tobacco). That figure dropped to 3.5% in 2016. Given the replaceability of NPS and the short timeframe, it is unlikely that enforcement efforts or prevention campaigns contributed substantially to such a precipitous drop.
[5] I discuss more in detail about the replacement of certain synthetic cannabinoids in the following chapter.

Ondocsin, and Mars 2017; Carroll et al. 2017) though this could change with time. According to the EMCDDA, in the Baltic nation of Estonia fentanyl has become the most commonly used opioid among injecting drug users and that "pockets" of fentanyl markets exist elsewhere in Scandinavia (Mounteney et al. 2011; EMCDDA 2016b; Hoskins 2016).

3.3 Defining the phenomenon

The NPS problem is mostly one of substitutes. Preference for NPS differ in the US and Europe, in part because the markets for traditional drugs differ. Most NPS arrive by international post or courier (Commission on Narcotic Drugs 2016), so supply-side factors, such as proximity to source country or trafficking routes, have less impact in shaping global NPS markets. Substances that have been most popular in European markets include methcathinones and phenethylamines, which mimic the effects of other traditional illicit stimulants and entactogens like cocaine and ecstasy (King 2014b). In contrast, American youth prevalence rates for cannabimimetic substances surpass those of their European counterparts, mirroring higher prevalence rates of cannabis in the US by young adults (EMCDDA 2017a). King has compared school surveys and found that 0.8% of Spanish teens used "spice" in 2010 in contrast with 11.4% of high school seniors in the US for 2011 (King 2014a).

Moreover, use of NPS more commonly found in Europe has not been as prominent in North America. For example, a search of the long list of substances recorded in the Drug Abuse Warning Network (DAWN) from 2012 (latest available) found no reported incidents of BZP (benzylpiperazine), mephedrone, MDPV (methylenedioxypyrovalerone), methadrone, or naphyrone, using both street and chemical names. More telling is the fact

that the National Survey on Drug Use and Health does not inquire about synthetic cannabis or cathinones either by chemical or street names. Monitoring the Future started asking high school students about their use of synthetic cannabis and cathinones ("bath salts") in 2011. In only five years, annual prevalence rates for synthetic cannabis has fallen from 11% to 3.5% for high school seniors (L. Johnson et al. 2017). Use of bath salts has remained low at about 1% (L. Johnson et al. 2017). To compare, young adults in Britain (ages 16-24) in 2015/16 reported an annual prevalence rate of another cathinone, mephedrone, at 0.3%, which has fallen from a height of 4.4% in 2010/11 (Home Office 2011, 2017).

Prevalence rates differ between young UK and US drug users. In the last ten years, youth in the US report higher cannabis prevalence rates than their UK counterparts by approximately a factor of two[6]. Though both countries have similar youth use rates of cocaine and ecstasy, some have suggested that the declining quality and access of these traditional drugs in the UK made NPS an attractive alternative for those seeking a similar mind-altering experience (Measham et al. 2010; Measham, Moore, and Østergaard 2011; K. Moore Dargan, Paul I., Wood, and Measham 2013).

NPS often substitute for traditional drugs. Very seldom do they achieve any appreciable market share. It is necessary to depart from treating NPS as a single problem of increasing numbers of new drugs. These substances vary considerably in terms of pharmacology, routes of distribution, and user profiles. Their only similarity is their ambiguous legal status

[6] Since 2007, UK cannabis past year prevalence for young adults (ages 16-24) has ranged from 13.5% to 18.6%; compared to a range of 27.5% to 33% for US adults (ages 18-25) for the same time period (Home Office 2017; SAMHSA 2017).

and unknown harms. By decomposing the NPS problem we can start to think about policies specific to NPS subtype as well as market niche.

Reuter and Pardo examined the drivers for NPS to explain the scope of the NPS market (Reuter and Pardo 2016a, 2016b). There are obvious economic factors, such as price and availability, which are common to traditional drugs. Yet, as a phenomenon, NPS serve four distinct and largely separate niches rather than the entire drug market. These are:

1) Drug users wishing to avoid criminal or legal sanctions but desiring substances that mimic the effects of prohibited drugs.

2) Individuals who are under supervision that attempt to circumvent drug testing by using undetectable substances.

3) Drug users that are attracted to new altered states of mind produced by entirely novel drugs.

4) Drug suppliers who sell NPS as controlled substances because they are cheaper or can be smuggled with less risk.

The first niche is what most associate with the NPS phenomenon. It includes individuals that skirt the law; a new substance produces similar effects to one that is banned and, because it is not yet prohibited itself, can sometimes be sold and consumed without threat of criminal sanction. Users in this category may be attracted to the legal high market of products sold in headshops, online or at nightclubs. Some individuals may find some NPS (particularly synthetic cannabinoids) more appealing than their parent drug due to price, perceptions of safety or ease of access (Vandrey et al. 2012; Spaderna, Addy, and D'Souza 2013).

The second niche generally comprises individuals who are subjected to routine drug testing. Those in this niche seek out an NPS similar to an existing drug but one that is undetectable in traditional drug testing assays. The growth of workplace testing

(Ironmonger 2014; Gunderson et al. 2014) makes this an increasingly important market niche. It can also include athletes (Heltsley et al. 2012) or those who work in security, like military service personnel (Berry-Cabán et al. 2012; Loeffler et al. 2012). Others that are under judicial supervision, such as prisoners, parolees or probationers may find NPS attractive as many of these substances may not be detectable in traditional drug screens, allowing them to avoid judicial sanctions (Perrone, Helgesen, and Fischer 2013; Featherstone 2015; S. Brown 2014). Note that it is not necessarily an issue of legality; a cannabimimetic that is not included in standard drug tests is helpful to the user even if it has been banned.

The testing regime component becomes increasingly important as current drug assays can only test against a referent metabolite. Existing drug testing screens, even the most comprehensive, can only test for the known universe of psychoactives[7]. This fact almost guarantees the demand for NPS from this niche.

The third niche applies to those seeking a new and attractive psychoactive or pleasurable experience. Arguably, this was the case for ecstasy during the 1970s and 1980s (Savlov 2000; Aleksander 2013); unlike other stimulants such as cocaine, it provided users with a unique entactogenic experience. Individuals in this niche are more discerning in their drug use, with fewer users reporting frequency or prevalence of drugs like crack or heroin, often using NPS that mimic hallucinogens (J. G. C. van Amsterdam et al. 2015; Soussan and Kjellgren 2016).

[7] This complicates public health and research efforts. Avoiding drug tests complicates sentry efforts since emergency department staff nor toxicologists know what to test for until an NPS has been seized and chemically analyzed.

The fourth niche stands alone from the others as a supply-driven phenomenon. Here, drug dealers have found enterprising ways to reduce costs and risks associated with supplying drugs. In this case, dealers will sell these substances as traditional drugs, rather than capitalize on their novelty or legality. This seems counterintuitive as NPS are often used to circumvent existing controls, avoid detection, or explore new drug-induced experiences. Rather, users are misled to purchase and consume these NPS. This has occurred with 25I-NBOMe sold as LSD (Suzuki, Poklis, and Poklis 2014), methylone or alpha-PVP sold as MDMA (ecstasy) (Palamar et al. 2016), or, more worryingly, synthetic opioids sold as heroin (Slavova et al. 2017; Ciccarone 2017; Carroll et al. 2017; Stogner 2015). In these instances, users are not looking for NPS but traditional psychoactives. Supply-side factors, rather than drivers of demand, result in the trade and use of these substances.

At this time, it is impossible to estimate the size of these four niches; nor is that likely to change in the foreseeable future. Stogner (2015) suggests a predictive framework based on five factors. These include existing user base of traditional drugs, costs of NPS to the user (including legality), subjective experience of new substances, their ease of acquisition, and the dependence potential of new drugs (Stogner 2015). In this regard, opioid NPS, like the many fentanyl analogs, align with most of these five factors,[8] whereas new tryptamines may meet one or two of these factors.

It is more than likely that many NPS sold in the "darknet" attracts the third niche above, which may use online reviews to guide their purchases (Aldridge and Décary-Hétu 2016). Novel drug experiences generally attract so called psychonauts, who typically use

[8] Opioid NPS meet the following factors: a large existing opioid-using population; low cost; easy to acquire online; and dependence-inducing.

psychedelic substances to alter their state of mind for various hedonic, healing, research, and spiritual purposes (Orsolini et al. 2015). This is generally the case with the tryptamine and phenethylamine classes of NPS. MDMA (ecstasy) was once an uncontrolled phenethylamine derivative that provided drug users with an entirely novel drug-induced experience when it became popular in the late 1970s and early 1980s.

Like ecstasy before, many NPS continue to serve the niche of those seeking novel altered states of consciousness. Research has compared user motivations and subjective effects of the tryptamine and phenethylamine classes of NPS. Several surveys of Australian NPS users have reported that individuals seek out and use substances such as the 2C-family, DMT (N,N-dimethyltryptamine), and DMT derivatives, like 5-MeO-DMT, because of particular qualities of those drugs, including their short duration of effect or fewer negative acute effects (Matthews et al. 2017; Sutherland et al. 2017). In the same surveys users report no difference in pleasurable effects between LSD and DMT, but suggest that DMT and the 2C-family may have attractive properties. For example, when smoked or insufflated the effects of DMT or 5-MeO-DMT last less than an hour, sometimes only fifteen minutes (Erowid 2015b, 2015a). In comparison the effects of traditional psychedelics such as LSD or psilocybin can last 6-11 or 4-7 hours, respectively (Erowid 2017, 2016). Short duration of effect, in addition to strength and pleasure, is an attractive attribute for some psychedelic substances (Sutherland et al. 2017). Other surveys of self-described psychonaut NPS users found that use of phenethylamine and tryptamine classes were the most popular classes, and that users were motivated by self-exploration, cognitive enhancement, or pleasure (Soussan and Kjellgren 2016).

The qualitative differences and effects among scores of various new hallucinogenic substances is well documented (A. Shulgin and Shulgin 1997, 1991). These qualitative differences, including strength, duration, physical and psychological effects, and degree and quality of unwanted side effects encourage continued experimentation by those in the third niche. Popular online forums and websites, like Erowid and Bluelight, provide informal qualitative research and trip reports (EMCDDA 2016c, chap. 7) to users and potential users on the various qualities and effects of different NPS. Much like the *Wine Spectator* magazine provides wine enthusiasts with the details of various varietals, such as the notes, ranking, flavor, bouquet, and color, users of websites like Erowid and Bluelight inform other users about the subjective experiences of many NPS, describing their drug-induced trips with great detail.

The potential for some yet foreseen NPS to create new pleasurable or desirable mind-altering effects is well within the realm of possibility. Yet, since the arrival of ecstasy in the 1980s and a few localized exceptions (e.g., mephedrone in some UK markets), no new chemical has achieved mass appeal. This holds true even though hundreds of chemicals have been developed in the last thirty years. It is possible that most new substances are imperfect substitutes for most available psychoactives. For a new drug to gain popularity, it must have some competitive attributes such that it 1) produces novel drug-induced or pleasurable experiences greater than or equal to those in the current market, 2) has fewer negative side effects or undesirable qualities, 3) can be readily accessed (i.e. a steady supply stream), and 4) is socially marketable.

The first three attributes are self-explanatory. But the fourth needs further explanation. Shulgin argues that drugs of desirable qualities may be marketable in an underground

sense, as users of a new drug encourage others to try it (A. T. Shulgin 1975). Becker posits that marijuana users learn about the drug, how to use it, and how to enjoy it from more experienced users (Becker 1953).

Information about a substance can be quickly disseminated through online forums and websites frequented by psychonauts. An enterprising chemist could derive a new drug from a combination of the many known or potentially discoverable chemical compounds. Some of these yet to be discovered chemicals may come from legitimate research, as was the case for the JWH series of synthetic cannabinoids. Some of these new substances may be sought after by users as new forms of pleasure, self-discovery, or perhaps therapeutic purposes. There is an incalculable number of potential chemicals that could generate many of the desired effects of some of the traditional psychedelics with fewer unwanted side effects. For example, development of a new serotogenic substance that allows users to have an analogous experience to LSD or MDMA, but in a fraction of the time without any adverse effects, could gain popularity in some recreational markets.

So why haven't we seen more popular NPS gain market share? There are various explanations for why no NPS, apart from ecstasy in the last thirty years, has gained wide general attraction. It could be that users are satisfied with existing drug experiences, or that new substances are not preferable or accessible to traditional psychoactives. Those that are quickly determined to cause dysphoric or unwanted effects are quickly discarded (A. T. Shulgin 1975). Similarly, others may attract negative media attention, dissuading some users from initiation. Others may gain popularity but also attract the attention of regulators. This puts a new substance at risk for control. This risk may deter some individuals from promoting the substance out of fear of regulatory scrutiny, keeping it underground for as

long as possible. Similarly, the scores of new substances available may make it difficult for even experienced users, such as psychonauts, to distinguish or gravitate to any single one.

Though niches are varied, I suggest that the NPS market share for niches one, two, and four may have a modest natural ceiling, which is related to the supply and demand of "parent" drugs. Only with niche three is there the possibility that an entirely novel substance attracts a new drug market. With the exception of opioid NPS, like fentanyl analogs, new drugs account for a small share of the total drug-related harms compared with traditional drugs. For example, in England and Wales during 2016, the ratio of deaths for controlled substances versus NPS was 21:1 (2593 versus 123) (Office for National Statistics 2017). NPS-related treatment admissions in 2013-14 totaled 1,641 out of a total of more than 69,000 (Home Office 2014, p. 12). Outside of fentanyl analogs, comparable figures for the US are harder to come by given low prevalence rates for most NPS. However, these numbers are likely modest given the staggering number of opioid-related overdoses in recent years.

Nonetheless, NPS collectively do represent a potential threat, for at least two distinct, almost complementary, reasons. First, a new substance could permeate existing markets out of popularity. If a substance turns out to be popular, the worry is that it may have the combination of features that made cocaine such a threat to public health. The first 20 or so experiences are attractive but for many users the drug turns out to be addictive and long-term dependence has dangerous behavioral and health consequences, especially if used with other intoxicants like alcohol. Second, an NPS might turn out to be a dangerous failure; harmful to users in those early experiences but tried by enough before the market,

nudged by public health authority warnings, transmits the message of danger effectively. The experience of Jamaica Ginger during Alcohol Prohibition in the US provides a good analogy (Parascandola 1995; Morgan and Penovich 1978): more than 35,000 users experienced long-term paralysis as the result of consuming a variant of alcohol combined with tricresyl phosphate, a neurotoxin, designed to deceive Prohibition inspectors testing for denaturing additives intended to discourage drinking. Arguably, this is part of the challenge of synthetic opioids that are increasingly responsible for opioid-related overdose deaths in North America. A substantial number of drug users overdose after unwittingly consuming heroin spiked with a fentanyl analog (Peterson 2016; Gladden 2016). Both the long-term success and the short-term dangerous failure represent serious potential harms.

In addition to these two potential harms, NPS add an ever increasing number of potential substances to the growing menu of drugs on offer. Polysubstance use is one such concern, making it hard to know *a priori* what relationship a potential NPS may have with other drugs. Though substitution remains an important element of the NPS phenomenon, so is complementarity. The introduction of new substances may interact quite dangerously with the cornucopia of substances on offer today (Hayden et al. 2014; Connor et al. 2014; Morley et al. 2015). This was part of the concern with the introduction of BZP into the markets of New Zealand, where it was used frequently and often harmfully with alcohol (Expert Advisory Committee on Drugs 2006, 2004).

This leads one to consider an additional question related to harm. The introduction and gaining popularity of any NPS may contribute to the overall level of harm, but in what way? Harms of BZP used in conjunction with alcohol may make the combination more harmful, while separate use of either substance may be less harmful, but we may not be

able to infer which substance is more harmful. Is BZP less harmful than alcohol even if it is not a substitute? The point being, polysubstance use complicates both policy and research when establishing certain causal factors related to harm.

Nonetheless, by decomposing the NPS phenomenon I show that different chemicals and market-related factors contribute to different degrees of use and thus potential harm. NPS is often cast as a monolithic problem by policymakers (Baumann and Volkow 2016; Madras 2017). However, thinking about the phenomenon's constituent parts provides a better understanding of how to proceed.

3.4 Policy literature review

The policy analytic literature on this topic is slim. To date, most of the NPS research focuses on the chemistry of the substances or its impact on public health. Though important in understanding the pharmacology and harms of new substances, there has been little critical analysis as to the framework of NPS regulation or policy responses, let alone the drivers of NPS supply and use. Scholars have thought about alternative regulatory frameworks that explicitly recognize the recreational elements of traditional drugs that have long been a part of our social atmosphere (M. Kleiman 1992; Stephen Rolles 2009; Steve Rolles and Murkin 2013; Babor et al. 2010; Babor 2010a).

One reason for the lack of policy-analytic literature regarding NPS is that this phenomenon is hard to assess. Rapid design and evolution of products that quickly enter and exit the market make assessments difficult. Given these challenges, the peer-review literature assessing regulatory frameworks has been limited. Winstock and Ramsey (2010), Hughes and Winstock (2011), Wilkins (2014) and Stevens et al (2015) are notable exceptions that

contain a number of important observations about the regulatory dilemmas posed by these substances (A. R. Winstock and Ramsey 2010; B. Hughes and Winstock 2012; Chris Wilkins 2014; Stevens et al. 2015).

Beyond the peer-reviewed literature, government-sponsored research and the gray literature make up most of the policy-analytic work on NPS. Early efforts by research groups and public agencies have been useful in describing and assessing potential policies toward NPS (Reuter 2011; EMCDDA 2010; B. Hughes and Evans-Brown 2015; B. Hughes and Bildaru 2009; Dargan and Wood 2013). The gray literature describes the history and trade in NPS, but also some of the alternative control mechanisms used by governments. In some instances, such literature has assessed the strengths and limitations of existing policies, yet little consideration is given to the costs or benefits of any particular policy (Sacco and Finklea 2016).

The majority of the policy-analytic literature up to this point has been descriptive, detailing what legal mechanisms exist or what innovate policies have been tried by different countries. Research has examined a handful of case studies, attempting to compare and contrast elements of chosen legal and regulatory frameworks. Most approaches considered, with one notable regulatory exception discussed later, seek to prohibit NPS supply and use.

In an effort to close this research gap and propose legal mechanisms to address the supply and use of NPS, several governments, including the Scottish, Welsh and UK governments, examined the sparse legal and regulatory frameworks for controlling new substances (National Assembly for Wales' Health and Social Care Committee 2015; Scottish

Government 2015; Home Office 2014). Most government-sponsored policy literature makes little effort to analyze the drivers behind the NPS phenomenon. This gap is a notable oversight. Generally, a policymaker is hesitant to consider alternative regulatory approaches, let alone the mechanisms behind supply and use of NPS. As detailed by some, the risk of permitting sale of a substance that later turns out to be harmful weighs considerably on any official (Dargan and Wood 2013; Reuter and Pardo 2016a). Likewise, the policymaker often neglects to consider any utility or consumer surplus that a substance might provide. There is implicit decision bias; few consider any potential gains or losses attributable to the use of a parent drug or its NPS mimetic (Reuter and Pardo 2016a, 2016b).

The risk calculation under such uncertainty and lack of information has resulted in a default option grounded explicitly in the precautionary principle. The overwhelming number of new substances detected has generated essentially a reflexive policy, requiring the invocation of a complicated process to ban a new substance flowing out of clandestine labs in response to the previous set of prohibitive regulations. Policymakers have given little thought to the drivers of NPS or the impact that bans may have on the wider market, justifying their early decisions on the grounds of the precautionary principle.

3.5 Precautionary principle and its application to psychoactives

Regulation does not take place in a vacuum. Policymakers must weigh the potential harms against the potential gains of any policy. The precautionary principle is one risk management mechanism in policy design and implementation. The definition of the principle that is most widely quoted is from the 1992 Rio Declaration, which states that: "where there are threats of serious or irreversible damage, lack of full scientific evidence

shall not be used as reason for postponing cost-effective measures to prevent environmental Degradation" (UNEP 1992). Simply, the precautionary principle implies that, in the absence of evidence, any potentially harmful act must first prove to be without harm before it can be allowed (Sunstein 2005). The principle has been adopted by several policy arenas after its founding in international environmental accords.

The interpretation of the principle by jurisdictions may vary. For example, the European Commission, implementing the Council's adoption of the principle in its Resolution of April 13, 1999, extends such interpretation to a broadly defined concept of "public health."

> The precautionary principle may be invoked where urgent measures are needed in the face of a possible danger to human, animal or plant health, or to protect the environment where scientific data do not permit a complete evaluation of the risk. It may not be used as a pretext for protectionist measures. This principle is applied mainly where there is a danger to public health. For example, it may be used to stop distribution or order withdrawal from the market of products likely to constitute a health hazard. (European Commission 2000)

Adoption of the above definition of the principle can logically extend to NPS, which often pose public health risks. However, is it appropriate to invoke such a broad rationale? Some have challenged the principle's broad application. For example, Sunstein (2005) argues that the above definition oversimplifies a traditional cost-benefit analysis, focusing narrowly on costs and not on benefits. Lowering the allowable level of arsenic in drinking water raises the cost of using municipal systems and may lead some households to use unregulated wells that have much higher levels of arsenic (Sunstein 2005).

Given the known harms of intoxication and the unknown risks from use of psychoactives of unknown origins, it seems reasonable to apply the principle to NPS. In this regard, the

principle states that the government has an affirmative duty to protect individuals and society from such hazards, favoring scheduling under narcotics control laws. Classifying an NPS as falling under the narcotics control legislation is tantamount to prohibiting its commerce, since at the time of the decision, it will not have been through sufficient testing to avoid being put into Schedule I, "no recognized medical use". Such restrictive scheduling can also impede future research on that substance.

However, the complication here is that giving deference to those harms ignores the harms that arise from the decision to prohibit. David Nutt has presented an articulate rebuttal on the application of the precautionary principle in several editorials (Nutt 2011, 2010), cautioning against banning mephedrone. He identifies specific potential harms from application of the precautionary principle. For example he points out that some of the substances banned might turn out to be substitutes for alcohol or cocaine that cause less harm to the user and others. Separately he points out that broadly invoking the precautionary principle inhibits the development of substances explicitly intended to substitute for more harmful intoxicants or treat addiction[9] since they would be subject to much tougher regulatory scrutiny.

Could the precautionary principle be harm enhancing when applied to new drugs? One emerging criticism of elevating the control of NPS to scheduling under narcotics laws is the possibility that chemical structural controls and scheduling might contribute to the development of newer, more dangerous substances that circumvent new prohibitions (J.

[9] At the time, the regulatory decision in the UK to schedule mephedrone, a cathinone, under generic controls limited research into new substances of similar chemical structure. Some of these substances may later be shown to have therapeutic benefits. For example, bupropion (Wellbutrin), which is used to treat nicotine addiction, is similar in chemical structure to cathinone.

van Amsterdam, Nutt, and van den Brink 2013). This argument has some legitimate ground. Until 2016 in the UK, controls of chemicals by emergency schedule encouraged the development of new chemicals. According to the Advisory Council on the Misuse of Drugs, each succeeding generation of synthetic cannabinoids has been more harmful than the preceding (Home Office 2014).

The precautionary principle may elevate harms in other ways beyond pharmacology. Invoking the precautionary principle to prohibit a substance, especially a substance of unknown harms with a modest market share supplied by online retailers or headshops, may have unintended market-wide consequences. For example, after the UK publicized its intention to prohibit synthetic cannabinoids but before the implementation of controls, headshops and other retailers liquidated their inventory by offering deep discounts (Beltgens 2017; Wadsworth, Drummond, and Deluca 2017). Flooding the market with cheap psychoactives in an effort to comply with the legal change could increase the frequency and intensity of use of these substances, especially in price-sensitive heavy users.

Further, those involved in a substance's production and distribution are now at risk of arrest and various penalties. That will affect remaining suppliers. Some firms who are willing to participate in a marginal activity without clear legal status will be unwilling to undertake a clearly illegal activity. That will leave a more risk-seeking and probably more violent group of entrepreneurs. It will also affect the character of the organizations involved. Organized crime (organizations that have more general criminal skills, including a capacity to corrupt and make credible threats of violence) may now become an important element of the production and/or distribution. After the UK controlled mephedrone in 2009, reports

of organized criminal activity in the distribution of 4-methylethcathinone (4-MEC), a substitute, appeared (Dargan and Wood 2013).

Lastly, the decision to prohibit on grounds of the precautionary principle oversimplifies the cost benefit analysis, as Sunstein (2005) notes. In the case of the UK, the decision to issue a blanket ban on all non-exempt psychoactives (which is discussed in detail later) was largely made on the grounds of reducing access to and use of new psychoactives. This oversimplification and justification of control under the precautionary principle conflated harm with prevalence. A ban on NPS would put an end to their retail in headshops or online, reducing access and thus use by the general public. At face value, national surveys suggest that past-year NPS prevalence declined a year after the law's implementation (from 0.7% to 0.4% for those aged 16-59; and from 2.6% to 1.2% for those aged 16-24)[10] (Home Office 2017). Yet, the blanket prohibition appears to have concentrated harm in vulnerable populations, such as the homeless, as evidenced by early research and news reports (Gray, Ralphs, and Norton 2017; Doward 2017). Preliminary studies and documented cases have been limited to a few urban areas. Gray, Ralphs and Norton (2017) interviewed 53 users of synthetic cannabinoids in Manchester, UK in 2016, during and after the blanket ban. They report that the typical user is homeless or has a temporary living situation, and that moving supply underground resulted in more violent trade.

Inventory liquidations and the move to street dealing by users or criminals suggests increased harm in some populations; much like Sunstein's example of lowering the allowable limit of arsenic in the water may have also increased harm in marginalized

[10] An alternative hypothesis is that fewer report using NPS now that they are effectively banned. Respondents are known to underreport their drug use in surveys (Kilmer et al. 2014).

populations that cannot access municipal water sources. It is too early to say if such harm merely reflects a transition cost as these drugs move from unregulated to prohibited status or if costs of prohibition will continue to weigh heavily on certain populations.

Sometimes regulatory controls are made in error. Coulson and Caulkins (2012) refer to the Type I/II error distinction, where regulators may be overly cautious, controlling a substance of relatively low harm (Type I), or not sufficiently cautious, allowing a substance to linger in the market while harms cumulate (Type II) (Coulson and Caulkins 2012). Being risk averse, regulators and politicians are overly cautious and avoid Type II errors (Reuter and Pardo 2016b).

Nonetheless, how should policymakers consider options prior to issuing a decision? NPS pose challenges as well as opportunities. Nuanced regulations that accept certain gains and losses may apply to certain NPS. Not all will fit, some might be deemed too risky and subjected to traditional controls (i.e. prohibition); but policymakers could apply more nuanced regulations. I turn to regulatory frameworks considered by jurisdictions facing the NPS phenomenon to see what can be learned.

3.6 Regulatory frameworks

The NPS phenomenon has garnered a considerable amount of attention in recent years (EMCDDA 2016b, 2010). The number of new substances is overwhelming existing international, regional, and national control mechanisms. Most regulatory and policy innovation has come from local and national efforts to quickly contain the NPS phenomenon, moving to control or restrict access to these new chemicals. However, I first examine things from a top-down approach, evaluating the international and regional

systems that have so far sought to regulate new psychoactives. Later I consider the five different regulatory frameworks applied at the national and sub-national level.

Decisions regarding NPS are often made with little information. Rushed or poorly-informed decisions regarding product approval or denial can result in error and sometimes harms. On the other hand, acting too slowly may cause problems to fester and avoidable harms to continue. Regulatory design matters. Policymakers should keep in mind that making such decisions without sufficient scientific evidence or data may result in unforeseen consequences as well as generate criticism and impugn the credibility of regulatory decisions. Often, regulators must make some tradeoff among competing dimensions: speed, regulatory rigor, accuracy, cost, political optics, bureaucratic complexity, etc. (Wilson 1989). I examine in greater detail the tradeoff between speed and accuracy among approaches described below. Other dimensions often factor into a final decision, but the NPS problem is often cast as one of celerity and appropriate regulatory rigor. No one approach dominates in all dimensions.

3.6.1 International and regional efforts

Two of the pillars of the international drug control system, the 1961 Single Convention and the 1971 Convention on Psychotropic Drugs, provide for a process to add new drugs to the list of those that are subject to control. An Expert Committee on Drug Dependence, consisting of international experts, is operated by the World Health Organization. Once the Expert Committee has decided that a substance should be subject to scheduling, that recommendation is considered by the Commission on Narcotic Drugs (CND) (a set of 43 nations chosen by the UN Economic and Social Council). Once approved by the CND, all

Member States must adopt a scheduling decision at least as stringent as that. The process is slow; the Expert Committee meets every year for a handful of days, handling just a small number of substances at each meeting. At the most recent meeting in March 2017 the Committee recommended that two new substances (both fentanyl analogs) be scheduled under the 1961 Convention and that eight new substances (cathinones and synthetic cannabinoids) be scheduled under the 1971 Convention (Commission on Narcotic Drugs 2017a). Several of these substances, such as 4-MEC and pentedrone (both cathinones), had been controlled by some Member States for nearly half a decade. There is no mechanism for emergency procedures such as have been adopted by various countries. Further, there are no alternative regulatory approaches beyond doing nothing or control by scheduling.

Apart from assessing new chemicals and recommending scheduling when requested by members, the UN system has continued to monitor trends at the national level, working with Member States to identify and notify the arrival of new psychoactives, and share information and best practices regarding detection and treatment of NPS (Commission on Narcotic Drugs 2017b). Other regional bodies have attempted to detect, analyze and regulate new chemicals more swiftly.

In 2005 the European Union promulgated Council Decision 2005/387/JHA[11] which created a set of procedures for dealing with potentially harmful new psychoactive substances that could become popular (Council of Europe 2005). The procedures are comprehensive, covering the whole process from detection through risk assessment to legal action. Risk

[11] The 2005 Council Decision succeeded an earlier program with a narrower scope: the Joint Action on New Synthetic Drugs, which had been in operation since 1997.

assessments are conducted on five criteria, which I reproduce from (B. Hughes and Bildaru 2009):

1. An assessment of risks caused by use of, manufacture of, and traffic in a new substance, as well as the potential involvement of organised crime;
2. The risks to be assessed include health and social risks, as well as the consequences of possible control measures;
3. The assessment is based on the analysis of scientific data and law enforcement information, made available by, e.g. health, social and law enforcement sources (but not necessarily limited to these);
4. The assessment may or may not take into account the same factors which warrant the placing of a substance under international control;
5. The assessment may be done in accordance with a formalised (legally based) procedure and it may be carried out by a scientific or expert body.

The point two includes assessments as to the social risks and consequences of control measures. Often there is a reflexive nature to controlling new substances without giving any thought to the harms that may arise from control (Stevens and Measham 2014). In certain circumstances, as discussed earlier, the decision to control founded on the precautionary principle may exacerbate certain harms. Most regulatory considerations ignore the potential of harm enhancement.

However, the first risk assessment criterion is confusing. NPS not sold as traditional drugs (e.g., synthetic cannabinoids and cathinones) are, by and large, distributed by marginal operators, such as headshops or online retailers. There is limited connection with serious organized crime that traffic and retail in substantial quantities of traditional drugs like heroin or cocaine. A decision to prohibit would likely result in greater organized criminal involvement; whereas a choice to regulate would mean that licensed firms replace those that have so far operated in the margins. It is not clear how an assessment should be carried out given a drug's ambiguous legal status. To date, the EMCDDA has formally assessed

the risks of some two dozen NPS as outlined by the Council Decision, a far cry from the over 600 substances monitored by the agency[12].

More to the point, this approach was determined to be slow at responding to the problem of NPS in Europe (European Commission 2013). In response, the Commission sought to expedite controls of potentially harmful substances, harmonize country responses and ensure internal commercial market procedures for products of legitimate use, and promote and respect fundamental rights (*Regulation Of The European Parliament And Of The Council* 2013).

According to the Commission, the proposed changes should reduce the time to detect and control a new substance from two years to ten months and also give emergency procedures to withdraw substances temporarily from the market immediately for a period of up to one year (European Commission 2013). Additionally, EU measures will be applicable to Member States without the need to transpose bans into national law. Interestingly, the new system will allow for a "graduated approach" to new substances that pose moderate harm, subjecting them to consumer safety restrictions whereas substances that pose severe harm will be submitted to control, including criminal sanctions for violations (*Regulation Of The European Parliament And Of The Council* 2013). See Figure 3.2 below from the Commission that compares the current and proposed systems.

[12] See http://www.emcdda.europa.eu/html.cfm/index16776EN.html

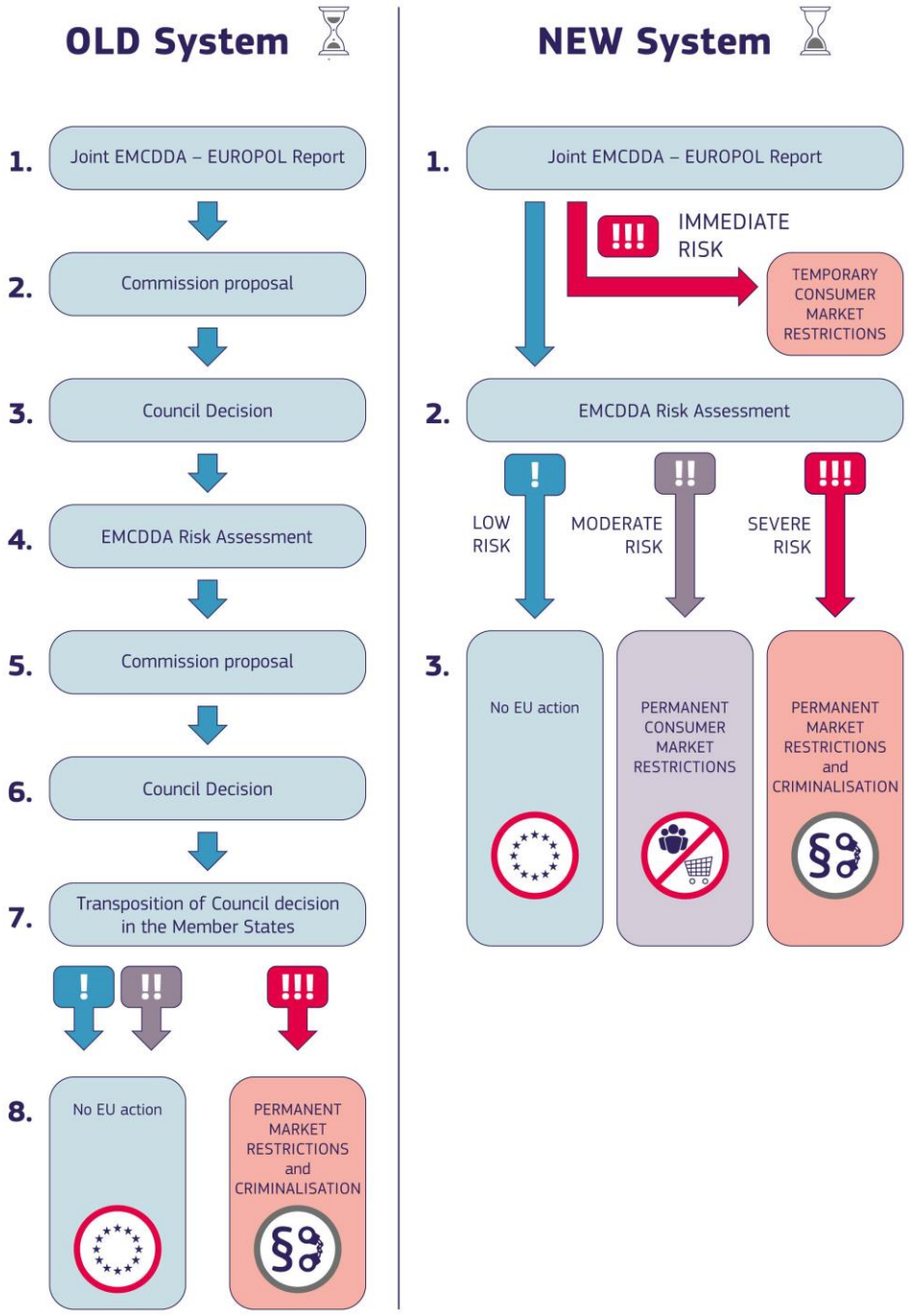


Figure 3.2: Decision-making under the old and proposed systems
Source: European Commission (2013)

The proposed EU framework is different for several reasons. First, it combines several regulatory frameworks discussed later, including scheduling of substances that pose a

severe risk, consumer protection and safety laws to restrict access to substances of moderate risk, and no regional restriction of the supply of low-risk psychoactives. Presumably, individual states may impose regulations (or bans) relevant to products of low-risk. Second, it restricts sovereignty by permitting the free movement of psychoactive substances of moderate risk across borders for commercial, industrial and research purposes.

These changes have been under consideration by European political bodies and Member States since 2013. Use of Union trade and administrative laws might be cause for concern for some members. The supranational structure of the EU system would protect the free movement of psychoactive substances that have commercial or industrial use[13] or the restricted access to substances that pose moderate risk (which would restrict use of such substances much like medicines) (*Regulation Of The European Parliament And Of The Council* 2013). Substances that have not been assessed are not subject to these free trade restrictions, allowing members to adopt domestic restrictions on new products. Yet after the risk assessment by the EMCDDA and Europol, if a substance is deemed to have some industrial or commercial utility, then members cannot issue national bans or restrict access to them.

The future of such sweeping changes in the EU is uncertain as the proposal has languished in the European legal system for some time. Some Member States may object to the European Market's protection of psychoactive substances with industrial or commercial

[13] Commercial and industrial use presumably would prohibit access to individual end-users as the term is defined as: any manufacture, processing, formulation, storage, mixing, production and sale to natural and legal persons other than consumers (*Regulation Of The European Parliament And Of The Council* 2013).

use. The sovereignty of the state with regard to the protection of the health and safety of its citizens runs counter to the protection of the free movement of mind-altering substances. In this manner, how have individual countries or their-subnational jurisdictions approached the NPS problem?

Apart from the broad international and regional approaches discussed above, there are different models of regulation that provide insights for making decisions about these new drugs. Five overarching frameworks are used to regulate the use and availability of substances that may be consumed by humans. Table 3.2 at the end of this section describes each of these frameworks. These are, in ascending order of restrictedness:

1. Foodstuff, dietary supplement, and consumer protection regulations
2. Regulations relating to specific commodities, such as tobacco and alcohol, but also substances with other uses, such as solvents.
3. Medicines regulations
4. The control of substances scheduled by international conventions and related national and domestic legislation
5. Total prohibition of psychoactives, except for narrow exemptions

In addition to the degree of control, different regulatory frameworks can and often do achieve similar ends. In many cases a jurisdiction may want to prohibit a new psychoactive from entering the market, but the time required to schedule a new substance, even under emergency scheduling orders, can take months or years. Some of the proposed frameworks discussed below can rapidly prohibit market access to NPS with fewer hurdles. Nonetheless, not all NPS should be thought of as causing the same level of harm and different regulatory mechanisms may be better suited for different NPS. The proposed EU

regulations is one example of a differentiated response to NPS; products of severe risk are subject to bans whereas products of low risk are met with no EU action.

3.6.2 Foodstuff, dietary supplement, and consumer protection laws

The first possible framework for regulating new substances that have no substantiated or claimed therapeutic or functional value is to treat them not as drugs, for which the government has to make safety and efficacy determination before letting them on the market or listing them under narcotics laws, but instead, like other products where there is a presumption of safety that can be challenged when the government has gathered data indicating public harm. This is a common approach to the regulation of food and dietary supplements in Western countries that are designed to safeguard consumers.

In the United States, if a food or supplement is found to be unsafe or dangerous, then the Food and Drug Administration (FDA) can require that the product be removed from the market. The Federal Trade Commission (FTC) can, and does, regulate the advertising for these products. Most importantly, the producers may not claim the product cures any disease or illness.

However, the experience with weight loss products in the United States offers a sobering lesson. These products are similar to NPS in that producers often continue to develop entirely new products, making claims about them which are difficult to validate. The FDA has difficulty obtaining information about adverse events involving such products (GAO 2002) since the producers do not have an obligation similar to that of pharmaceutical manufacturers to monitor post-market experience. The GAO (2002) report described the problem in detail, concluding that it is difficult to study the safety and efficacy of products

that contain multiple and sometimes proprietary ingredients. This complicates regulatory action as it is often hard to identify patterns or combinations of ingredients that are associated with adverse effects (GAO 2002).

There are many ways in which the regulation of weight loss products and their advertising could be strengthened. For example, the producers could be required to conduct post-market monitoring and to list all ingredients. While it would prevent or delay the adverse consequences of prohibition for drugs that turn out not to be harmful, it allows those that truly are dangerous to linger in the market, with the apparent endorsement of the government, sometimes for a long period. Because these products are distributed in a legal market, their legal status can sometimes provide false reassurance about government regulation. Approximately half of Americans believe that weight loss products are approved for safety and efficacy before they can be sold to the public (Pillitteri et al. 2008).

Complicating this is the fact that a substance, after gaining some measure of appeal, may be difficult to remove from the market. Even when regulators can point to a direct causal mechanism of effect of harm, it still can be difficult to restrict access to substances that have found their way into the daily lives of ordinary citizens. Recent debate over efforts to restrict access to prescription opioids is one example (Lopez 2015).

Here I turn to the case of kratom and the challenges of regulating psychoactive substances for which harms not are readily apparent. Kratom is a plant found in South East Asia that has been used for centuries as a form of traditional medicine and contains mitragynine and 7-hydroxymitragynine, among other alkaloids. Though it is not a synthetic compound traditionally associated with the NPS phenomenon, it is psychoactive. The substance is not

subject to international control accords though several South East Asian countries control it under national law. The EMCDDA found kratom to be one of the most frequently identified NPS sold online in 2011 (EMCDDA 2011). Little is understood about the plant or its psychoactive compounds, which appear to have both stimulant and opioid-like effects at varying doses (Warner, Kaufman, and Grundmann 2016).

Kratom products arrived in the US market about a decade ago, and are advertised and sold online for the self-treatment of chronic pain and in some cases opioid withdrawal (DEA 2013; Warner, Kaufman, and Grundmann 2016). Evidence of kratom's therapeutic value and harms are not well established, though there is growing concern of its harms and abuse potential. Recent literature reviews have indicated that kratom has been associated with adverse effects and even death (Warner, Kaufman, and Grundmann 2016). On the other hand, recent studies of kratom and its active ingredients suggest that the plant may have some unique therapeutic analgesic value, though more research is needed (Warner, Kaufman, and Grundmann 2016; Vázquez López et al. 2017). At this time, the DEA does not recognize any legitimate medical use for the plant or its psychoactive alkaloids, mitragynine and 7-hydroxymitragynine (DEA 2013).

From its arrival until 2014, kratom was sold online and in stores as tea, powder, and extracts without any regulatory oversight or prohibitions at the state or federal level. In late 2014 the FDA concluded that kratom was a botanical dietary ingredient and subject to regulation under the Federal Food, Drug, and Cosmetic Act (FDA 2014). Regulators found that there was insufficient evidence of the supplement's safety and moved to prohibit imports (FDA 2014). Subsequently, news reports of adverse effects encouraged several state governments to schedule kratom as Schedule I under state narcotics laws (Warner, Kaufman, and

Grundmann 2016). In August 2016, the DEA declared its intention to prohibit kratom under federal law via scheduling, citing hundreds of calls to poison control centers and other health risks (DEA 2016).

For the first time ever, DEA reversed course after a coalition of kratom consumers, importers, and politicians publicly lobbied against scheduling. DEA received over 23,000 public comments, of which only 113 were in favor of prohibiting the plant (Wing 2017). Since then, the DEA has asked for a "scientific and medical evaluation and scheduling recommendation" from the FDA (Ingraham 2016). As of now, kratom is subject to regulation under the Federal Food, Drug, and Cosmetic Act. Several companies have attempted to obtain regulatory approval for botanical extracts made from kratom to alleviate pain (Roberts 2017; PR Newswire 2017). It is unclear how the FDA will continue to view raw kratom. Apart from limited federal controls, several states have maintained prohibition under narcotics laws. Some states ban sales and possession, only for minors (Warner, Kaufman, and Grundmann 2016). Nonetheless, the plant is available through online retailers even while federal regulators study the substance. The FDA's regulatory oversight and partial enforcement has been met with limited public outcry, though there is some concern that products face lack evidence of their effectiveness (FDA 2017).

In this case consumers were successful in slowing the control of kratom, pointing to the potential adverse effects of harm had the plant been removed from the market, including concern about the restriction of mild analgesics and a return to prescription opioids (Ingraham 2016). It's unclear at this time if such concerns were warranted as the harms of kratom use are not well established. Nonetheless, the continued use of kratom and the limited harms associated with that use may be mitigated under a foodstuff or consumer

regulatory approach, including stronger warning and dosing labels. There is no great sense of urgency or public outcry to prohibit the substance, but more could be done to reduce health risks to consumers.

Besides foodstuff regulations, consumer protection laws have been utilized to quickly restrict the distribution of NPS, typically synthetic cannabinoids and methcathinones, sold in corner stores. In mid-2015, Washington, DC amended its business code to allow authorities to fine and revoke business licenses of stores selling uncontrolled drug analogs or substances marketed with the intention of drug use (Council of the District of Columbia 2015). Authorities have curtailed the in-store distribution of NPS, though some accounts indicate that retail has moved to the street (Thompson 2015).

In the UK, consumer protection laws, such as the General Product Safety Regulations (GPSR), have been used to regulate the sale of unsafe products via prosecution, forfeitures, license suspension, and fines. Instances of local authorities using the GPSR to seize NPS have been documented, but policymakers there concluded that use of such laws were problematic in the long term given their underlying objective to create better regulated markets, rather than prohibiting trade (Home Office 2014).

In these instances, consumer safety laws attempt to overcome the lengthy process of traditional scheduling by pointing to circumstantial factors related with the supply or retail of NPS. These factors include product price, marketing, mode of sale, product warning labels, and its resemblance to controlled substances, among other things. The National Association of Model State Drug Laws (NAMSDL) refers to these laws in the US as "Economic Sanctions" laws aimed at deterring retailers from selling NPS by providing

authorities the means to revoke or suspend business licenses, seize products, and impose civil penalties for deceptive trade practices (NAMSDL 2017).

Though this strategy has some minor advantages, namely speed of control. These regulatory approaches are often stretched when applied to new psychoactives. Suppliers may shift retail to street dealers, as in the case of Washington, DC. Regulators may also find it difficult to apply imprecise or circumstantial factors to products that merely *appear* to be sold as psychoactives, prohibiting—rather than regulating—trade, as was the case in the UK under the GPSR. I note that in recent years both Washington, DC and the UK have moved to control many synthetic cannabinoids under traditional narcotics laws. Yet, after the arrival of certain harmful or presumably unsafe NPS, foodstuff, dietary supplement, and consumer protection laws have been utilized to swiftly limit access and availability of substances while regulators study or consider alternative regulatory frameworks of control, including approaches discussed below.

The approach of regulating NPS via foodstuff or consumer protection laws has both advantages and disadvantages. The principal advantage of this approach is that a government may use the law to swiftly target and remove substances, so long as they have not gained some mass appeal (as indicated by the case of kratom). Their principal disadvantage is that they are ill-suited to dealing appropriately with the distribution and use of psychoactives of moderate and severe harm. Treating harmful NPS as foodstuffs may endanger the public and is likely to be an inappropriate framework for regulating their trade as such an approach falsely conveys some degree of safety.

3.6.3 Specific commodity regulation

Alcohol and tobacco are two licit psychoactives that have been regulated as articles of commerce throughout modern history (Courtwright 2009). Both are subjected to a set of detailed regulations, governing their production, distribution, and use (Babor 2010a; Rabin and Sugarman 2001). There is no global accord for the regulation of alcohol, apart from international trade agreements, but there is an international Framework Convention on Tobacco Control. Yet this accord is far less intrusive on individual nations' policies than the conventions for controlled drugs. In addition to alcohol and tobacco regulations, some jurisdictions are applying commodity-specific regulations to cannabis, a popular psychoactive of low risk, for adults or those that can establish medical need (J. P. Caulkins, Kilmer, and Kleiman 2016).

Given the continuing interest in making comparisons between the harmfulness of the two principal legal drugs, alcohol and tobacco, and of those that are banned under the narcotics laws, it has been suggested that the alcohol and tobacco regulatory systems could provide a useful model. Yet as schemes for the assessment of new products, there is little to be learned from either substance. Given that harms of new psychoactives may not be apparent for some time, extending access to such substances, albeit under regulation, for general consumption is problematic. Rather, lessons learned from alcohol and tobacco may be better suited to drugs whose harms are better established. Such is the case with cannabis in the US, which is now regulated similarly to alcohol in eight states.

New alcohol or tobacco products may attract regulatory attention if they represent an exaggeration of existing forms, as for example when attention was drawn in the US to drinks that contained caffeine as well alcohol or alcoholic drinks that were designed to appeal to youth. However, regulation has not had to deal systematically with the issue of

distinctive new substances, with one important exception. E-cigarettes are the new product that has most stretched existing tobacco regulatory systems. There is controversy in the public health community as to whether these devices, which allow for nicotine consumption with fewer adverse effects associated with conventional cigarettes are a net positive or negative (Abrams 2014). The latter concern arises from a fear that they will lead to more initiation to nicotine and perhaps later smoking of conventional cigarettes. Evidence of any public health gains to date from e-cigarettes is mixed (Bullen et al. 2013; Leventhal et al. 2015; Wills et al. 2016).

In many respects e-cigarettes raise just the same kind of issues as NPS. A novel product has to be assessed in relationship to what is currently on the market. Substitution is at the heart of this matter; will e-cigarettes prove to substitute for the much more dangerous products that dominate the market now or will they turn out to be ways of extending the reach of those products? The difficulty in learning from the regulation of e-cigarettes is similar to NPS; research is limited. It is simply impossible at this stage to say what the right response to these products is. The analogy with NPS is also strained in that the harms of NPS are likely to be manifest in the short-term and any benefits (substitution for other more dangerous substances) only in the long-run, the opposite of the pattern for e-cigarettes.

Nonetheless, society has crafted regulations for the provision of these substances whose harms are recognized and quantifiable. Some sets of regulations are better than others, but society has learned a great deal about how to regulate alcohol and tobacco (Babor 2010a; Rabin and Sugarman 2001). Under that framework, could regulations for new psychoactives be considered? In this case, such a rubric would explicitly recognize non-

medical (i.e. hedonic) utility of new psychoactives. Only a few contemporary examples exist.

New Zealand's storied history with NPS is particular and noteworthy. A remote island nation that is geographically isolated and domestically poor in traditional illicit substances, New Zealand first experienced wide usage of NPS with the emergence of 1-benzylpiperazine (BZP) at the turn of the century. It became a widely used drug between 2004-2008, after which time the government prohibited it. This is probably the richest and best-documented case of a government struggling with an array of choices for regulating an entirely new drug that was popular but whose dangers were not yet well understood (Sheridan et al. 2007; C Wilkins et al. 2006; Gee et al. 2005). After a brief attempt at regulating BZP for non-medical (i.e. recreational) use, the island nation then attempted to regulate the wider NPS market under a standalone regulatory framework. I consider both these attempts below.

BZP first appeared in "party pills" in 2000. The government initially attempted to regulate the drug in 2005, when it was placed in a new schedule within the Misuse of Drugs Act as a "Restricted Substance," Class D. This scheduling prohibited sale to anyone under 18 and prohibited various promotional activities, which had previously been widespread; otherwise other aspects of the trade (e.g., hours of sale, potency, labeling, etc.) in BZP was unregulated (Sheridan and Butler 2010). As reported by the New Zealand Law Commission's (2010) review of drug policy, "BZP was the fourth most widely used drug in 2007/08. Approximately 6% of respondents had used BZP in the previous 12 months, while 13.5% had used BZP at some point in their lives" (New Zealand and Law Commission 2010)

The New Zealand Expert Advisory Commission on Drugs (EACD) reviewed regulatory options in 2004 and 2006 (Expert Advisory Committee on Drugs 2004, 2006). The EACD concluded that the risks to users from BZP were modest; the variability of potency of preparations being sold as BZP (without formal regulation) was amongst the most important sources of risk. Acute problems were often the result of combining BZP with alcohol or other drugs. The public health risks were also assessed as modest and there was emphasis on the dangers to the population resulting from its ambiguous legal status. The general public assumed it was regulated, whereas it was merely not prohibited. Only voluntary guidelines from an industry association governed quality, but were not thought to be effective. The Expert Advisory Committee concluded that,

> "While it is the EACD's view that the research has now demonstrated that BZP does pose a moderate risk of harm, newer substances may be shown to pose a low risk of harm but still be worthy of restrictions. The Committee's view is that the implementation of restrictions should place the burden of proof on the person supplying the substance to demonstrate the safety of a new psychoactive substance" (Expert Advisory Committee on Drugs 2006).

In April 2008, the New Zealand government moved to schedule the drug as Class A under the Drugs Misuse Act of 1975; this amounted effectively to full prohibition. BZP was the only substance that was scheduled under Class D, which is now defunct. There was a six-month transition period in which purchase, possession and use were not prohibited.

New Zealand's Class D ("restricted substance") under the Misuse of Drugs Act was superseded by the passage of the Psychoactive Substances Act of 2013 (PSA). This act formalized the process of regulated production and supply of low-risk NPS under the Ministry of Health. To date, this is the only national legal framework regulating the production, distribution, and use of NPS for trade as a commodity.

The New Zealand PSA requires that producers clinically test the harm of their substance, allowing only those with "no more than low risk of harm" to be regulated and sold in the market. Producers bear the cost of testing, must accurately label the ingredients and chemicals, are limited to point of sale advertising, and pay other licensing fees of $NZ180,000 per product (Parliament of New Zealand 2013; Diemen 2014). The PSA ostensibly shifts the burden of proof of harm, a costly and increasingly onerous endeavor given the explosion in development of new chemicals, from the government to the producers. Other regulations apply, including retail and age restrictions, limits on imports, pharmacovigilance, warning labels, and recommended doses (Chris Wilkins 2014).

Prior to the law's enactment, the government estimated that between 200 and 300 unregulated NPS were sold in nearly 3,500 outlets across the country, mostly convenience stores and gas stations. Most of the primary products or ingredients come in bulk from China. Domestic producers then manufacture products and packaging for retail sale (Mackie 2014). Only those domestic entities with licenses for manufacture and distribution, including online, were allowed to operate under the new law.

Shortly after the PSA came into force, regulators issued nine manufacturer licenses and created a regulatory authority and an advisory committee for the writing of further regulations. However, before the promulgation of final regulations, the Act allowed on market some 47 existing psychoactive products, mostly synthetic forms of cannabis, under interim license (Rychert, Wilkins, and Witten 2017). During this transitional phase, no new products were granted approval and twelve products were removed due to safety concerns under powers outlined by the PSA. Remarkably, the number of retail outlets of NPS shrank by upwards of 95% after the law came into effect to some 150-170 remaining

stores (Hannah 2014), though some consumers began buying products from foreign suppliers online (R. Brown 2014).

Full market regulation of NPS had never been considered before. Yet New Zealand's pioneering experience has not unfolded as planned. The government's lack of defining "low risk" was confusing and concerning to the general public (Chris Wilkins 2014; Rychert, Wilkins, and Witten 2017). This, along with restrictions on animal testing in New Zealand itself and the steep cost of product approval, have discouraged the application and development of new products. The cost of clinical testing mentioned by Wilkins (2014), estimated to be about NZ$1-2 million per product and could take 18-24 months, poses a cost prohibitive challenge in bringing new, low-harm products to market in such a small country. The issuance of interim licenses was needed to bridge a gap between the previously existing unregulated industry and the soon to be regulated market.

These difficulties seemed to have overwhelmed the political and regulatory will of the country. Not a year after its passage, with regulations still under consideration, the government revoked all interim licenses, removing all interim-approved products from market (Chris Wilkins and Rychert 2016). Some have attributed the government's about face to political concerns and the public and media's perception of problematic retail outlets and confusion over the definition of "low harm". No approved NPS are on market at this time.

New Zealand's recent experience is an example of the many challenges facing full market regulation of NPS. Recent accounts suggest that the industry is reluctant to apply for approval given the regulatory hurdles and the public's aversion to animal testing. Without

the use of animal testing required to establish what constitutes "low harm" it is unlikely that any products will be brought to market in New Zealand. Critics have suggested that such complications make the PSA "unworkable" (Chris Wilkins and Rychert 2016).

Ironically, efforts to move away from prohibition by regulating the production, distribution, and use of new psychoactives resulted in their full prohibition, at least in New Zealand. Part of the difficulty remains with the country's prohibition on use of animal testing to establish low harm. However, harms will exist as few psychoactive products that cause intoxication are wholly safe by any standard of measurement. Complicating this is the fact that NPS are taken in conjunction with other substances, typically alcohol, making pharmacovigilance more challenging (Chris Wilkins 2014). Furthermore, costs and time of product testing act as barriers to entry, leaving many would be firms out of the licit market.

Specific regulation for NPS that permit their use by adults for non-medical purposes seems to be confounded by establishing low harm. It remains to be seen if others can succeed where New Zealand failed. Wilkins and Rychert think that some existing "failed pharmaceutical," which never achieved any therapeutic value but has a desirable psychoactive effect, may succeed (Chris Wilkins and Rychert 2016). But this is a rather limited list of possible chemicals.

Nonetheless, had this regulatory framework prevailed, what is to guard against regulatory capture of yet another set of risky psychoactives, alongside alcohol and tobacco? Regulatory capture, or when private interests subvert or coopt the government's authority to appropriately regulate industry to the public's benefit, is especially a concern when

permitting the distribution of commodities that have the potential for harm. There are many lessons to be learned from the experience with alcohol and tobacco (Miller and Harkins 2010; Wexler 2011). Initial research from New Zealand suggests that during the interim period, when a handful of substances were granted market access, manufacturers of legal highs acted not dissimilarly from the alcohol industry. Rychert and Wilkins (2016) reported that the legal high industry lobbied to influence the development of future regulations (Rychert and Wilkins 2016). Such private-public partnerships are worrisome as the industry, acting in its best interest, is likely to seek loose restrictions and low taxes.

3.6.4 Regulating under medicines legislation

Stricter still would be a regime to control NPS through laws that regulate medicines and other products marketed and sold in pharmacies. Though a "failed pharmaceutical" may one day get approved as a psychoactive for recreational use under an NPS-specific regulatory framework in places like New Zealand, NPS could be permitted under existing medicines laws. However, this has not been the focus or goal in most instances where NPS have been subjected to medicines laws. The difference here is that this approach, so far, has been used to prohibit access and availability of a new psychoactive without going through a lengthy risk assessment required by narcotics laws.

Many jurisdictions have used medicines laws to provide more stringent and enforceable controls on marketing and distribution. For example, the sale of many over-the-counter cold remedies has been restricted in recent years to prevent illicit manufacture of methamphetamines (Cunningham et al. 2012). Hughes and Winstock (2012) have discussed the utility of declaring a new psychoactive substance as a medicine and

withholding market authorization (B. Hughes and Winstock 2012). In many medicines laws, the unauthorized supply of medicines is a criminal offense, albeit subject to less severe sanctions than those found for the unauthorized supply of drugs controlled by narcotics laws.

Classifying an NPS as a medicine and withholding market authorization is a more agile and proportional response (A. Winstock and Wilkins 2011). It requires only administrative action; products that have not been proven safe or effective cannot be distributed. There are two important distinctions under medicines laws. First, use-related acts are not criminalized. Second, those supplying unauthorized medicines face less-severe penalties than for narcotics-related offenses[14]. This is an important distinction given society's growing reluctance to incarcerate non-violent drug-related offenders (Doherty, Horowitz, and Suis 2014).

In recent years, many European countries had responded quickly to NPS by classifying new substances as medicines. Hughes and Winstock have documented that several NPS were successfully pulled from markets in a handful of European countries:

> BZP was first controlled under medicines legislation in Spain, as was mephedrone in Finland; both substances are classified under the Dutch medicines law, which punishes unauthorized supply by up to 6 years in prison. The mixtures known as 'Spice' (containing a range of potent synthetic cannabinoid agonist substances with no history of medical use) were rapidly controlled under medicines legislation in the United Kingdom and Germany, before the state completed the procedure to bring them under drugs control legislation. In Austria, banning import and supply

[14] In the United States, under the Food, Drug, and Cosmetic Act, the introduction or delivery of misbranded or adulterated products faces a penalty of one year in prison. Whereas under the Controlled Substances Act, the distribution or dispensing of a Schedule I or II controlled substance (apart from specified drugs like heroin, cocaine, methamphetamine, etc. that are subject to mandatory minimums) faces a penalty of up to twenty years of prison; offenses related to Schedule III substances face up to 10 years (US Congress 1938, 1970).

> under medicines legislation was chosen specifically in order to avoid criminalizing users (B. Hughes and Winstock 2012).

However, in 2014 the Court of Justice of the European Union ruled against Member States using medicines laws to control NPS after two individuals in Germany convicted of "unlawful sale of unsafe medical products" appealed their conviction (European Court of Justice 2014). After all, this did involve an obvious artifice; the substances involved were never intended to serve as medicines. This ruling has led Member States to discard this option, returning to emergency and temporary controls as a stop gap measure before proceeding with full control under the narcotics law.[15]

Under US law, companies can seek and obtain an Investigational New Drug (IND) application[16] for commercial or research purposes. These are often used for experimental drugs under clinical investigation that lack market authorization (Code of Federal Regulations 1987). The objective under federal regulations is to allow limited research of substances that show therapeutic promise. Investigators must show that the new drug will not expose patients to unreasonable risk when used in early studies. This is often done after the manufacturer or investigator has screened the new molecule for acute toxicity in animal studies. IND was used to research the medicinal benefits of cannabis decades ago (Russo et al. 2002).

[15] Finland for example issued a government decree to ban NPS that were previously classified as medicines under the Medicines Act until they could later be controlled under the Narcotics Act. http://www.fimea.fi/web/en/-/designer-drugs-to-be-covered-under-the-narcotics-act

[16] More on Investigational New Drug Applications can be found at FDA's website. https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm

It is unlikely NPS used for non-therapeutic purposes would be allowed to proceed under such a regulatory framework for medicines. Nonetheless, it is instructive to examine how this might look for a new substance. I briefly examine the case of one particular case.

During the height of the HIV/AIDS crisis, efforts were made to fast-track research into anti-retroviral drugs, such as Zidovudine (AZT). Research was trialed under the IND framework, first under Phase I/II trials to determine safety, pharmacokinetics, and later efficacy in hundreds of patients (Simoni-Wastila and Lasagna 1990). AZT's potential to treat the disease was so encouraging that it was granted a treatment IND, allowing additional patients to gain access to the drug. Under this framework physicians, pharmacists, and patients were required to register with suppliers in order for regulators to not only control supply but collect data on adverse effects and drug interactions. Patients were also required to give consent for treatment (Simoni-Wastila and Lasagna 1990). The pressing public health concerns surrounding the HIV/AIDS crisis made fast-tracking AZT under IND feasible.

Some low-risk NPS that show some therapeutic promise could be candidates for IND. It is plausible that a psychoactive chemical may have some to-be-determined therapeutic value, as could be the case for MDMA, which shows promise in treating post-traumatic stress disorder (Wan 2017). The current opioid epidemic is such a crisis that the Trump Administration's Opioid Commission has called for advancing research into alternative pain management and substitution therapies (Christie et al. 2017). Use of experimental psychoactives to cease opioid dependency is not new. Some substances, such as ibogaine, a naturally occurring hallucinogen that has been controlled as a Schedule I substance in the US for decades, has shown promise in treating opioid dependency (T. K. Brown and Alper

2017; Noller, Frampton, and Yazar-Klosinski 2017). The current opioid epidemic is such a pressing public health issue that it may warrant experimental fast-tracking of an NPS that shows some promise. This is the case with one ibogaine analog, 18-MC, which was granted IND status in 2014 (Gaita 2014; Hamilton 2014).

However, this hardly protects against the eventual risk of abuse in a recreational setting, especially if the drug has some desirable qualities (what regulators often consider “abuse liability” (Calderon, Hunt, and Klein 2017)). Arguably this was the case for many of the synthetic cannabinoids, which were originally developed to understand the endocannabinoid system (Wiley et al. 2011). Some were investigated for their therapeutic purposes long before they arrive in recreational markets (Huffman 2000, 2005; Bátkai et al. 2007).

Nonetheless, could the medicines law be used to permit and regulate the production, distribution, and use of NPS outside of a currently recognized medical setting? Medicines laws are designed to protect the health and wellbeing of individuals and society. Only approved products with therapeutic value are permitted in the market. Society’s narrow interpretation of therapeutic value limits access to substances to treat disease, not enhance our abilities, performance or experiences. Is it unreasonable to consider such utility and the possibility that some NPS could benefit otherwise healthy individuals? In a recent op-ed, Mark Kleiman states:

> Our current medico-legal system is not yet equipped to handle drugs that can improve on "normal": make us "better than well." (For example, Viagra was approved for the treatment of "erectile dysfunction"; the FDA would not have recognized a claim that it improved normal male sexual performance or satisfaction, which is, of course, why most of its users take it.) But that is not the

> only possible interpretation of the plain language of the Food, Drug, and Cosmetic Act: There's no logical reason why a drug couldn't be shown to be "safe and effective" at improving the well-being of healthy people in some regard (M. A. R. Kleiman 2016).

Kleiman (2016) speaks specifically about the nonmedical utility of hallucinogens, like psilocybin or LSD. It's not unforeseeable that some new psychoactives could be utilized to enhance an individual's cognitive abilities, provide insight, or offer some form hedonic experience, as well as treat complex psychological states such as depression or anxiety (R. R. Griffiths and Grob 2010; Grob et al. 2011).

However, the problem remains that approved substances must show therapeutic benefits and safety before given market authorization. Substances that have no medical utility are often restricted by regulators, especially when scheduled under narcotics laws. The use of medical legislation seems better suited for products that have undergone research to show their benefits in treating sickness or improving performance. The application of medical laws, up to now, has been to quickly remove NPS from the marketplace. Yet with recent court rulings in Europe, this approach may be limited. The only possible way medicines laws may be appropriate to regulating NPS is if society were to recognize and accept the benefit-risk tradeoff of certain substances, such as performance enhancement, cognitive enhancement, or merely pleasure.

3.6.5 Narcotics laws

The default policy for decades has been to schedule new substances under existing narcotics laws. This is the case for the international and regional systems, which were discussed earlier. Here I focus mostly on US federal law, supplementing with examples from elsewhere. Since the 1930s, states in the US have passed similar narcotics laws and

scheduling regimes that generally follow federal law; today most mirror the federal Controlled Substances Act (Musto 1999). There are slight deviations, especially when it comes to new drugs, but the regulatory framework is generally the same across states and to some extent across countries.

Under most national laws, psychoactive substances subject to control are listed by schedules. These range by degree of harm as well as medical utility. I do not examine the definition or details of scheduling order, though I note this has been a common debate in drug policy (M. A. R. Kleiman 2012; Coulson and Caulkins 2012; Humphreys 2016). It is only important to point out that substances without "currently accepted medical use" are subject to Schedule I, the strictest classification. In the US and in most other countries, substances can be added to the list by legislative action; Congress can and does list substances to the Schedules of the Controlled Substances Act (CSA). Most recently Congress passed the Synthetic Drug Abuse Prevention Act of 2012 which added 26 new substances to Schedule I of the CSA, including 15 cannabimimetics and 11 cathinones (Sacco and Finklea 2016).

In addition to legislative action, regulatory agencies can also control substances after assessing their abuse potential and harms. I note in Figure 3.1 the instances in which the Drug Enforcement Administration has scheduled substances. In order to control a chemical under the CSA, the DEA, in coordination with other federal agencies, must conduct an "eight factor analysis" that takes into account the abuse potential, pharmacology, scientific knowledge, history and patterns of abuse, duration and significance of abuse, the public health risk, dependence liability, and if the chemical is an immediate precursor of a controlled substance (US Congress 1970). This regulatory approach has been criticized for

being too slow and too limiting. More often than not, there is little information once a new substance has been identified, complicating risk analysis and thus scheduling decisions. It took four years for the government to schedule MDMA (Kay 2002). Efforts have been made to extend the regulatory authority's powers to temporarily control new substances while risk assessments are conducted. Under the CSA, the DEA has the power to rapidly control a new chemical up to 24 months[17] (with a potential 12 month extension) while conducting the eight factor analysis risk assessments.

These temporary measures are best thought of as stopgaps. Recently, the length of temporary controls were doubled to give regulators more time to gather information on new chemicals. Given these challenges, there are three additional avenues for control of substances that apply to narcotics laws: analog controls, generic controls, and neurochemical controls.

Analog controls focus on a substance's similarity to controlled drugs. Analog controls can take a few different forms. An NPS can be chemically or pharmacologically similar to a controlled substance. Some countries only include one of these components (Home Office 2014). In the United States, the Federal Analog Act of 1986 makes it a criminal offense to knowingly supply a "controlled substance analog" for human consumption (US Congress 1986). In this case, an analog must have a "substantially similar" chemical structure to a controlled substance in Schedule I or II, or have a pharmacologically similar effect to a controlled substance in Schedule I or II by causing substantially "similar stimulant, depressant, or hallucinogenic effects on the central nervous system" (US Congress 1986).

[17] This was increased from 12 months by the passage of the Synthetic Drug Abuse Prevention Act of 2012.

This is an important detail. Some NPS may have pharmacological effects similar to controlled substances without having a similar chemical structure. This is the case with many synthetic cannabinoid compounds (JWH-018, JWH-250, CP-59,540, etc.) as well as some non-controlled dissociative alkaloids found plants like *Salvia divinorum* (Stevens et al. 2015; J. van Amsterdam, Nutt, and van den Brink 2013). The inclusion of a similar pharmacological effect broadens the legal definition of an analog.

The Federal Analog Act has been the traditional mechanism with which NPS are, in essence, subject to control in the US. Yet, it is an imperfect regulatory mechanism. Between 2011 and 2014, there have been over 130 indictments, most pleading guilty to lesser charges (Home Office 2014). In many cases the courts have found the litigated substance to be an analog and henceforward treated as a Schedule I substance, indicating considerable deference to the government's interpretation of the law. Investigation and prosecution under the law are costly and time consuming (Home Office 2014). Furthermore, juries, not chemists or pharmacologists, are deliberating on the structural similarity of substances and their intended psychoactive effects. Still, many suppliers and retailers have circumvented the Analog Act by labeling packages with warnings, stating that the product is "Not intended for human consumption".

The costly legal case-by-case approach under the Analog Act does not issue notifications to the public as to which new chemicals are controlled, as is the case by regulation when a substance is controlled administratively. Congress is now working to expand control of new chemicals by amending the CSA to include an analog schedule. The bipartisan Stop the Importation and Trafficking of Synthetic Analogues Act of 2017 (SITSA), sponsored by the Senate Judiciary Chair Chuck Grassley and ranking member Dianne Feinstein, will

add a sixth and separate schedule for analogs, Schedule A, to the CSA (Grassley 2017). Sponsors of the bill point to the growing problem of synthetic cannabinoids but in particular fentanyl analogs which "represent the deadly convergence of the synthetic drug problem and the opioid epidemic" (Grassley and Feinstein 2017).

The act does several things apart from creating a new drug schedule. New chemicals would only have to meet three of the eight factors (pharmacology[18], abuse potential, and dependence liability) to be considered an analog. The Attorney General, under the act, would be able to temporarily schedule an analog for up to five years (with an additional six month extension) after determining that the chemical in question meets the definition of an analog. The reduced three-factor threshold is meant to cut the time needed to temporarily schedule new substances. The bill also schedules 13 fentanyl analogs under Schedule A (Grassley and Feinstein 2017).

The bill's sponsors aim to "strike a balance" by treating manufacture and distribution of Schedule A substances the same as Schedule III (which includes substances like buprenorphine, ketamine, and Marinol) (Grassley and Feinstein 2017). Offenders would face no more than 10 years in prison. Notably the bill explicitly excludes penalties for simple possession of Schedule A substances (Grassley 2017).

The bill allows regulators to act swiftly but critics argue that scheduling low-risk substances, like kratom, under Schedule A may harm users who rely on the supplement to treat chronic pain (Ingraham 2017). Of greater concern is the narrow exemption for

[18] Such as similar chemical structure or pharmacological effect as controlled substances listed in Schedules I-V.

research. The bill's language allows for the Attorney General to register and license research of Schedule A substances, so long as such research is consistent with the "public interest". There is no statutory role for other government agencies or departments, such as the Department of Health and Human Services or the Food and Drug Administration. It is hard to imagine that a law enforcement agency has the capacity to weigh all realms of the "public interest" to determine acceptable research for potential industrial, commercial, or medical products. As discussed earlier, such a narrow exemption for research ignores many benefits, including non-medical, which new substances may offer.

Analogs focus on the chemical or pharmacological similarity that a new substance has with an existing controlled substance. Generic controls, on the other hand, focus on the parent structure of a controlled substance. The idea behind these controls is to futureproof whole sets of compounds that are similar to controlled substances by scheduling molecular families. The UK was the first to experiment with generic controls in the 1960s. According to King in Dargan and Wood (2013), the UK's Misuse of Drugs Act of 1971 contains several generic control groups for different families of substances (Dargan and Wood 2013, chap. 1).

King suggests that generic controls have advantages, avoiding the regulatory complications of assessing and listing new chemicals. However, the law is often very detailed and precise with regard to the chemical composition of parent molecules and the possible molecular substitutions that can occur (Dargan and Wood 2013, chap. 1). This can be problematic for some regulators as it requires a substantial understanding of chemistry. Nonetheless, generic controls can stand the test of time. As King notes, almost 80% of the

phenethylamines published in Alexander Shulgin's PIHKAL[19], 40 cathinone derivatives, and approximately 30 synthetic cannabinoids reported since 2012 were covered by generic legislation (Dargan and Wood 2013, chap. 1).

Apart from the complex regulatory design required to govern whole families of chemicals, other criticism remains. King points to several of these. First, bans on whole families of chemicals impedes research and development. Second, some chemicals within controlled families have legitimate therapeutic properties, necessitating the listing of specific exempted chemicals. Third, generic controls are often hard to operationalize or understand outside of specialized professional groups; police seize a substance but must ascertain if the pill or powder belongs to a particular family rather than checking to see if the chemical in question is listed. Though a substance is effectively prohibited under generic controls, it is often not apparent to many individual regulators (Dargan and Wood 2013, chap. 1). These all increase the administrative burden and complexity of the law for both the industry as well as the state. Fourth, generic controls do not assess risk nor are the controls tied to any degree of harm associated with the supply or use of a chemical (J. van Amsterdam, Nutt, and van den Brink 2013). Lastly, generic controls may actually encourage the development of new psychoactives. King notes that such laws may provide a guide for clandestine chemists (King 2014b).

The last approach to controlling NPS within the framework of the narcotics law is perhaps the newest given recent advancements in neuroscience and chemistry. The neurochemical approach blends the analog and generic approaches to regulate new psychoactives based

[19] An anthology published in 1991 of 179 phenethylamines discovered or designed by the prolific American chemist (A. Shulgin and Shulgin 1991).

on their pharmacological action. It was one of a handful of approaches recently considered by the UK government (Home Office 2014). Here a substance is subject to control if it has an effect or binds to a certain receptor in the central nervous system. This approach was recently introduced, albeit partially, in the United States under the Synthetic Drug Abuse Prevention Act of 2012. The law added "cannabimimetic agents" to Schedule I of the CSA. Cannabimimetic agents are defined as any substance that is a "cannabinoid receptor type 1 (CB1) agonist as demonstrated by binding studies and functional assays *within five structural classes*" (emphasis added) (Sacco and Finklea 2016). The law is limited to five structural classes. Had no structural classes been defined or included, it is conceivable that the law could be interpreted to include synthetic THC (dronabinol) and naturally occurring endocannabinoids, such as anandamide. Because the law limited the definition of what constitutes a cannabimimetic agent to five structural classes, this is much like the generic approach considered earlier.

This last approach, because of its narrow definition and structural inclusion of cannabinoid classes, suffers from some of the same shortcomings that plagues the generic approach. Principal among them is the fact that a new synthetic cannabinoid can escape control if they fall outside of the listed structural classes. Further, it does not consider new or to be discovered neurological mechanisms. It only applies to known neuro receptors.

3.6.6 Total Ban

In order to simplify the approach to controlling NPS as well as preempt rather than react to the arrival of new psychoactives, some countries have implemented total bans. Such an approach criminally prohibits and sanctions, albeit less severely than offenses for

controlled substances, the importation, manufacture or supply of psychoactives, with a narrow exemption for medicines, alcohol, tobacco, foodstuffs, and other controlled substances already listed under existing laws. In some cases laws exempt research. Often psychoactivity, not harms, has to be indicated to prohibit the chemical and criminalize related offenses. Rather than supersede existing drug control laws, blanket bans have thus far operated simultaneously with existing narcotics laws.

Here, speed is favored over regulatory accuracy (defined as evaluation or supervision of control); no risk assessment or listing is required as any non-exempted psychoactive chemical is prohibited. This approach has been adopted by a handful a countries, including Australia (2015), Ireland (2010), Poland (2011), Romania (2012), and the United Kingdom (2016). Because New Zealand (2013) has yet to approve any product, its law effectively acts as a total ban (Rychert, Wilkins, and Witten 2017). However, the law's goal is not prohibition, but regulation. Its inclusion here and in the accompanying table is merely expository.

I elaborate on these cases below. Table 3.1 reproduces the definition of pyschoactivity established in the law, alongside penalties, exemptions, and other details. The definition of psychoactivity varies, though Ireland, Australia and the UK have similar wording[20]. With the exception of the UK and Poland, blanket bans statutorily limit the definition of psychoactivity to some measure of harm (e.g., "significant disturbance" or similar effects to controlled substances). All cases include clear exemptions for other items that are subject to existing regulatory frameworks, such as food, tobacco, alcohol, medicines and the like.

[20] Australia and the UK adapted much language from Ireland's Psychoactive Substances Act of 2010.

Though the UK statute does not tie the definition of psychoactivity to harm or controlled substances, it is the only one of the five blanket bans that includes a clear statutory exemption for research.

None of the cases criminalize or sanction use of psychoactives. Much like SITSA bill in the US Congress, personal possession and use of NPS is not criminalized by total bans. This departs from traditional narcotics controls, which criminalize the unauthorized possession of controlled substances for personal use. Penalties for supply-related acts vary with the UK being the most severe; nonetheless all include some form of incarceration. Under Australian Commonwealth law, the federal government can regulate importation; other supply-related offenses are addressed by state and territorial law. Two of Australia's states, New South Wales (2013) and Western Australia (2015), have enacted similar laws with the same Commonwealth definition and exemptions in order to criminally prohibit supply-related acts like manufacturing, distribution, and promotion (Parliament of New South Wales 2013; Parliament of Western Australia 2015). This suggests that in Australia's six other states and territories, domestic supply of NPS are not regulated nor subject to criminal prohibition.

Table 3.1: Comparative analysis of blanket bans and defining psychoactivity

	Definition of psychoactivity	Limiting criteria	Listed or defined exemptions	Penalties for supply-related offenses	Enforcement
United Nations 1971 Convention	The substance has the capacity to produce(i) (1) A state of dependence, and(2) Central nervous system stimulation or depression, resulting in hallucinations or disturbances in motor function or thinking or behaviour or perception or mood, or(ii) Similar abuse and similar ill effects as a substance in Schedule I, II, III or IV	Sufficient evidence that the substance is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control	Parties may make reservations, including for domestic plants in the wild that are traditionally used for magical or religious rites by small and clearly determined groups.	Subject to constitutional limits, parties shall adopt serious offences that are liable to adequate punishment, including imprisonment or other deprivation of liberty.	Member states
Ireland	Substance, product, preparation, plant, fungus or natural organism which has, when consumed by a person, the capacity to—(a) produce stimulation or depression of the central nervous system of the person, resulting in hallucinations or a significant disturbance in, or significant change to, motor function, thinking, behaviour, perception, awareness or mood, or (b) cause a state of dependence, including physical or psychological addiction	Substance must cause "significant disturbance"	Medicine, veterinary products, liquor/alcohol, tobacco, food, drugs already controlled by legislation, other substances as may be specified by legislators	Fine up to 5000 euro Minor offense: up to 1 year prison Serious offense: up to 5 years prison	Law enforcement
Poland	Substance, product or plant used instead of, or for the same purposes as, a controlled drug, and whose manufacture or placing on the market is not regulated by separate provisions.	Substance is regulated by other laws.	Substances that are regulated by other consumer and general safety laws	Fine up to 250,000 euro Up to 1 year prison	State sanitary inspector

	Definition of psychoactivity	Limiting criteria	Listed or defined exemptions	Penalties for supply-related offenses	Enforcement
Romania	Product likely to provoke a psychoactive effect similar to those caused by controlled substances. These effects are defined as stimulation or inhibition of the central nervous system provoking 'changes in functions and mental processes and behaviour', or 'causing dependency'	Substance's effects must similar to those of controlled substances.	Substances that are regulated by other laws	Between three months and three years in prison depending if substance psychoactive effects are known. Advertising faces one year in prison	Ministry of Health, National Authority for Consumer Protection, National Health Veterinary and Food Safety Authority, Ministry of Internal Affairs, Ministry for Information Society
Australia	A psychoactive substance means any substance that, when a person consumes it, has the capacity to induce a psychoactive effect. A psychoactive effect, in relation to a person, means: (a) stimulation or depression of the person's central nervous system, resulting in hallucinations or in a significant disturbance in, or significant change to, motor function, thinking, behaviour, perception, awareness or mood; or (b) causing a state of dependence, including physical or psychological addiction	Substance must cause "significant" disturbance or change	Food, tobacco, medicines and other therapeutic goods, agricultural products, veterinary products, industrial chemicals, plants/fungi, otherwise controlled drugs/plants, prohibited imports, or other substances as may be specified by legislators	Importation of psychoactive substance subject to five years prison. Importation of a serious drug alternative subject to three years prison.	Law enforcement
United Kingdom	Substance which—(a) is capable of producing a psychoactive effect in a person who consumes it, and (b) is not an exempted substance. For the purposes of this Act a substance produces a psychoactive effect in a person if, by stimulating or depressing the person's central nervous system, it affects the person's mental functioning or emotional state.	Substance is exempted	Controlled drugs, medicinal products, alcohol, tobacco/nicotine, caffeine, and food Research activities exempted.	Up to seven years in prison.	Law enforcement

	Definition of psychoactivity	Limiting criteria	Listed or defined exemptions	Penalties for supply-related offenses	Enforcement
New Zealand	Psychoactive substance means a substance, mixture, preparation, article, device, or thing that is capable of inducing a psychoactive effect (by any means) in an individual who uses the psychoactive substance. Psychoactive effect, in relation to an individual who is using or has used a psychoactive substance, means the effect of the substance on the individual's mind	Substance must effect the "mind" or produce some change in behavior. Prohibited psychoactive substances pose more than low risk of harm to users.	Controlled drugs, precursor substances, medicines, herbal remedies, dietary supplements, food, alcohol, and tobacco. Research is licensed.	Up to two years prison or a fine of $500,000 for corporate offenses.	Psychoactive Substances Regulatory Authority

Sources: B. Hughes and Evans-Brown 2015; Barratt, Seear, and Lancaster 2017; Parliament of New Zealand 2013; Parliament of Ireland 2010; Parliament of the United Kingdom and Northern Ireland 2016; Parliament of the Commonwealth of Australia 2015

Evaluations of the impact of these laws are still ongoing. Nevertheless, Ireland and the UK have generated the most research and discussion; below I focus on these two cases. Little or no English-language evaluations exist for other cases though there is some descriptive analysis of Australia's recent law (Barratt, Seear, and Lancaster 2017).

In 2010, Ireland was the first country to adopt this novel approach to controlling the supply of new drugs with the passage of the Criminal Justice (Psychoactive Substances) Act of 2010 (PSA). The Irish PSA, as well as the UK PSA for that matter, was largely designed with shuttering retail supply of NPS. The Irish PSA criminalizes "a person who sells a psychoactive substance knowing or being reckless as to whether that substances is being acquired or supplied for human consumption". According to Kavanagh and Power (2014), the law leaves little room for interpretation: "if the accused [party] gives any indication (e.g. product labelling, website information, verbal communications) that the substance or product offered for sale is psychoactive, then no further proof of pharmacological activity is required" (Kavanagh and Power 2014). That is, law enforcement may act if supply of non-exempted psychoactives is suspected. However, prosecuting such offenses is difficult to operationalize. As of mid-2015, only five prosecutions have been brought to court, about one a year (McVeigh 2015).

This approach, so far, is not as heavy handed as traditional narcotics control laws. The Irish PSA features graduated law enforcement mechanisms to shut down supply. Those that fail to comply face modest penalties of 5000 euro fines or twelve months jail for summary conviction and up to five years imprisonment on an indictment conviction. Compare that with up to a statutory maximum of life in prison for supply offenses under the Irish Misuse of Drugs Act.

Though the Irish PSA is aimed at restricting the sale of uncontrolled psychoactive substances, and by some accounts was successful in eliminating their sale in headshops (Home Office 2014; Kavanagh and Power 2014) and reduced the incidence of reported NPS use for clients seeking treatment as well as youth prevalence (Kavanagh and Power 2014; Smyth et al. 2015; Smyth 2017), the net effects of the blanket prohibition of NPS are still not well understood. Early reports discuss displacement to heroin and prescription drugs as well as a developing illicit street market for certain NPS (Home Office 2014; K. Moore Dargan, Paul I., Wood, and Measham 2013).

So far, total bans have been met with criticism for being overly broad in their application to any psychoactive substance (definition divorced from harm), their narrow scope of exempted substances, and the difficulty of operationalizing psychoactivity for enforcement purposes (Stevens et al. 2015; Reuter and Pardo 2016a). This last point was and remains an issue especially for the UK, which enacted a total ban mid-2016 (ACMD 2015a, 2015b, 2015c).

In 2016, the British government, despite a flurry of criticism (Stevens et al. 2015; Ramsbotham et al. 2015), adopted a total ban on all psychoactive substances other than those on a list of exemptions, including medicines, alcohol, tobacco, and substances already scheduled under the Misuse of Drugs Act; the law included an exemption for scientific research. It attains its apparent simplicity however by ignoring a major conceptual and empirical difficulty, namely how to define psychoactivity. The Chair of the Advisory Council on the Misuse of Drugs (ACMD) testified to a House of Commons committee to the effect that he did not believe psychoactivity as a concept could be usefully operationalized without human testing, which would not be possible under the act (Iversen

2015b). Implementation of the law was delayed for over five months while officials from the Home Office addressed issues operationalizing the ban (Travis 2016). In the end, the Home Office issued an Explanatory Note[21] elaborating on the definition of psychoactivity, stating that a substance produces a psychoactive effect:

> By speeding up or slowing down activity on the central nervous system, psychoactive substances cause an alteration in the individual's state of consciousness by producing a range of effects including, but not limited to: hallucinations; changes in alertness, perception of time and space, mood or empathy with others; and drowsiness (Home Office 2016a).

To demonstrate this, the Home Office adopted guidance from the ACMD (Home Office 2016c, 2016b) that was first rejected during the drafting of the law. Prior to passage, the ACMD recommended that the bill's definition a psychoactive substance be amended to:

> Any compound, which is capable of producing a pharmacological response on the central nervous system or which produces a chemical response *in vitro*, identical or pharmacologically similar to substances controlled under the Misuse of Drugs Act 1971 (ACMD 2015c).

To this effect, the ACMD recommended that forensic labs, law enforcement and prosecuting agencies, and expert witnesses adopt this definition and employ two tests to determine a psychoactive effect. First that the compound binds to a list of receptors[22] known to produce psychoactive effects similar to those of controlled substances. And second, that the compound activates a response in the receptor (Home Office 2016c, 2016b). This proposed definition, which again was first rejected, narrows the scope of the law, tying new substances to similar pharmacological effects of controlled substances.

[21] Explanatory Notes are issued to explain an Act of Parliament and provide information to develop policy.
[22] Such as CB1 (targeted by cannabinoids), μ-opioid (targeted by opioids) and NMDA (targeted by ketamine) receptors. Government documents suggest that new receptors could be added should new drug mechanisms or actions appear.

Nonetheless, the definition enshrined in the law is quite broad. It implies that any substance, other than those exempted, has at least the risk of causing harm and is thus prohibited. Not only does it include new substances about which next to nothing is known but also some substances which are known to be of minimal to moderate harm. Though most NPS seek to imitate existing prohibited substances, critics have pointed out the law goes well beyond such substances. For example, much has been made of the fact that supply of 'laughing gas' (nitrous oxide), far from a *new* psychoactive substance (having been discovered in the 18th century), has been banned, even though its use is legitimate in certain food and medical products and the ACMD did not believe that its harms warranted scheduling under the Misuse of Drugs Act (Iversen 2015b). There was worry that poppers (alkyl nitrites) also would fall under the ban even though just four years earlier the ACMD concluded that poppers are "not seen to be capable of having 'harmful effects' sufficient to constitute a societal problem" (ACMD 2011). In a last minute decision, the Home Office minister agreed with the ACMD's technical assessment that poppers do not "directly stimulate or depress the central nervous system" and therefore fall outside of the definition of a psychoactive substance under the law (ACMD 2016a). The technical quirk being that alkyl nitrites do not cross the blood-brain barrier and thus do not *directly* act in a psychoactive manner on the brain.

As discussed above, early assessments of UK's blanket ban suggest that headshops and online retailers have stopped selling NPS or shut down (Beltgens 2017; Wadsworth, Drummond, and Deluca 2017). In the first six months, the Home Office reported that 31 headshops have closed, almost 500 arrests and convictions had occurred, with four individuals sentenced to prison (Home Office 2016e). National surveys report a decline in

prevalence of NPS, but that is matched by a two thirds increase of past-year use of cocaine in 16-24 year olds (from a recent low of 3% in 2012/2013 to just under 5% in 2016/2017) and an increase of about a third for past-year use of MDMA in 16-24 year olds (from a recent low of 3% in 2012/2013 to 4.3% in 2016/2017) (Home Office 2017). Declining prevalence in new drugs could reflect the market's return to traditional drugs of use. Yet, because surveys are not longitudinal, it is difficult to put forward a more convincing claim of back substitution or if users are more reluctant to report NPS use now that such substances are controlled by law. Nonetheless, the blanket prohibition appears to have concentrated harm in vulnerable populations, as discussed earlier (Gray, Ralphs, and Norton 2017; Doward 2017).

Psychoactivity, not harm, is the determining factor. The ACMD did not believe that nitrous oxide warranted control even though it is a popular recreational drug, and recommended that alternative measures be taken further in the supply chain to reduce diversion (Iversen 2015b, 2015a). Its control would amount to a Type I error. Law enforcement has aggressively tackled nitrous oxide distribution with the help of the PSA. Though hundreds have been arrested or convicted under the new law, most have been for offenses related to the supply of nitrous oxide. In the first six months of the law coming into effect, the Metropolitan Police Service, whose jurisdiction is the greater London area, reported that there were 178 offenses under the Psychoactive Substances Act. Of those, 57% were for unauthorized supply of nitrous oxide or possession of canisters of nitrous oxide with intent to supply; 20% of offenses did not state the type of suspected substance, and the remainder were for synthetic cannabinoids or other substances (Metropolitan Police 2017). Nitrous oxide dealers could just be easy targets. Inflating balloons with gas canisters and handing

them to buyers on the street is likely to draw a lot more attention than a typical hand-to-hand transaction.

Subsequently, the courts first rejected the control of nitrous oxide under the PSA. Two recent cases had successfully challenged the law's definition of psychoactivity when applied to nitrous oxide (Rawlinson 2017). Lawyers argued that these products are exempted as they are medical products. These rulings were later overturned in an appeals court. Prosecutors did not deny the medical classification of nitrous oxide, but argued that the quantity of 8 gram canisters suggested unlawful supply under the PSA (Baber 2017). In these circumstances nitrous oxide was intended for recreational and not exempted medical or therapeutic purposes:

> The canisters in question were in fact manufactured for use unconnected with medical purposes, widely available and distributed for use in catering, which in itself is a strong indicator that they were not medicinal products. Furthermore, the purpose for which it was intended to supply the canisters was purely recreational with nothing whatsoever to do with health (Fortson 2017).

Interestingly, the prosecution focused on the circumstances of the provision of nitrous oxide and not the chemical itself. This is similar to the consumer protection approach described earlier. Yet, what if suppliers were using medical-grade tanks instead of canisters? Presumably, the state would argue that the setting in which provision occurred was outside the normal bounds of medical application, such as in a doctor or dentist's office. This line of reasoning does not deny nitrous oxide's medical utility or psychoactivity, just the manner in which it was supplied.

This seems to undermine the PSA for two reasons. First, the government must now prove that the supply of medical products was intended for non-medical purposes. The rationale

behind the PSA was to reduce the prosecutorial burden: supply of any non-exempted psychoactive is a criminal offense. Second, the PSA now duplicates existing laws that prohibit the unauthorized supply of medical products, such as the Medicines Act of 1968. It is unclear how this legal redundancy is going to be addressed. One could imagine similar shortcomings with regard to the possession and supply of other solvents, like gasoline, which are not exempted in the PSA but have commercial and industrial applications.

Because the PSA does not differentiate harmful psychoactives from innocuous or low-risk substances, some drugs may escape appropriate controls and penalties. Not a year after the passage of the law, under the advice of the ACMD, the government scheduled a new generation of synthetic cannabinoids using generic controls in the Misuse of Drugs Act (Home Office 2016d; Parliament of the United Kingdom and Northern Ireland 2016b). Synthetic cannabinoids were subject to the PSA because of their psychoactivity. Nonetheless, their harm warranted further controls according to the ACMD (ACMD 2014, 2016b). Under the Misuse of Drugs Act, simple possession of these substances is now criminally sanctioned and supply-related offenses face stiffer penalties. The inappropriateness of control of synthetic cannabinoids suggests that their control under the PSA was an example of a Type II error.

The harms caused by these substances warranted stricter control, especially when compared to the penalties for and harms caused by cannabis. Some qualitative surveys suggest that users prefer natural cannabis to synthetic cannabis (Perrone, Helgesen, and Fischer 2013; Sutherland et al. 2017).. Under the PSA, users faced no punitive threat for possessing or using synthetic cannabinoids, giving these substances an attractive advantage over natural cannabis. Scheduling these chemicals under the Misuse of Drugs Act, where

cannabis is controlled, would raise the cost (in this case legal sanctions) users faced for possessing cannabimimetics.

Under a blanket ban the government is no longer simply reactive. The existing process for assessing an NPS under the Misuse of Drugs Act (MDA) in Britain is time consuming and requires an almost ritual, rather than expert, judgment by the ACMD on new substances. The government must make a decision at a time when there are minimal data on the harms of the drug or its potential for substitution. If it is possible to develop clear and legally operational definitions, the total ban ought to reduce the cost of managing the NPS problem (Home Office 2015). Yet the tradeoff made by blanket bans is one of speed over regulatory accuracy. As I note in the cases above, definitions of psychoactivity can apply to a wide range of substances, some of which may be of low risk. Putting aside the normative debate of drug prohibition; the uniform control of any and all psychoactive chemicals will result in misclassification.

Going forward, the British government is planning an evaluation of the PSA sometime during 2018/2019. Thinking about the total ban and its impact on the drugs market, I propose a brief framework for such an assessment. This evaluation framework focuses on the UK Psychoactive Substances Act but could also apply to any jurisdiction that is considering a total ban.

A comprehensive evaluation should consider changes made by the PSA not only in the market of new psychoactives, such as headshops and online retailers, but the wider drug market. As this chapter has argued, different NPS are related to different market niches, which translate into different risks and outcomes. Therefore, assessments should vary

according to substance class, if possible, rather than "NPS" as a whole. Outcomes of interest should include 1) those related to drug user health; 2) the wider drug market and crime; and 3) regulatory and political outcomes relevant to the law's operationalization and enforcement.

Existing data gathering and monitoring systems can gauge some shifts in drug use and drug market activity. For example, I have discussed the early assessments of changing prevalence rates. However, a more refined evaluation of users could determine any claims of back substitution. Likewise, surveys would need to ascertain which class of NPS is used. Given that so many new chemicals rapidly enter and exit the market, this may be difficult as users may not be aware of what drug they are taking. Additional data sources, such as, urinalysis, toxicology reports, and forensic analysis of seizures, might improve measurement. A separate qualitative survey of NPS or drug users might help confirm or deny the back substitution hypothesis. Likewise, such surveys may help assess if NPS consumers migrated to more harmful traditional drugs, as was suggested in Ireland by homeless synthetic cannabinoid users initiating heroin (Home Office 2014).

In addition to prevalence, the evaluation should focus on harmful use of NPS in certain vulnerable populations. Politicians may claim victory with the closing of headshops, but that does not mean the problem disappeared. The PSA may have encouraged greater use among homeless and institutionalized populations by dumping product into street markets. Several public health indicators can be used to gauge changes in the levels of harms. Trends in emergency department episodes, calls to poison control centers, deaths, and incidents of emergency medical service calls can provide some additional dimensions to assess changes in harms.

Studies suggest that supply networks of NPS are moving underground and that some users may have taken to dealing (Gray, Ralphs, and Norton 2017). Others have shown that headshops and online retailers have stopped selling NPS. Law enforcement data can help map the transformation of the NPS market, determining if organized crime becomes involved in trafficking and supply. Likewise, law enforcement should monitor the post-ban NPS market to determine if suppliers have become more violent, as some predict.

The evaluation should determine the size and scope of NPS that enter the market, recording the number and volume of newly discovered psychoactives. Law enforcement data on the quantity and type of seizures will help evaluate changes in the NPS market. As I've argued in this chapter, the total ban may be appropriately suited for some market niches, such as users that seek legal alternatives to traditional drugs. However, the ban will do little to change supplier behavior when it comes to importation and distribution of substances like fentanyl analogs, which are cheap alternatives to heroin. Any evaluation will need to look closely at the trends in the quantity and type of seizures by substance type. It might be that the number of new synthetic cannabinoids entering the market falls while the number or volume of new fentanyl analogs continues to increase. Does this mean that the total ban failed?

Measuring political and regulatory outcomes related to the operationalization and enforcement of the law are less clear. Data from government labs will help determine how well the law is operationalized. The lab's ability to accurately determine psychoactivity in a timely manner is crucial. The evaluation should include data and findings from government labs, including the number of new drugs discovered and their pharmacology. Counting the number of headshop or online store closures may indicate a shift in the market

rather than a reduction in total supply. Other law enforcement data, such as the number and type of violations under the PSA, are important indicators that help gauge how police and the courts are enforcing the law. As shown, early reports of the number and type of arrests and prosecutions imply that law enforcement has focused efforts on nitrous oxide dealers. The number and type of convictions are also important indicators of the law's legitimacy. It appears that several rulings against the government in two specific cases have challenged the law's legitimacy with respect to the ban of nitrous oxide. Substantial court challenges and appeals may indicate that the law is politically and legally infeasible or problematic. Inferences can be drawn from other indicators, such as civil sanctions, like cease and desist or "Prohibition orders".

Given the legislative redundancy between the Misuse of Drugs Act and the Psychoactive Substances Act, an assessment should also evaluate the complexity of enforcement on the ground. Have law enforcement efforts been complicated by such competing laws? A complete assessment of the impact of the PSA will need to evaluate law enforcement's efforts (as opposed to outputs). This may require a specific survey aimed at police and prosecutors who are charged with enforcing the law. What adaptations or policies were needed to implement the PSA alongside the Misuse of Drugs Act?

The reclassification of synthetic cannabinoids under the Misuse of Drugs Act suggests that the PSA may have made a Type I error. Likewise, the court's rulings on nitrous oxide suggests another legislative error. Counting the instances in which substances are re-scheduled or the law amended to account for such errors will help determine how feasible and necessary the law is, at least on a political level.

I close this subsection with a classification table of the five regulatory frameworks considered. Table 3.2 points to the advantages and limitations of the alternative frameworks that have been considered in this section, together with the application of the variants of the existing scheduling system. These frameworks are a limited set of options for states that have considered regulating NPS. Policymakers should recognize that no single approach is perfect; all have pitfalls and problems.

Table 3.2: Summary of main regulatory options available

Type of Regulatory Framework	Examples of Use	Strengths/Advantages	Problems/Considerations
Foodstuffs regulations	Weight loss products Performance enhancement products	Permits access to substances that might substitute for more dangerous drugs (kratom) Avoids illicit markets Little/no impact on incarceration	Rapid product turnover Difficulty/cost of evaluating individual products Public presumes that government has approved Allows too much exposure to dangerous products; presumption of safety
Regulation of specific commodities	Alcohol regulation Tobacco regulation New Zealand's restricted access and Psychoactive Substances Act	Regulatory accuracy Avoids illicit markets Little/no impact on incarceration	No relevant examples of applicability to "legal highs" due to product turnover. Difficultly establishing products of low-risk. Regulatory capture.
Medicines regulations	Mephedrone and BZP in several EU states	Safety Avoids some illicit market activity Less impact on incarceration	Deceptive since NPS not medicines Manufacturers/potential users advocate for approval Production and ingredients tightly controlled; safety and efficacy proven Products denied market approval may migrate to illicit market

Narcotics laws: Scheduling and regulation of illicit substances Analog Generic Neurochemical	U.N. Conventions National laws	Reduces the attractiveness of some mimetic drugs (no longer sought out due to legality). Generics/neurochemical approaches can futureproof controls.	Slow to address new substances, though new temporary controls and generic controls have proven somewhat effective Costly to prosecute Furthers development of substances outside of controls Biased towards prohibition Illicit markets, incarceration
Total ban of any new psychoactive substance, with narrow exemptions	Irish, Australian and UK Psychoactive Substances Act	Preemptive rather than reactive. Focus is on suppliers, not users	No possibility of developing less harmful recreational drugs Difficulty of operationalizing psychoactivity Misspecification of controls and harms (Type I/II errors) Biased towards prohibition Illicit markets, incarceration

3.7 Application and tradeoffs

Excluding new opioids, like non-controlled synthetic opioids in North America[23], Coulson and Caulkins (2012) make a valid point when they note that there have been no major disasters (large numbers of deaths or serious injuries/infections on the one hand; large and violent illegal markets on the other) associated with new substances in recent years. The current system of prohibition may be too cautious but it has apparently not made many errors on the other side, allowing dangerous drugs to be legally distributed and it is hard to see that that caution has caused great harm, even if the range of pleasures has been limited.

The problem nonetheless remains potentially a serious one for developed nations. The growth of sophisticated chemical labs, legal and clandestine, in developing countries with minimal regulatory surveillance, makes the future threat look particularly troubling. The hazards are amplified by the discovery of new uses of a growing array of existing substances. The current fentanyl crisis in North America is one powerful example of how regulatory inaction contributes to harm.

There is a history of critiques of the systems applied to regulating the distribution of psychoactive substances. The most common criticism is that the results of the current system lack rationality; drugs that are very dangerous (most notably alcohol and cigarettes) are hardly regulated at all, whereas substances with fairly modest harms to individuals and societies are prohibited (Nutt 2009). The decision by UK Prime Minister Gordon Brown in 2008 to schedule cannabis as a Class B rather than a Class C substance (i.e. more strictly), before hearing from the Advisory Council on the Misuse of Drugs, only increased

[23] Opioid NPS are driven by supply-side factors, making them somewhat qualitatively different.

cynicism in Britain that the system reified social and political attitudes rather than reflected scientific analysis. Twenty years earlier, a similar decision by the DEA on keeping cannabis as Schedule I, overturning a well-documented positive finding by an administrative law judge, had generated similar cynicism in the USA.[24] Type I errors have occurred. For over thirty years, drug research advocates have mounted a campaign, even suing the DEA, to reclassify MDMA. Recently, the FDA classified the drug as a "breakthrough" therapy, fast-tracking research into its therapeutic benefits for post-traumatic stress disorder (Wan 2017).

Consider jurisdictions that have made recent legal changes criminalizing the supply of any psychoactive substance (with obvious exclusions for alcohol, tobacco and medicines) which have not been evaluated for harms or is not controlled under existing drug laws. This is arguably an example both of the precautionary principle gone awry and of the state's authoritative role to dictate what altered experiences its citizens can have. Though it removes pressures from the state to act when a new drug emerges, the approach is likely to make many classification errors.

So what considerations should the government make when regulating new substances? Many have attempted to define the inherent risk of psychoactive substances as the basis for making regulatory decisions, including prohibition (Gable 2004; Nutt et al. 2007; J. van Amsterdam et al. 2010; Taylor et al. 2012). This however is only one factor that governments need to take into account, particularly with respect to prohibition. For

[24] For the administrative law judge's decision see http://www.druglibrary.org/schaffer/library/studies/young/index.html A defense of the current scheduling can be found at Basis for the Recommendation for Maintaining Marijuana in Schedule I of the Controlled Substances Act, 20037–20076, Department of Health and Human Services, Volume 66, Number 75, Federal Register, 18 April 2001. Retrieved on 2007-04-28

example, the likely adverse consequences of creating an illegal market is one possibly important characteristic omitted from the analysis (Nutt et al. 2007). Some chemicals, which can only be acquired by diversion from large scale and sophisticated pharmaceutical production system (e.g. methaqualone) may present much less of an enforcement problem than others that can be relatively easily manufactured in small batches, occasionally with substantial environmental hazards.[25] The size of the existing user base is another factor that can affect regulatory decision-making. The DEA's reversal on scheduling kratom is perhaps the most recent example of this.

Box 3.1 provides a list of items that might be considered in making decisions about which regulatory framework applies to a new substance. A scan of that list suggests just how few of them involve information that is likely to be available at the time of regulatory decisions.

[25] Small scale manufacture of methamphetamine in the US is known to have caused considerable danger to the workers and others in their households.

Box 3.1: A summary of factors relevant to making decisions about regulation of new drugs

Use-related harms
- To individual
- To society
- Complementarity with other psychoactives (e.g., alcohol)
- Addictive potential

Size of markets
- Prevalence of parent drug
- Prevalence of mimetic

Supply
- Ready and affordable access to new substances or precursors

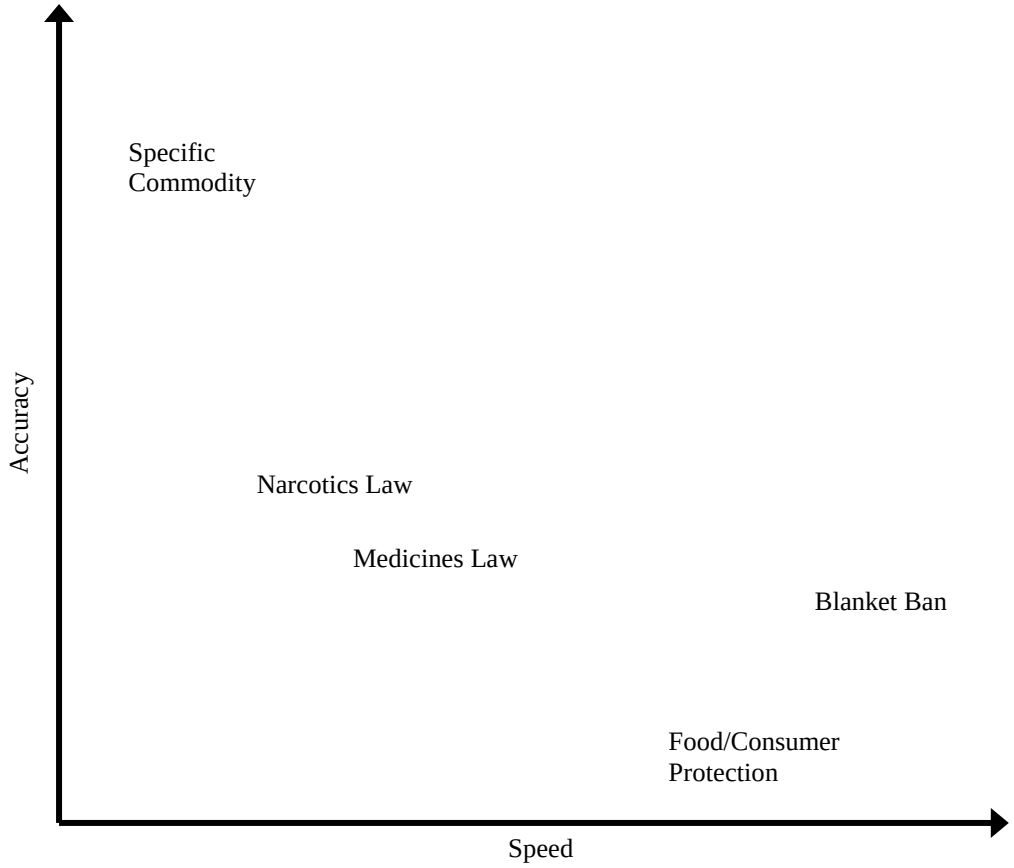
Regulatory considerations
- Costs of regulation
- Toxicovigilance
- Time required to decide

Harms and costs arising from prohibition
- Organized crime
- Criminalization of users
- Preventing potential substitution for more harmful substance
- Loss of potential for quality control/information provision

Benefits to users
- Pleasure
- Medical
- Performance enhancement

Time is another important criteria. Policymakers must recognize that any regulatory decision made in haste may be less precise, leading to Type I/II errors. At the same time, moving slowly to regulate a new substance may have lasting public health consequences (it took decades before health officials moved to appropriately regulate tobacco). Each of the aforementioned frameworks make an implicit tradeoff between speed and accuracy. I plot each below in Figure 3.3, showing more or less where they fall relative to each other.

Figure 3.3: Regulatory tradeoffs for controlling NPS



Here I conceptualize tradeoffs between speed and accuracy when determining appropriate regulatory frameworks for new substances. Blanket bans are obviously very rapid; new substances are immediately controlled by the fact that they are psychoactive. Yet, as discussed earlier, this approach sacrifices accuracy for speed. Immediate control of new psychoactives may result in Type I/II errors. Likewise, food and consumer protection laws are swift to act, but are rarely precise or appropriate for many psychoactives, particularly synthetics[26]. On the other end, specific commodity approaches are very precise, but slow or cumbersome in their design and require more nuanced enforcement. Tobacco and

[26] Some herbal psychoactive supplements of low risk, such as kava or St. John's-wort, have been regulated under this framework with minimal public concern.

alcohol have been legal for generations and society is still drafting new rules governing their supply and use. New Zealand's approach, perhaps out of sheer coincidence, takes the form of a blanket ban in part because approving low-risk products for the market is resource and time intensive. Similarly, medicines and narcotics laws are more precise, but often require time to conduct harms assessments when determining the appropriate set of controls. Even emergency or temporary controls are not initiated until after some measure of harm has been quantified (overdose deaths, emergency department episodes, calls to poison control centers, etc.).

Figure 3.3 above demonstrates the tradeoffs when thinking about regulating NPS. That said, NPS are not monolithic. The harms range considerably by type of substance; some regulatory approaches may be better suited for certain NPS than others.

3.8 Conclusion: Applying frameworks to NPS

The preceding sections amount to a conceptual framework for thinking about how to regulate NPS. It is mostly descriptive and offers little in the way of obvious policy options. Considering options for new substances, policymakers and practitioners often make much of the overwhelming number of NPS. The problem seems daunting at first, but in Sections 3.2 and 3.3 I show that NPS are not monolithic. New chemicals enter and exit the market, often without notice. Substances differ by chemical class, with synthetic cannabinoids and cathinones making up the largest portion (more than 60% of number of seizures in Europe), and differ in terms of market niches. Policymakers should keep that in mind, maintaining flexibility when approaching the phenomenon.

It is hard to imagine that incontrovertibly harmful NPS would or should be available for commerce. Even New Zealand's Psychoactive Substances Act, which had been hailed as a move away from reflexive prohibition (Chris Wilkins et al. 2013; Sumnall 2013), recognizes that substances of moderate and high risk should be prohibited. Granted the law does little in the way to define what an acceptable degree of harm is, it still recognizes different degrees of harm. To that end, all of the frameworks considered offer mechanisms to prohibit the supply of substances that pose a danger to the public.

If the principal goal is to prohibit dangerous NPS, then we first must ask, "which NPS pose the greatest threat?" The opioid class of NPS, though small in terms of numbers of new chemicals or volume sold, pose the greatest public health threat for several reasons. First, they are sold as traditional drugs, deceiving users, exposing them to new risks, and making it harder to dose. Second, the potency and pharmacodynamics of many fentanyl analogs makes these substances more dangerous than other opioids already in the market (Ciccarone 2017; Faul et al. 2017). Given the growing number of deaths related to the fentanyls (provisionally estimated at 20,000 in 2016) (CDC 2017; Daniulaityte 2017), policymakers should move quickly. In this case, a generic approach would futureproof drug laws, reducing the regulatory burden and time required to control or determine whether or not a new opioid is an analog. The downsides of generic controls have been discussed. Some of those shortcomings seem modest compared to the threat posed by new opioids. Yet, extending control over new opioids under a generic approach and criminalizing their possession could exacerbate other social harms, especially if law enforcement targets users. Further, generic controls may provide a guide to innovative chemists, encouraging them to develop new opioids that fall outside the list of generic controls. Likewise, a neurochemical

approach could be considered. Though this is complicated by the fact that various opioid substances (which interact with opioid receptors in the central nervous system) are listed under different schedules in the law, requiring extensive listing of exemptions.

That said, fentanyl analogs are cheaper than heroin and minute amounts can be shipped easily by post directly from source countries. It remains to be seen if controlling new fentanyls will have any immediate or direct effect on supply since their price and potency make them attractive substitutes for heroin dealers. Nonetheless, their control could give law enforcement additional tools to interdict product and prosecute offenders.

It seems that with new opioids the dangers are clearer. Arriving at a decision to control is easier than for drugs whose harms are less apparent. The frameworks discussed earlier offer possible alternatives for regulating some NPS. Some of these approaches require the policymaker and the general public to weigh the benefits of use of any particular substance, such as pleasure or substitution, against their harms. This is often very complicated for new drugs, but it can happen. For example, kratom's imminent scheduling by DEA was reversed by a concerted public effort that focused on the drug's benefits (pain relief, substitution, etc.). But it's hard to imagine that an unpopular drug of equal harm and benefits to kratom would have escaped prohibition under scheduling.

If there were a general consensus regarding the benefits and risks of new substances, then perhaps a framework could be adapted out of the medicines legislation that applies to NPS. Using the examples of the Investigational New Drug applications in the US and restricted access from New Zealand's now defunct Class D, a regulatory scheme could be developed that would allow limited access to substances that meet certain criteria, namely low risk

and high substitution potential. This could only occur after an NPS had established itself in the market, as was the case of BZP in New Zealand. Only then would researchers and policymakers be able to 1) gauge harm (counting overdoses, emergency room episodes, or calls to poison control centers) and 2) establish if the substance substituted for drugs of greater harm (for example, if users preferred a substance to cocaine or alcohol). If this particular substance met such criteria, then restricted access could be granted to individuals.

In Table 3.3 below I provide a logic model applying specific regulatory approaches to certain NPS, taking into account the considerations and strengths of each approach for each class of substance. I include and separate out plant-based NPS from synthetic NPS.

Table 3.3: Logic model for regulating different classes of NPS

NPS class	Substances	Driven by Market Niche	Potential regulatory approach	Considerations	Strengths
Synthetic opioids	Synthetic opioids, e.g. fentanyl analogs	Suppliers	Generic or neurochemical controls	Supply-side factors make such drugs attractive; control may have little impact on harm in market. Generic controls may encourage development of new substances whose harm could be greater. Neurochemical controls may be hard to operationalize given medical utility of opioids.	Immediately controls most or all new opioid NPS.
Cannabinoids	Spice, K2 (JWH-018, XLR11)	Those circumventing drug testing Those avoiding criminal sanction	Specific commodity regulations	Requires society to recognize benefits and risks of recreational use Complications establishing low risk Interaction with other drugs in market (substitution with cannabis?). Perhaps relaxing prohibition for natural cannabis poses less of a challenge?	Reduces average harm per dose. Avoids illicit market
			Analog and temporary listing controls	Resources are required to maintain toxicovigilance and conduct harms assessments of new chemicals.	Eliminates some drivers by removing legality.

Synthetic stimulants, tryptamines, and phenethylamines	Mephedrone, pentylone, alpha-PVP, BZP, MMDA, 5-MeO-DiPT	Those circumventing drug testing Those avoiding criminal sanction Those seeking new mind-altering experiences	Specific commodity regulations Modified medicines law	Requires society to recognize benefits and risks of recreational use Complications establishing low risk Interaction with other drugs in market (substitution or complementarity?). How to quantify substitution from more harmful psychoactive? Perhaps relaxing prohibition for existing psychoactives (e.g., MDMA, psilocybin) poses less of a challenge?	Reduces average harm per dose. Potential substitution away from more harmful psychoactives. Avoids illicit market
			Analog and temporary listing controls	Resources are required to maintain toxicovigilance and conduct harms assessments of new chemicals.	Eliminates some drivers by removing legality.
Plant-based	Kratom, khat, betel nut	Typically substitution or used as traditional medicine/cultural use.	Foodstuff and consumer regulations	Presumption of safety even if products have some risk. Continued monitoring of health impacts.	Avoids illicit market Potential substitution

Barring a significant shift in social values toward new mind-altering experiences, the NPS phenomenon will likely continue to confound policymakers and the general public. The default position is to prohibit new substances (Reuter and Pardo 2016b). It is unlikely that policymakers would allow new substances into the market for medical or recreational use in the near future. The fact that it has taken more than thirty years for US regulators to recognize the potential therapeutic benefits of MDMA and the ongoing debate over recreational use of cannabis are two clear examples of how little consideration is given to the nonmedical benefits of psychoactives outside of alcohol and nicotine. Problems of establishing low risk, as is the case in New Zealand with BZP and its moribund Psychoactive Substances Act, complicates efforts to regulate new psychoactives for non-medical use. Understanding the market niches and drivers behind NPS are instructive. Instead of thinking about how to control each NPS as they arrive, as I show in this chapter, one alternative would be to consider regulatory mechanisms for parent drugs whose harms and benefits are established or better understood by public health officials, policymakers, and the general public. As most NPS substitute for controlled substances and their use is driven by market niches that seek out drugs of similar psychoactive properties, then permitting regulated access to cannabis or ecstasy could put downward pressure on the demand for synthetic cannabinoids and some cathinones.

It is unlikely that society is willing to let individuals access cocaine or methamphetamine, but a growing number of jurisdictions recognize either medicinal or recreational benefits of cannabis and have relaxed restrictions on that drug. In the next chapter I examine the impact that access to cannabis has on synthetic cannabis use. Nonetheless, the same logic applies to other drugs besides cannabis. For example, heroin-assisted therapy is shown to

reduce use of street drugs (Strang, Groshkova, and Metrebian 2012), which is important given that fentanyl and its analogs have permeated many illicit markets in North America.

In summary, this chapter has examined in detail the NPS phenomenon, deconstructing the scope of the problem as well as the drivers motivating its demand and supply in the market. It then assessed the various regulatory options considered by jurisdictions, evaluating a few key examples. Finally, the chapter underlined the considerations and tradeoffs that policymakers ought to think about when weighing responses. This chapter should provide insight and rationale when approaching the NPS phenomenon by deconstructing and demystifying it.

4 Access to cannabis and its relationship with synthetic cannabis receptor agonists

4.1 Introduction

In the last decade, the United States has witnessed several important developments related to cannabis policy, such as the passage of state medical and recreational cannabis laws as well as the establishment of physical storefronts, known as dispensaries. At the same time, many markets have seen the introduction of new substances that mimic the effects of tetrahydrocannabinol (THC), the principal psychoactive agent in cannabis. Starting in the 1990s, states sought to liberalize access to cannabis for medical purposes. These state-level policies unfolded unevenly across the United States. The recent introduction of synthetic cannabinoid receptor agonists (SCRA) into the US drug market is a possible response to the demand for cannabis by particular market niches not affected by the loosening of state-cannabis laws (minors, populations subjected to regular drug screens, etc.) (Reuter and Pardo 2016a).

Cannabis and SCRA are likely substitutes. Both interact with CB1 and CB2 receptors in the body, producing similar effects (Gurney et al. 2014). That said, additional factors may relate with the use of either substance. Price and availability of either drug may encourage certain users to use SCRA. Many SCRA are relatively cheap compared with natural cannabis, and given their legal status as uncontrolled analogs, they are often more accessible (Barratt, Cakic, and Lenton 2013; Sweeney et al. 2016). Here I attempt to evaluate how policies that shape one drug market may impact the use of mimetic drugs.

4.1.1 State cannabis policy reforms

In the United States, medical cannabis started in 1996 when California voters passed a referendum (Proposition 215), allowing individuals suffering from terminal illness to use herbal cannabis (Mead 1998). Reforms at the state level continued in the waning years of the 20th century, with a handful of states passing laws to allow doctors to recommend medical cannabis or allow for a legal defense for individual use of medical cannabis. The permission for use of products derived from the cannabis flower has now spread to 29 states, the District of Columbia, and Puerto Rico. Another 16 states allow limited access to low-THC/high-CBD products (National Conference of State Legislatures 2016).

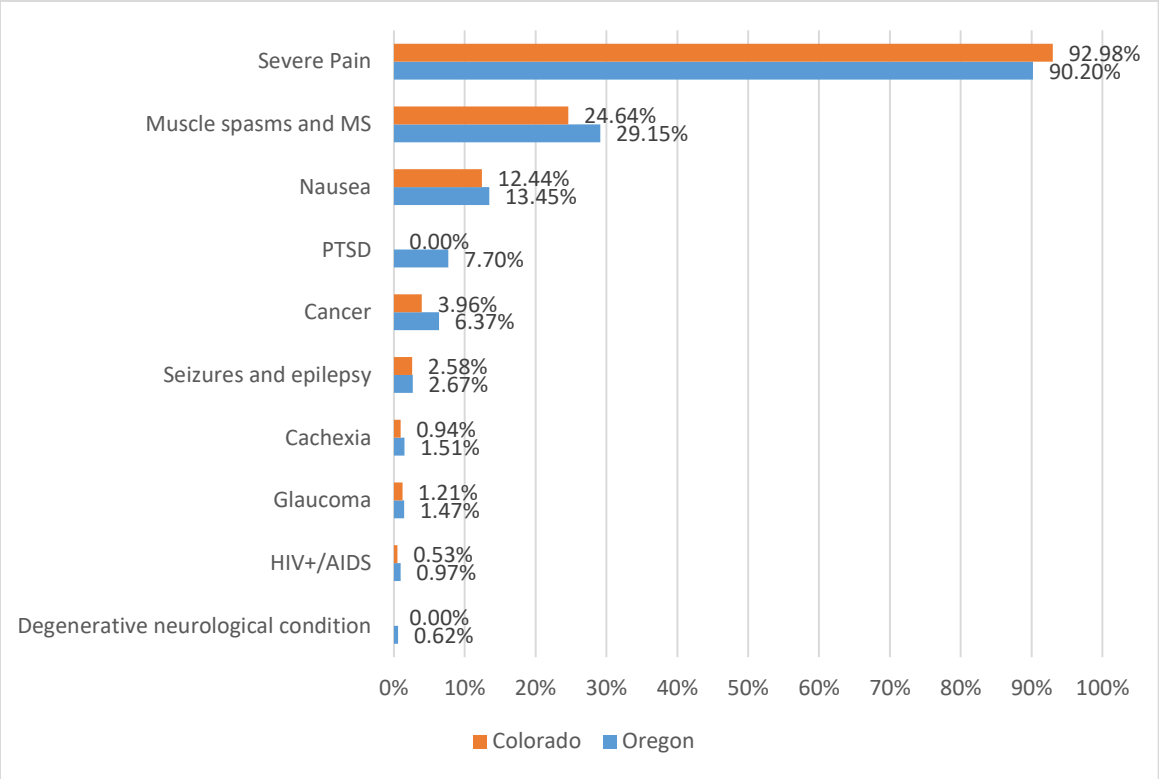
State medical cannabis laws and policies vary greatly in terms of regulations governing supply and use. Some are more restrictive than others, limiting access to individuals suffering from certain illnesses or establishing strict limits on the production and distribution of the substance to at-home cultivation by patients and caregivers. In the most permissive regimes, states include pain as a qualifying condition and/or legally protect and regulate the operation of dispensaries. In some of these states, patients with a recommendation can access a wide array of cannabis and cannabis-derived products. Some dispensaries openly advertise their wares and services to patients at point of sale, with others promoting their business to the general public (Rosalie Liccardo Pacula et al. 2013).

Loosely regulated medical cannabis allows any individual to obtain cannabis with a simple doctor's recommendation. Several states impose limits as to what ailments qualify, but some allow for hard to diagnose conditions such as chronic pain. For example, one study that surveyed over 4,000 potential medical cannabis patients in California found that the typical individual was a white male in his early 30s, who started using cannabis in his teens

and reported few disabilities (O'Connell and Bou-Matar 2007). This hardly sounds like someone with a terminal condition.

Of the 30 jurisdictions in the US that allow for medical cannabis, several allow doctors to recommend for any illness for which the drug can provide relief. Several of these states, including California and Washington, have not maintained patient registries, making it difficult to evaluate who uses medical cannabis and for what purposes. However, data from Oregon and Colorado, two states with robust medical cannabis markets, show the majority of patients report using the drug to treat pain, which cannot be independently confirmed (see Figure 4.1 below). This is not to discredit the use of the drug to treat pain, but rather to infer that a substantial portion of individuals seeking access to the drug for recreational purposes do so through the medical system.

Figure 4.1: Qualifying ailments for medical marijuana in Colorado and Oregon, July 2016



Note that patients may report multiple qualifying ailments

When it comes to distribution of medical cannabis, some states, such as New York, restrict the sale of the drug to non-smokable forms. Others require patients to register with the state and designate a single supplier, such as Minnesota or DC. Even within states, regulations may vary. Some states allow for local bans and municipal ordinances that may regulate additional aspects of supply of cannabis. Research has suggested details matter when it comes to studying medical cannabis laws and such policies should not be viewed in monochromatic terms, with findings showing that dispensaries have strong associations with outcomes (Powell, Pacula, and Jacobson 2015; Rosalie Liccardo Pacula et al. 2013; Rosalie L. Pacula et al. 2015). In this case, the existence of physical establishments that promote their product should not be viewed in similar terms to states that allow individuals to grow a small amount of the drug at home for personal consumption.

4.1.2 Synthetic cannabinoid receptor agonists

Synthetic cannabinoid receptor agonists (SCRA), also known as cannabimimetics or synthetic cannabis, are synthetic chemicals designed to mimic the psychoactive effects of THC by interacting with cannabinoid receptors in the brain. Since 2004, these products have commonly been sold as legal alternatives to cannabis under brand names such as "K2" or "spice" (Hoyte et al. 2012). However, these substances are part of a continually evolving family of chemicals. Once one is controlled, manufacturers alter their chemical compound to circumvent existing drug controls (Reuter and Pardo 2016a; Gurney et al. 2014). New SCRA are constantly emerging, and in terms of prevalence and seizures, make up a significant portion of the new psychoactive substances (NPS) market (EMCDDA 2016a).

However, unlike THC which is found naturally in cannabis or synthesized for pharmaceutical purposes like marinol, little is known about the harms of most SCRAs. A chemical's binding affinity to cannabinoid receptors in the brain can be many times stronger than THC (Gurney et al. 2014; Wiley et al. 2014). Review articles have documented numerous adverse, and sometimes life-threatening, effects from SCRA use. Though little is known about many of these new chemicals, including any published *in vivo* testing in animals (Lindigkeit et al. 2009), the acute health harms to the user posed by SCRA are much more serious than those from THC.

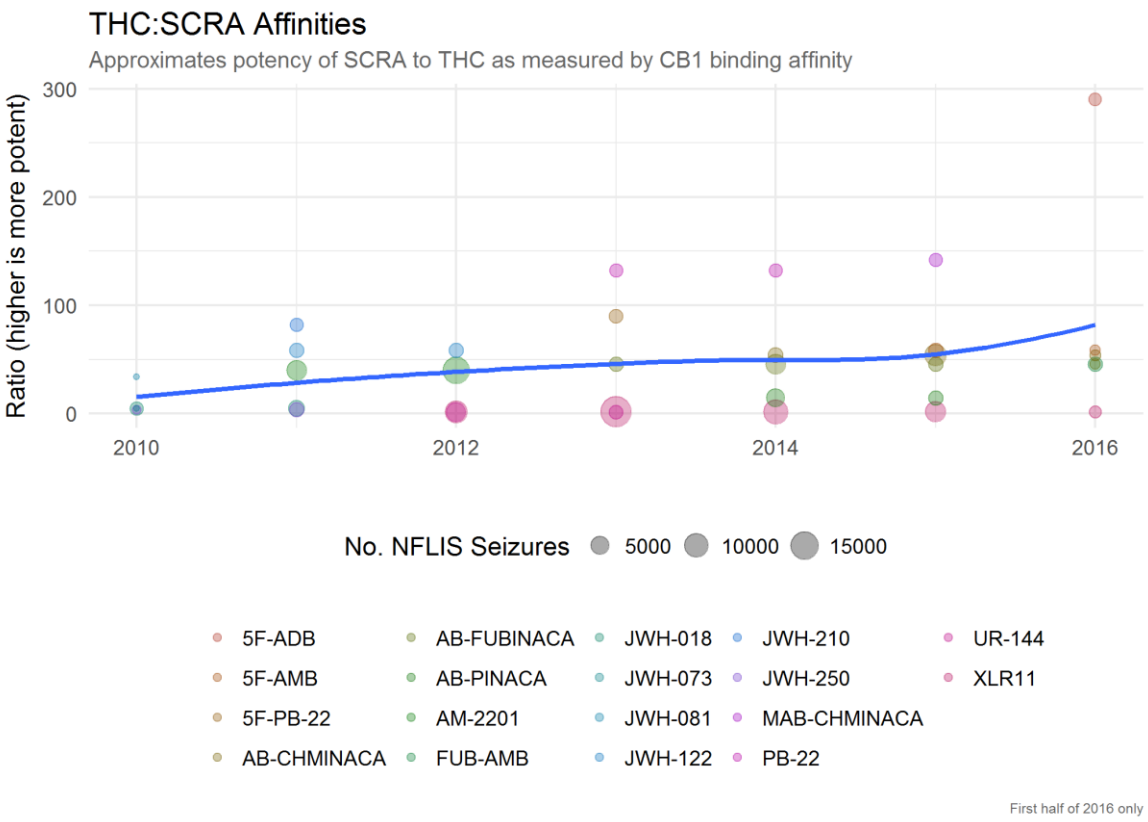
To complicate matters, the traditional pattern of control seems to have increased harm. Once brought to the attention of authorities, the substance is often controlled under emergency administrative powers, resulting in its prohibition. This encourages the development of new substances, sometimes in a matter of weeks (Lindigkeit et al. 2009).

This continued cat and mouse game appears to have contributed to the growing number of new substances (Reuter and Pardo 2016a). Moreover, newer SCRA are often more potent than those of previous generations (Home Office 2014).

Figure 4.2 plots the change of SCRA in the market over time, supporting what the UK Home Office reports regarding increasing potency over time. Using seizure data reported by US authorities and toxicology literature on SCRA potency, Figure 4.2 shows the increasing potency of new chemicals. I calculated the ratio of binding affinity to CB1 receptors of THC to SCRA for the most popular SCRA in a market in a given year[27]. This ratio is an approximate measure of each new chemical's potency. Since 2010, average SCRA potency in the market place has increased sevenfold.

[27] Only SCRA with 5% or more market share, as measured by number of seizures to the National Forensic Laboratory Information System (NFLIS).

Figure 4.2: THC to SCRA Affinities



4.1.3 Literature review

The literature on medical cannabis laws has started to assess population-level impacts. Several studies examine the relationship between cannabis laws and other substances. Some research suggests liberalized cannabis laws may shape consumption of other psychoactives (Rosalie L. Pacula et al. 2015; J. Caulkins et al. 2015; Mark Anderson, Hansen, and Rees 2013; Rosalie L. Pacula et al. 2015; Hayes and Brown 2014; Bachhuber et al. 2014). Some studies suggest cannabis may be a substitute for other drugs sought out for pleasure or pain relief (e.g. alcohol or prescription opioids). The literature has started

to tease out the differences in state medical cannabis laws. From studies, it appears that the physical presence of dispensaries, which engage in advertising and product promotion, have the greatest association with reductions in consumption of alcohol and prescription opioids in certain populations (Powell, Pacula, and Jacobson 2015; Mark Anderson, Hansen, and Rees 2013).

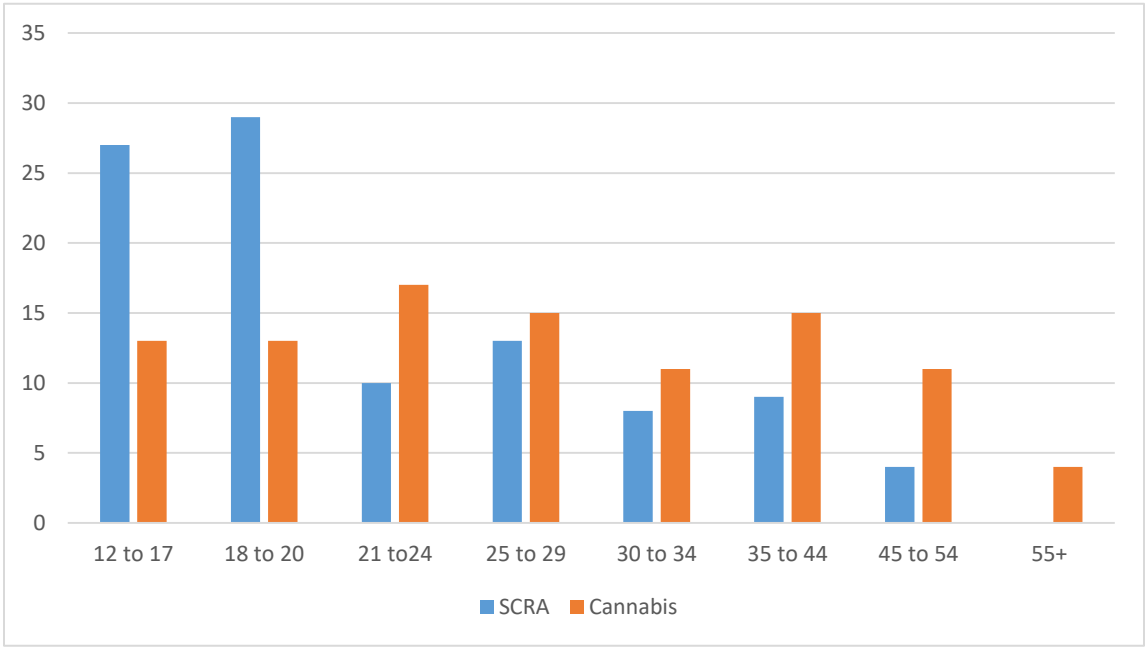
To date, the literature on SCRA has been limited to studying the pharmacology, pharmacokinetics, chemical design, and health effects of these new substances (Gurney et al. 2014; King 2014a; Gunderson et al. 2014). Some studies analyze user demographics (Hoyte et al. 2012). Some qualitative research has focused on the motivations for SCRA use (Sutherland et al. 2017), while others have examined SCRA exposures and health outcomes (Cairns et al. 2017; Waugh et al. 2016). A recent study of new psychoactives purchased from online retailers in Europe reported that SCRA were largely absent from online retailers or in Dutch drug user surveys (Brunt et al. 2017). Authors suggest that access to good quality herbal cannabis via coffeeshops may reduce the demand for non-controlled substitutes.

One substantial impediment to studying SCRA is the fact that new chemicals enter and exit the market very quickly. Given this, few reliable data exist for measuring SCRA-related trends. For example, the International Statistical Classification of Diseases and Related Health Problems (ICD) has yet to include synthetic cannabis exposure in its codebook, leaving few standardized options for emergency room physicians or coroners to properly code exposures, overdoses or deaths.

The Substance Abuse and Mental Health Services Administration (SAMHSA) maintained the Drug Abuse Warning Network (DAWN), which monitored emergency department

episodes for drug use. DAWN was discontinued in 2011, but reported estimates of emergency department visits for SCRA for 2010 and 2011. Data from DAWN come from several participating emergency departments in metropolitan areas in the US. In this case, DAWN used its own catchment areas and methodology to determine SCRA-involved emergency department episodes. Nonetheless, in one DAWN report, 60% of emergency department episodes for SCRA are from individuals under 21 (Bush and Woodwell 2013). Figure 4.3 suggests SCRA use is more prevalent in adolescents, as reported by the proportions of SCRA visits to emergency rooms. One possible explanation is that access to cannabis, even in states that allow the drug to be used medicinally or recreationally, is often more restrictive for those under 18 or 21.

Figure 4.3: Age distribution of synthetic cannabinoid and cannabis-related emergency department (%) visits: 2011; DAWN



That said, the literature has been helpful in assessing the pharmacology of SCRA. Of the known SCRAs, the binding affinity to CB1 receptors can range between 0.02 to 700 times

stronger than THC (Debruyne and Le Boisselier 2015; Gurney et al. 2014). Unlike THC, which is a partial agonist, many SCRA are full agonists, meaning they elicit a maximal response when binding to the receptor (Gurney et al. 2014; Obafemi et al. 2015). In their review, Gurney et al. measure the ratio of CB2 to CB1 affinity as a potential indicator of recreational use. The authors found high ratios in many of the analyzed SCRA, indicating these substances are attractive to users who desire THC-like intoxication.

Though the intended goal of SCRA use is THC-like intoxication, these substances impact users differently than cannabis. Review articles on SCRA suggest these substances are causally linked to adverse effects and reactions, including severe agitation, anxiety, nausea, vomiting, tachycardia, elevated blood pressure, tremors, seizures, hallucinations, paranoia, and even death (Debruyne and Le Boisselier 2015; Bush and Woodwell 2013; Cairns et al. 2017; Waugh et al. 2016).

However, the literature to date on cannabis-SCRA substitution is practically nonexistent. Reuter and Pardo (2016) hypothesize that a portion of NPS users use these drugs to circumvent existing drug prohibitions, yet desire similar mind-altering experiences. Qualitative research has pointed out a substitution effect for certain NPS and parent drugs, like stimulants or other entactogens (K. Moore Dargan, Paul I., Wood, and Measham 2013; Reuter and Pardo 2016a). Others have specifically examined the relationship drug testing has on certain populations and found that those subjected to regular drug testing sought out SCRA to avoid detection of cannabis use (Perrone, Helgesen, and Fischer 2013). One empirical analysis of individuals under judicial supervision (parolees, probationers, etc.) found elevated rates of SCRA in urinalysis results, supporting the hypothesis that SCRA are used to avoid cannabis detection (CESAR 2013). In addition, more than half of

individuals visiting the emergency department in 2011 for SCRA did not test positive for cannabis (CESAR 2013). Media reports suggest SCRA use is high among homeless populations, which are often subjected to judicial supervision and drug testing (Karlamangla 2016; Rosenberg and Schweber 2016; Casey 2015). A survey in Australia reported users were motivated to use SCRAs because of their legality and availability, rather than their novelty or effects (Sutherland et al. 2017). However, the relationship between cannabis and SCRA in the market has not been tested empirically.

Here I examine the association between SCRA use and state policies that permit access to cannabis for medical or recreational purposes. The hypothesis is that states with liberal cannabis policies, as defined by allowing medical dispensaries or higher concentrations of medical cannabis patient counts, have, on average, lower rates of SCRA use, as measured by calls to poison control centers.

4.2 Data and Methodology

As mentioned earlier, ICD-10 codes do not include SCRA poisonings. Therefore, I cannot use emergency department episodes or overdose deaths, as they are improperly coded. Given the novelty of many of these substances, the only sentry data available come from poison control centers. State and regional poison control centers report call episodes to the National Poison Data System (formerly the Toxic Exposure Surveillance System) which is maintained by the American Association of Poison Control Centers (AAPCC).

Poison centers cover the entire US population, reporting in almost real-time the nature and chemical of exposure. There are 55 centers throughout the United States and its territories, staffed by specialists trained in toxicology to receive spontaneous calls from caregivers,

patients, intimates, and health care providers regarding potentially dangerous exposures to a variety of poisons (Dasgupta et al. 2012; Mowry et al. 2016). According to the latest annual report from the AAPCC, poison control centers logged more than 2.1 million human chemical exposures in 2015. Approximately 68.5% of all calls originated from residential sites (own or other), and 22.2% originated from a health care facility (Mowry et al. 2016). These were similar figures from the previous year's report (Mowry et al. 2015).

The use of poison control center calls as an early warning system is well documented in the literature. Toxicovigilance is paramount to identifying and investigating exposure to new toxins, including new psychoactive substances such as SCRA. In fact, exposure incidents from the National Poison Data System have been used to assess, in almost real time, public health threats posed by chemical weapons, toxic chemicals, and prescription drug misuse (J. M. Davis et al. 2014; Dasgupta et al. 2012; Thundiyil, Kearney, and Olson 2007; Watson et al. 2005). Davis et al. (2014) have discussed the importance that poison control data play for sentinel reporting on prescription drug exposure. In that study, authors found National Poison Data System (NPDS) data are highly correlated with other confirmatory data, including emergency department data such as DAWN (J. M. Davis et al. 2014). A similar study found that calls to poison control centers for methadone are correlated with poisoning mortality rates reported on death certificates, and that call data may be useful for timely surveillance of such outcomes (Dasgupta et al. 2012).

The use of poison control center data to measure SCRA is not new. Some researchers have evaluated the impact of legal SCRA prohibitions on calls to poison control centers, suggesting quick bans and media campaigns may be effective at reducing SCRA exposures

(Cairns et al. 2017). Others have evaluated user characteristics and adverse reactions within a population (Vandrey et al. 2012; Hoyte et al. 2012; Waugh et al. 2016).

4.2.1 Dependent Variable

Since 2010, the AAPCC has collected incident reports any time an individual (or healthcare professional) calls a poison control center due to a suspected SCRA exposure. From AAPCC I obtained aggregate state-level exposure counts for 2015 and 2016, or 102 observations. This allows me to conduct an exploratory study of the data in the hopes of acquiring funds to purchase additional years of exposure calls. Adding additional years of observations accomplishes two things. First, it allows me to include additional years of medical cannabis policy and market variation. Adding states as far back as 2011 will allow me to measure some of the changes of cannabis policy as several states in this series only recently opened operational dispensaries. Second, it improves the measure of my outcome variable, calls to poison control centers. As shown in Figure 4.2, SCRA vary considerably from year to year. Inclusion of additional years of data will help identify some of these harms given that average potency of SCRA seizures has increased in recent years. Nevertheless, I created panel data to control for state-level idiosyncratic and time-dependent effects for these two years with the notion of expanding this analysis once more data are obtained. State-aggregate exposure counts are logged-normalized. No state-years reported less than a single call; the median was 38 calls.

4.2.2 Independent Variables

State-level cannabis policies are tracked by various sources, including the Prescription Drug Abuse Policy System, which has a medical marijuana portal. Others include the

National Alliance on Model State Drug Laws (NAMSDL), the Alcohol Policy Information System (which also has a cannabis law portal), and the National Conference of State Legislatures. I am interested in the effect that access to medical cannabis has on our dependent variable of calls to poison control centers for SCRA exposure. In this case, I determine whether or not a state has an operating medical cannabis dispensary in a given year. This is a binary variable, and mostly time invariant for the two years of observations.

In addition to the above binary variable indicating an operational dispensary, I also collected patient registry counts for states that maintain statewide medical cannabis patient registries from 2010 to 2016. Using similar sources reported by Smart (2015), including scouring state registry websites and annual reports, I was able to obtain or calculate average annual count of medical cannabis patients for twenty states. Calculating an annual average of registered patients reduces bias that may be introduced by taking year-end counts. California and Washington never maintained statewide registries and Maine's was voluntary until 2016. Patient registry counts were log-normalized[28] and are included in a sensitivity analysis where I substitute patient counts, which vary across states, for operational dispensaries.

Medical cannabis regulations vary considerably, and thus patient counts may serve as a more precise measure of access to cannabis. For example, though a populous state like New York has a medical cannabis law and operational dispensaries, it does not include pain as a qualifying illness. In 2016, the number of patients in that state came to just over

[28] I added 1 to state-years with 0 patient counts to prevent loss of data prior to log-normalization.

7,000. Thus, patient registry counts may better approximate medical cannabis access in a given state and year than binary dispensary indicators.

One alternative method of measuring medical cannabis saturation would be to try to triangulate medical cannabis patient counts with past-month cannabis prevalence rates at the state level. Unfortunately, the National Survey on Drug Use and Health reports statewide prevalence rates with a two year lag and are unavailable for 2015-2016. Future analyses stemming from this paper could use statewide past-month prevalence rates to instrument for patient counts. This would provide some rough approximation for states that do not report patient counts (e.g., California and Washington). This assumes, however, that respondents are accurately reporting their cannabis use. Underreporting aside, some individuals may be reporting SCRA use for cannabis use or they may be concurrently using both substances. Such reporting inaccuracies may bias the utility of using statewide past-month prevalence as a substituting or instrumental variable for registration counts.

The proliferation of SCRA makes this issue particularly challenging not only for regulators, but for researchers. DEA's National Forensic Laboratory Information System (NFLIS) systematically collects results from drug chemistry analyses from participating laboratories across the country. As of 2016, 278 labs from 47 states report their results to NFLIS. I used these results to determine the type, number, and proportion of SCRA that existed in the national market in a given year (NFLIS 2015, 2013, 2010).

NAMSDL publishes information on state laws controlling SCRA. Here I determine when a particular SCRA was controlled by state and year from 2011 to 2016. I use a cutoff of five or more months to determine when a state controls a particular SCRA. Data from NFLIS and NAMSDL allow me to construct state-year variables to measure the level of

control of popular SCRA. This is a weighted average of the number of popular SCRA controlled by a state in a given year. I use NFLIS data to construct the weight of popular SCRA in the national market, as reported in Table 4.1.

Data on other possible confounders, such as population of those aged 12-24, homelessness, and unemployment are obtained from the CDC, Census Bureau, Department of Housing and Urban Development, and the Department of Labor. I chose the range of 12-24 years for two reasons. First, this is an age range when drug experimentation is at its height. As Monitoring the Future reports in recent survey years, use of SCRA is highest for high school seniors (L. Johnson et al. 2017). Figure 4.3 also suggests that SCRA exposures are greater for those under 21. Second, access to medical cannabis is generally more restrictive for minors under the age of 18 (and completely prohibited for those under 21 in the case of the nine jurisdictions where recreational cannabis is permitted).

4.2.3 Analytical approach

Given the lack of a longer time series in this constructed panel data set, I have settled on a standard difference-in-difference approach. Initially, I considered a synthetic control approach utilized elsewhere (Abadie and Gardeazabal 2003). However, lack of sufficient pre-treatment outcomes prevents me from utilizing this method to create appropriate controls. For this preliminary analysis, I use standard econometric approaches, adapting from other recent methods to consider the small sample size.

I log-transformed the dependent variable of SCRA exposure calls to normalize the distribution and aid with interpretation. The temporal nature of the data allow me to control for year-to-year variability in the market. Further, cluster-robust standard errors can be

biased in small sample sizes (Pustejovsky and Tipton 2016; Gelman et al. 2005; Bafumi and Gelman 2007). In order to overcome problems of bias in hypothesis testing due to small sample issues, I employ a bias-reduced linearization (BRL) approach proposed by McCaffrey and Bell (2003) and reproduced by Pustejovsky and Tipton (2016). Their degrees-of-freedom correction uses Satterthwaite approximation to reduce Type I errors.

Reported below are a series of regressions, with covariates added in each step. First, I run a simple pooled model with just a binary medical cannabis dispensary variable on the right hand side. This simple model is as follows:

$$\ln(calls_{it}) = \beta_1 mmd_{it} + \epsilon_{it}$$

Next, I add additional demographic covariates, which may impact rates of SCRA use. Here I specify a vector of state-level covariates X_{it}. This includes state-level values for log of homeless population, percentage of the state aged 12-24, log of population, and unemployment rate.

$$\ln(calls_{it}) = \beta_1 mmd_{it} + \beta_2 X_{it} + \epsilon_{it}$$

Finally, I add additional vector of SCRA-specific controls, Z_{it}, which includes the weighted variable of SCRA control laws.

$$\ln(calls_{it}) = \beta_1 mmd_{it} + \beta_2 X_{it} + \beta_3 Z_{it} + \epsilon_{it}$$

Given the time-invariant nature of our binary explanatory predictor, I use a random effects approach to assess the between variation among states over time, while clustering within each state to correct for heteroscedasticity and serial correlation (McCaffrey and Bell 2003; Arellano 1993). Under random effects, the assumption that the unobserved state-level

effects are uncorrelated with our regressors must hold, otherwise estimated coefficients are biased. I conduct a post-estimation artificial Hausman Test described by Pustejovsky and Tipton (2016) to determine if the unobserved effects are correlated with regressors.

The random effects model is as follows:

$$\ln(calls_{it}) = \beta_1 mmd_{it} + \beta_2 X_{it} + \beta_3 Z_{it} + \delta T_t + \alpha_i + \epsilon_{it}$$

The model includes a primary predictor, mmd_{it}, which is a binary variable indicating if a state has an operational medical marijuana dispensary in time period *t*. I also specify a vector of state-level covariates X_{it} (log of homeless population, log of population, percentage of population aged 12-24, and unemployment rate), Z_{it}, a vector of the weighted variable measuring the number and type of SCRA laws in place in each state, and T_t to account for year-specific effects. Individual-specific variation is captured by α_i. The error term, ϵ_{it}, contains idiosyncratic errors that are tested post-estimation for endogeneity.

In order to test for endogeneity, I include group time-demeaned covariates as additional regressors. In this case, $\overline{mmd}_{it} = mmd_{it} - \frac{1}{T}\sum_t mmd_{it}$, $\bar{X}_{it} = X_{it} - \frac{1}{T}\sum_t X_{it}$ for all other demographic covariates, and $\bar{Z}_{it} = Z_{it} - \frac{1}{T}\sum_t Z_{it}$ for our SCRA control variable. Estimating the following model allows me to conduct an artificial Hausman Test post estimation:

$$\ln(calls_{it}) = \beta_1 mmd_{it} + \gamma_1 \overline{mmd}_{it} + \beta_2 X_{it} + \gamma_2 \bar{X}_{it} + \beta_3 Z_{it} + \gamma_3 \bar{Z}_{it} + \delta T_t + \alpha_i + \epsilon_{it}$$

Here, the βs capture the between estimator and the γs capture the differences between the within-groups and between-group coefficients of our explanatory variables. Adding these coefficients gives me the within estimator as reported by a fixed-effects approach. Per

Pustejovsky and Tipton (2016), if the γs are zero, then the random effects estimator is unbiased. Employing their method, I can test if $H_0: \gamma_1 = \gamma_2 = \gamma_3 = 0$ by using an F-test and the BRL-adjusted clustered-robust standard errors.

Because the explanatory binary variable of operating medical cannabis dispensaries does not vary over time, with a few exceptions where states opened stores in the second year of the series, I also conduct a sensitivity analysis by replacing the binary regressor with the log of registered patients. Several states in the data set allow for patients to obtain medical cannabis without operational dispensaries. In some instances, these markets allow individuals to grow at home. These include states with longstanding medical marijuana markets, including Alaska and Hawaii, which have yet or only recently opened regulated dispensaries. Other states with operational dispensaries may be quite limited in terms of qualifying illness. In these cases, patient counts may be more accurate. I removed California, Washington, and Maine because they do not require patients to register or report no patient counts.

Given the count nature of the outcome variable of interest, I also specified a Poisson regression for comparison alongside the above models. This last specification is just one additional robustness check.

4.3 *Results*

4.3.1 Descriptive results

For the two years in the panel, there was an average of 102 (sd = 230) SCRA calls, ranging from 1 to 1,729. After log-normalization, I report an average of 3.51 (sd = 1.56) with a minimum of 0 and a maximum of 7.46. Figure 4.4 displays the log of SCRA calls per

100,000 inhabitants. I note the concentration of exposures are highest in the south and Appalachia, though New York and Minnesota also stand out. This last point is interesting as both states restrict patients to non-smokable forms of medical cannabis (National Conference of State Legislatures 2016).

Table 4.1 reports the most popular SCRA (as measured by the number of NFLIS submissions in a given year). Assuming NFLIS data are representative, then the SCRA market is dominated by a handful of chemicals in a given year, even though almost 170 different SCRA are known to exist to date (EMCDDA 2017b). NFLIS data also suggest shifts in popular SCRA from year to year. For example, in 2010 JWH-018 was frequently reported, by 2012 this chemical made up fewer than 5% of reports. Likewise, XLR11, which accounted for 60% of laboratory reports in 2013 dwindled year-over-year to just 11% by 2016.

Table 4.1: SCRA Reports, percentage of total reports by year reported to NFLIS

	2010		2011		2012		2013		2014		2015		2016	
1	JWH-018	64%	AM-2201	28%	AM-2201	33%	XLR11	60%	XLR11	33%	AB-CHMINACA	26%	FUB-AMB	19%
2	JWH-250	14%	JWH-018	16%	XLR11	21%	AB-FUBINACA	8%	AB-FUBINACA	19%	XLR11	24%	5F-ADB	13%
3	JWH-073	8%	JWH-122	11%	UR-144	14%	UR-144	7%	AB-PINACA	15%	AB-PINACA	8%	XLR11	11%
4	JWH-081	5%	JWH-250	11%	JWH-122	6%	5F-PB-22	6%	AB-CHMINACA	8%	AB-FUBINACA	8%	AB-CHMINACA	7%
5	Other SCRA	9%	JWH-210	8%	Other SCRA	26%	PB-22	6%	PB-22	6%	5F-AMB	8%	5F-AMB	6%
6			Other SCRA	26%			Other SCRA	13%	Other SCRA	19%	MAB-CHMINACA	6%	Other SCRA	44%
7											Other SCRA	20%		

Figure 4.4: Rates of Synthetic Cannabinoid Exposure Calls by State

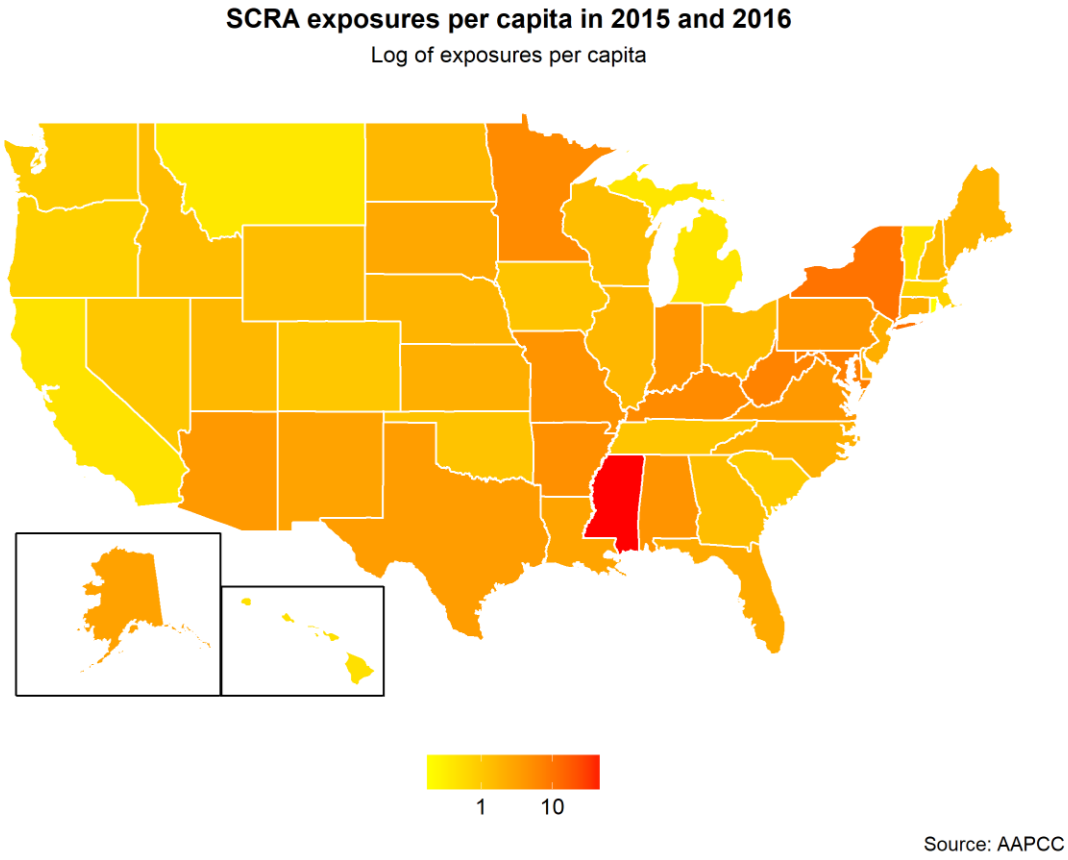
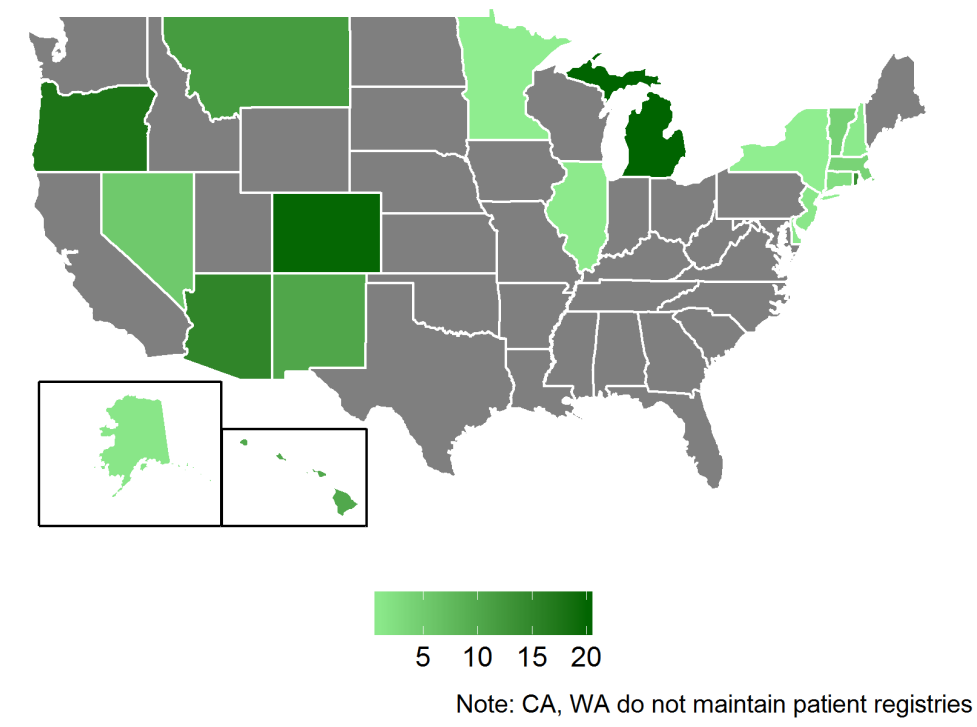


Table 4.2 provides descriptive statistics for states with and without operational dispensaries. The far-right column includes correlation coefficients for each variable and the calls to poison control centers for SCRA exposure for all observations. There is modest and positive correlation for some of the variables considered, including log of homeless population. The correlation coefficient for log of registered medical cannabis patients is negative. Figure 4.5 reports the average annual number of registered medical cannabis patients for 2015 and 2016. Registration rates are highest in Michigan, Colorado, and Oregon. I omit California, Maine, and Washington which do not maintain mandatory patient registries.

Table 4.2: Descriptive statistics for states with and without operational dispensaries

	No dispensary n = 63		Dispensary n = 39		Correlation with rate of SCRA calls to poison control (all observations)
	mean	sd	mean	sd	
Log of SCRA calls	3.830	1.509	2.999	1.510	0.619
Log of population	15.215	0.982	15.058	1.123	0.349
Percentage of population aged 12-24	17.607	1.038	17.052	0.733	0.028
Log of homeless population	8.365	0.918	8.524	1.143	0.366
Unemployment	4.748	1.048	5.026	1.051	0.177
SCRA control laws	0.331	0.244	0.180	0.217	0.150
Ordinal score of SCRA reports to NFLIS	2.603	1.314	1.564	1.209	0.161
Log of registered MMJ patients	0.645	2.243	8.558	3.295	-0.199

Figure 4.5: Registered medical marijuana patients per 1000



4.3.2 Regression results

The full regression results for models considered are reported below. All inferences are calculated with cluster-robust standard errors as described by Pustejovsky and Tipton (2016). I omit coefficients for yearly controls to save output space. In Model I, the sign on the binary variable for medical cannabis dispensaries is negative, as expected. Model II is the second model statement above, the pooled effects model with demographic controls, but no time controls. In Model III, I control for SCRA-specific laws in addition to demographic factors. Model IV is a two-way fixed effects model for comparison.

Models VI and VIII include a random effects estimator to allow states to have their own intercept as well as time fixed effects. Models VII and IX include estimates for the de-meaned covariates, γ_i, which capture the differences between the within-groups and between-group coefficients. In this model specification, β_i captures the between estimator. Adding β_i to its corresponding γ_i gives us the within estimator as expected under fixed effects approach.

Models V, VIII, and IX are the sensitivity analyses where I replace the binary variable indicating operational medical cannabis dispensary with log of registered medical cannabis patients after removing California, Maine, and Washington.

Results of the artificial Hausman Test elaborated by Pustejovsky and Tipton (2016) are reported in the last row of Table 4.4. Results show that I fail to reject the null hypothesis that the coefficients of the de-meaned regressors are equal to zero, suggesting unobserved idiosyncratic errors are uncorrelated with our explanatory variables. Given the count nature

of calls to poison control centers, I report the estimates from two Poisson regressions in Models X and XI.

Again, these findings are preliminary given I only have two years of observations. I am hesitant to read too much into these results, though early findings support my initial hypothesis. In all models considered, operational dispensaries and registered patient count are negatively (and in some specifications significantly) associated with fewer SCRA exposure calls to poison control centers. The random effects models (Models VI and VIII), which estimate a weighted average of the within-group and between-group regressions, report a statistically significant and negative relationship with access to cannabis and SCRA calls to poison control centers. Results in Model VI show that operational medical cannabis dispensaries are associated with 45% fewer calls to poison control centers. Model VIII, which includes patient counts instead of the binary dispensary variable, reports that a 10% increase in the number of registered patients is associated with approximately 1% fewer SCRA poison control center calls.

In order to help with interpretation, I calculated the average patient growth rate for states that registered patients between 2015 and 2016. According to my calculation in this data set of two time periods, patient counts grew, on average, by about 78%. In other words, between 2015 and 2016 the number of calls to poison control centers decreased, on average, by about 7.3% for states that have medical cannabis registries, after controlling for potential confounders.

Poisson model specifications report similar magnitude of effects, though the coefficient for operational medical cannabis dispensary is non-significant ($p = 0.21$) in Model X. The coefficient for log of registered patients in Model XI is significant and the same in effect

size as that reported in Model VIII. A 10% increase in patient counts is associated with about 1% fewer SCRA calls to poison control centers.

Table 4.3: Regression results, SCRA exposure calls to poison control centers

Regressors	Model I	Model II	Model III	Model IV	Model V	Model VI	Model VII	Model VIII†	Model IX†	Model X	Model XI†
Operational dispensary	-0.830** (0.390)	-0.866*** (0.292)	-0.746** (0.294)	-0.132 (0.463)		-0.606** (0.259)	-0.791** (0.322)			-0.619 (0.433)	
Log of MMJ patients					-0.064 (0.063)			-0.093*** (0.026)	-0.102*** (0.030)		-0.093** (0.029)
Log of population		0.735 (0.419)	0.715 (0.433)	12.241 (14.044)	9.487 (14.578)	0.843 (0.484)	0.769 (0.474)	0.712 (0.391)	0.654* (0.354)	31.117 (19.933)	28.288 (19.256)
Percentage aged 12-24		-0.022 (0.115)	-0.033 (0.119)	1.262 (1.099)	1.315 (1.153)	-0.063 (0.112)	-0.070 (0.125)	-0.028 (0.100)	-0.013 (0.102)	1.280 (1.304)	1.630 (1.464)
Log of homeless population		0.305 (0.430)	0.299 (0.442)	0.779 (1.215)	1.003 (1.268)	0.215 (0.491)	0.252 (0.481)	0.437 (0.401)	0.463 (0.367)	2.176 (2.497)	2.900 (2.642)
Unemployment rate		0.323** (0.151)	0.336** (0.147)	-0.181 (0.256)	-0.203 (0.263)	0.181 (0.140)	0.307* (0.155)	0.238* (0.129)	0.364*** (0.133)	0.044 (0.213)	0.031 (0.216)
State SCRA law index			0.879 (0.535)	0.084 (0.635)	-0.085 (0.650)	0.457 (0.476)	0.606 (0.641)	0.305 (0.473)	0.397 (0.590)	-1.110 (0.674)	-1.263 (0.715)
γ_1Operational dispensary							0.659 (0.574)				
γ_1Log of MMJ patients									0.038 (0.071)		
γ_2Log of population							11.472 (13.952)		8.833 (14.482)		
γ_2Percentage aged 12-24							1.332 (1.130)		1.328 (1.168)		
γ_3Log of homeless population							0.527 (1.494)		0.540 (1.473)		
γ_4Unemployment rate							-0.489* (0.268)		-0.567** (0.264)		
γ_5State SCRA law index							-0.522 (0.819)		-0.482 (0.770)		
Specification	Pooled	Pooled	Pooled	Fixed effects	Fixed effects	Random effects	Random effects	Random effects	Random effects	Poisson with state fixed effects	Poisson with state fixed effects
Time fixed effects	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Observations	102	102	102	102	96	102	102	96	96	102	96
R^2	0.068	0.639	0.656	0.059	0.076	0.613	0.653	0.667	0.706	-	-
Akaike Inf. Crit.	-	-	-	-	-	-		-		1,586.851	1,464.280
Artificial Hausman Test $H_0: \gamma_1 = \gamma_2 ... = \gamma_5 = 0$	-	-	-	-	-	-	F = 0.861 Df = 16 P = 0.544	-	F = 0.694 Df = 11 P = 0.66	-	-

Note: Clustered-robust standard errors are calculated using bias-reduced linearization as proposed by Pustejovsky and Tipton (2016). Inferences are calculated using Satterthwaite approximation with a degrees of freedom correction. † Without California, Washington, and Maine. *p<0.1; **p<0.05; ***p<0.01

4.4 Discussion

To date, research has not empirically evaluated the relationship between cannabis and SCRA in the market. Most of the literature on SCRA has focused on the various chemicals or their association with adverse effects and negative social outcomes. Some of the qualitative research suggests SCRA users prefer natural cannabis to synthetic, and that SCRA use is driven largely by access or legality (Sutherland et al. 2017). This research helps to close a gap in the literature by evaluating how access to cannabis relates with SCRA exposure, as measured by calls to poison control centers.

These preliminary results suggest access to medical cannabis is associated with fewer SCRA calls to poison control centers. In various models considered, either operational dispensaries or medical cannabis market saturation (as measured by patient rates) are significantly associated with fewer SCRA exposure calls to poison control centers after controlling for demographic and legal variables that may impact SCRA use.

Qualitative literature discussed earlier suggests that, all things being equal, users prefer cannabis to SCRA. States that legally permit medical cannabis have reduced legal and social barriers to access and thus greater availability. Residents of states that permit medical cannabis, especially in states with greater medical cannabis market saturation, may not seek out SCRA as an alternative form of THC-like intoxication. The obvious exceptions being those that are legally prohibited from using cannabis for medical or recreational purposes, such as minors or those subject to regular drug testing.

If these preliminary results are replicated and it can be shown that cannabis and SCRA are substitutes, then comparing harms across drugs takes on additional urgency. The literature

on health harms of SCRA show that these substances are related to a broad list of harmful health outcomes. However, the analysis in this body of work has not assessed the comparative harms between smoking cannabis and smoking an SCRA. This was implicitly assumed given the toxicological literature and media reports. The harms evaluations becomes even more complicated when comparing use of SCRA and the consumption of cannabis in potentially more risky forms. Ingesting high potency cannabis products, like concentrates or edibles, may be of equal intoxicative harm to some SCRA.

Another complicating factor is the introduction of prevalence to the equation. Total harm is a function of prevalence multiplied by average harm per dose multiplied by frequency of use (MacCoun and Reuter 2001). A large increase in prevalence of cannabis users may increase total harm, such that it swamps the total harm attributed to less-popular SCRA. The discussion of harms often ignores prevalence and intensity (frequency), but they are important factors in the equation. Nevertheless, the known harms from cannabis, both at the individual and population level, may be easier to manage than the unknown harms of SCRA.

These preliminary results suggest that access to medical cannabis may reduce demand for SCRA. However, though these preliminary results support qualitative literature, alternative explanations for such results remain. Considerable measurement error on calls to poison controls centers may correlate with access to medical cannabis. Perhaps access to cannabis also increases adverse reactions, emergency department episodes, or calls to poison control centers due to overdose or accidental ingestion. Some of these calls for SCRA exposures by individuals or intimates may be under-reported due to misclassification. For example, if adverse reactions to cannabis increase after dispensaries become operational, then

perhaps some SCRA exposures are misclassified as cannabis-involved. During the same time period (2014-2016) cannabis-related calls to poison control centers has increased (Mowry et al. 2016, 2015). It is more likely that increases in calls for cannabis are due to the increased availability of cannabis as states have adopted medical and recreational cannabis laws.

Another potential confounding factor is that loosening restrictions on cannabis may cause short-term price spikes, at least until suppliers increase inventory. Yet price declines for cannabis have been reported in the medium to long-term. One recent market study of Washington state shows that price per gram has fallen by more than half since recreational markets became operational (Smart et al. 2017). Nevertheless, price shocks due to undersupply may occur in the first months, making SCRA an attractive alternative to price-sensitive users.

Price is a very important component of measuring elasticities between likely substitutes. Beyond price, are additional qualitative factors that might also go into a user's decision to purchase and consume either cannabis or an SCRA. Some of these complicate such elasticity and price comparisons. For example, dollars per hour of intoxication and the intensity and quality of cannabis versus SCRA-involved intoxication. Some SCRA may be attractive for their duration or intensity of effect. Yet, the variation of SCRA available continues to change year to year, if not month to month. This fact alone may make cannabis more attractive to users who prefer product consistency. Going forward, analysis might take into account some of these qualitative differences between cannabis or SCRA intoxication. At this moment, little is known about the pharmacology of many SCRA.

Though this preliminary analysis suggests a substitution, SCRA will continue to service certain market niches. Price and availability will continue to attract certain segments of the population, especially the most vulnerable. Additionally, individuals subjected to drug screening may still use SCRA as a method of avoiding detection (Reuter and Pardo 2016a). For example, states that permit medical cannabis allow employers to discipline employees for their off-hour cannabis use (Berman 2015). Access to cannabis may be limited for some other populations, including minors, making SCRA an attractive alternative.

4.4.1 Limitations

These results are preliminary. After obtaining additional observations going back to 2010, I plan to conduct a more rigorous analysis. I would prefer to run a fixed-effects model with more time periods to hold state-level time-invariant unobservables.

Another limitation is that poison control center data may fail to accurately measure such outcome data. It is possible that certain limitations within states may impede accurate measures or individuals reporting to poison control centers. Some states may have better poison control centers or access to poison control centers. Drug users may not be aware of what they are taking, especially when it comes to SCRA, suggesting much of the limitations of self-reported or unconfirmed data. Utilization of urinalysis or other confirmatory data are preferred. A fixed effects approach would help to eliminate issues of time-invariant unobservables, such as differences across state poison control centers. Cannabis prices may affect an individual's decision to use either substance. Additional analysis with the inclusion of cannabis prices would improve the measure of elasticity in price between cannabis and SCRA.

The dependent variable of SCRA exposures is spatially autocorrelated for 2016. After obtaining additional time periods, I may need to control for spatial autocorrelation.

4.4.2 Strengths

To my knowledge, this is the first empirical assessment of the relationship between cannabis and SCRA in the wider drug market. These preliminary results across all models considered report similar magnitude and direction. Even when I replace the binary variable of operational dispensaries with medical cannabis patient counts, I report a similar association.

As more states experiment with changes in cannabis policy and as the number of SCRA increase, it is necessary for research to continue to evaluate the relationship between these two likely substitutes. Early research here suggests the two drugs are substitutes. Policymakers should evaluate the wider drug market when considering policy changes. Additionally, policies should aim at reducing SCRA exposure given the serious health dangers posed by use of these new chemicals. For example, policymakers may want to reconsider regular cannabis drug testing, or at least sanctions for positive tests, if users continue to gravitate to SCRA as a means to circumvent detection.

5 Conclusion and Policy Implications

The main objective of this dissertation is to shed light on several important motivating factors behind drug use as well as on policies designed to regulate drug taking behavior. When it comes to the use of psychoactive substances, both pain and pleasure are important drivers. Because they are so intrinsic to the human condition, policy should be mindful of such factors. This seems obvious enough, but it warrants reiteration. An oversimplified understanding of pain management resulted in oversupply of opioid analgesics, contributing in part to today's opioid crisis. Likewise, most of the government and policy literature on NPS ignore or brush off pleasure as a driving factor of NPS use. This is a lacuna given that most NPS mimic popular drugs under control. Explicit recognition of the benefits of pleasure forces policymakers to pay attention to some of the important drivers behind use of drugs, especially new drugs. In this final chapter I summarize the common themes and relevant policy implications, suggesting areas of future research.

In Chapter 1 I define two motivating factors behind drug use. Policymakers and society recognize many of the harms and some of the benefits of use of psychoactives. In terms of harms, use of psychoactives to alleviate pain may also result in their abuse, as discussed in Chapter 2. By and large, pleasure remains absent from the contemporary drug policy discussion. Most policymakers and researchers continue to keep pleasure at arm's length. Chapter 1 discusses some of the pleasure-seeking motivation for drug use, expanding on these drivers in later chapters.

As social norms change and the harms of certain drugs are understood, society may start to recognize the benefits of particular mind-altering substances, including mere recreation. This is best exemplified by cannabis. The plant was prohibited for generations until social

norms surrounding palliative care opened up space for its use to treat pain (Musto 1999; Mead 1998). Today it is now recognized as a legitimate source of adult pleasure in 9 US jurisdictions. As history has shown, attitudes surrounding psychoactives has transformed some medicines into sources of acceptable pleasures. Courtwright (2009) notes that alcohol and tobacco were both used medicinally for generations until they became commodities of everyday trade (Courtwright 2009). Researching the non-therapeutic benefits of psychoactives has been difficult given measurement imprecision and a general lack of agreement of what is an acceptable form of psychoactive "pleasure".

I discuss some of these considerations and approaches when regulating new psychoactive substances, which often mimic controlled drugs, in Chapter 3. The flood of new substances and the almost instinctual efforts by regulators to control them overwhelms the capacity and design of existing drug control laws. Many governments are unsure of how to appropriately regulate substances whose harms and benefits are unknown, often defaulting to bans out of deference to the precautionary principle. In most cases, politicians prefer caution, avoiding Type II errors of allowing on market harmful products.

However, some drugs may be of low risk or hold some potential utility. I have outlined several policy approaches and considerations for weighing options when it comes to regulating new substances. Perhaps the most important contribution made in that chapter is that the NPS market is driven by four distinct niches. Policies aimed at controlling the phenomenon may not have much of an impact on certain niches. For example, drug suppliers eager to cut costs may not be deterred by blanket bans. As long as there is a market demand, chemical innovations may be driven by a need to minimize cost over avoiding legal prohibitions. Those subject to regular drug testing may continue to seek out

analog substances that do not show up in conventional drug screens. Lastly, those seeking entirely new mind-altering experiences may continue to drive some demand for new substances. Blanket bans have so far focused on those that use NPS because of their legality and accessibility in corner stores and headshops.

That said, the NPS phenomenon continues to puzzle regulators and scholars for different reasons. Regulators are overwhelmed by the number of drugs. Yet with over 600 new substances monitored by research groups and international bodies, only a handful have gained any appreciable market share over the medium-term. It seems odd that no NPS, besides ecstasy some decades ago, has entered and remained in drug markets. Could it be that drug users are sated by drugs on offer and that NPS, at best, mimic traditional drugs of choice? It seems likely that some new drug will gain substantial appeal in years to come.

Presently, most new drugs mimic controlled substances, principally cannabis or ecstasy. One possible approach to the NPS phenomenon is to permit and regulate the use of parent substances. Could the regulation of low-risk drugs like cannabis discourage the development and use of mimetics? Access to cannabis appears to compete with synthetic cannabinoids, as discussed in Chapter 4.

The research in this dissertation expands on important and pressing areas in contemporary drug policy. The risks of opioid pain relievers for pain management, especially for chronic pain, increasingly outweigh the benefits. Today's opioid crisis is far from over. Chapter 2 discusses state efforts to limit access to prescription opioids and thus reduce their abuse. As states continue to limit patient access to prescription opioids, research in this body of work shows that the strength of prescription drug monitoring programs (PMPs) are negatively associated with prescription opioid overdose deaths and emergency department

episodes. Limits to supply of prescription opioids are necessary to reducing the flow of new opioid misuse. Research detailed in Chapter 2 moves away from treating policy interventions dichotomously, scoring the strength of PMP regulations across states and over time, to show that different regulatory mechanisms or combinations of mechanisms are a more precise approach to measuring policy.

In a panel of 867 observations for all states and sixteen years, a one point increase in PMP score is associated with a 1% reduction in prescription opioid overdose deaths and a 0.7% reduction in emergency department episodes. When removing the weighted analysis, I show that PMP strength is associated with an even greater reduction in OPR overdose deaths, upwards of nearly 2% fewer deaths for each one point increase. It has been argued (Alpert, Powell, and Pacula 2017) that restrictions on the supply of prescription drugs may encourage some portion of chronic prescription opioid users to migrate to the illicit market. In Chapter 2 I do not report any such significant positive relationship between PMP strength and heroin or synthetic opioid overdose deaths or heroin-involved emergency department episodes. This could be because such shifts in the market have only started to occur more recently. Lags in data reporting may impede assessments of such relationships or there may be substantial measurement error in coding certain opioid-involved overdose deaths (Ruhm 2017).

Ongoing research and monitoring are paramount to determine if PMPs are associated with such displacement. Nonetheless, the work in this dissertation suggests that PMPs might be one useful policy mechanism to deter doctor shopping, reduce over prescription, and slow the flow of prescription opioid misuse. The recent Presidential Commission report on opioids recommends that state and federal governments work to improve or strengthen

PMPs to address over prescription (Christie et al. 2017). This and future research could help guide policies regarding the design of such interventions.

Future research stemming from work in Chapter 2 could very well include adjusted opioid overdose death counts to correct for underreporting in death certificates. Ruhm (2017) has estimated adjusted death counts for recent years and has shown that corrected opioid and heroin-involved deaths (that is, the sum of observed opioid overdose deaths with drug overdoses that were previously attributed to "unspecified drugs, medicaments, and biologicals") were, respectively, 24 and 22% greater than the observed counts (Ruhm 2017). Using these adjusted death counts, models may be able to better approximate any PMP displacement effect. Likewise, future research should evaluate the different policy designs behind naloxone provision. So far, models in Chapter 2 report a positive and significant correlation between some heroin overdose outcomes and access to naloxone. This could be due to the dichotomous nature of how access to naloxone is measured in models. Legal data from PDAPS could be utilized to better approximate the quality of naloxone provision laws in states.

As prescribing practices change and social awareness of the dangers posed by prescription opioids increase, policymakers and healthcare providers will need to consider alternative pain management therapies as well as mechanisms to prevent prescription opioid users from entering the illicit opioid market where harm is substantially greater. PMPs are one tool to help stem the flow, but they should be considered as part of a policy suite that includes efforts to reduce demand or maintain the stock of dependent patients on some medication-assisted therapy to discourage individuals from sourcing opioids in the illicit market. This is particularly important as an increasing number of opioids found in illicit

markets contain powerful, sometimes uncontrolled synthetic opioids. The rise of new, uncontrolled opioids has complicated enforcement and regulatory efforts of many governments. As Senators Grassley and Feinstein have noted: the synthetic opioid crisis today is a frightening confluence of our opioid problem and emerging drug threats (Grassley 2017).

The introduction of uncontrolled synthetic opioids complicates or impedes many traditional drug policy efforts and control mechanisms. Chapter 3 goes into detail about the drivers behind new psychoactive substances (NPS) and a conceptual framework of how governments assess the harms and regulate the supply and use of substances that pose potential threats to health and public safety. In the case of new opioids, supply-side factors may be contributing to their introduction into the market of illicit street opioids. The harms posed by these synthetic opioids make decisions to control rather straightforward.

However, harms vary by drug and differentiating policy responses may help reduce regulatory error and unintended harms. I have argued that the supply and use of psychoactives has both costs and benefits. More often than not, policymakers and researchers focus on the costs and neglect many nonmedical benefits of substances. This is a blind spot. Research in this dissertation suggests that explicit recognition of such benefits can inform policy design. Recognizing the utility of nonmedical drug use opens up alternative approaches to regulating psychoactives. This should not be interpreted as an endorsement for "legalization," rather giving deference to nuance can improve how to proceed in the face of seemingly overwhelming complexity.

The challenge of regulating NPS is one such overwhelmingly complex problem. The longstanding approach of controlling emerging drugs through narcotics laws is

increasingly strained, encouraging some countries to abandon it in favor of blanket bans. I have argued in Chapter 3 that blanket bans will have an impact on drug markets. In some cases these bans may result in misclassification of controls for substances. As I show, in the UK the blanket ban has been met with skepticism, court challenges, and political pushback. The government in that country is due to evaluate the impacts of the Psychoactive Substances Act in the coming year. Opportunities to evaluate the impacts of such a sweeping and historic law will yield additional information and guidance for future policy. In Chapter 3 I have included some details as to what an evaluation might consider and which indicators policymakers should consider in preliminary evaluations.

Chapter 3 deconstructs the NPS phenomenon, showing that different substances and different market niches pose different challenges and opportunities. After discussing these factors, I provide a detailed assessment of what jurisdictions around the world are doing to address the regulatory challenges posed by NPS. The chapter then provides a logic model, applying several of these frameworks to popular NPS in markets today. After considering benefits, including pleasure and substitution, I show how certain regulatory approaches may apply to different NPS types. Policymakers should keep in mind that the phenomenon is varied, and that policy responses should be differentiated depending on type of substance and market niche. Deconstructing the wider phenomenon could help disentangle policy responses.

In some cases, low-risk psychoactives, especially those that have gained substantial popularity, may be appropriately regulated under different frameworks. Kratom, for example, may be suited for dietary supplement regulations. After nearly ten years in the market, prohibiting kratom might be politically tricky and cause undesirable outcomes.

User groups have defined interests, such as pain relief and substitution away from more powerful analgesics, and are broad enough to compel regulators to consider alternatives to outright prohibition. Commodity-specific regulations, such as those that govern the production and use of other recreational psychoactives like alcohol and tobacco, were also considered in Chapter 3. The experience in New Zealand is cautionary about the difficulties of creating a new regulatory regime for NPS. The lack of data for many of these new substances impedes regulatory decision-making. In addition, policymakers are reluctant to allow on market a substance whose harms are little understood only to benefit a small proportion of the population. After three years, New Zealand's innovative regulatory approach to new psychoactives has languished without regulating the production and distribution of NPS. Difficulties in the law that prevent animal testing impede much of its progress. Nevertheless, the law explicitly recognizes the recreational outlet provided by some new psychoactives. That, in and of itself, is innovative.

There are certain substances that continue to be harmful yet attractive to certain users. Because NPS generally substitute for traditional psychoactives, I posit that relaxing access to traditional parent drugs might deter use of their mimetics. In Chapter 4 I empirically assess this hypothesis for one class of drug, showing that states in the US that have legal access to medical cannabis are associated with fewer calls to poison control centers for synthetic cannabinoids after controlling for several factors that relate to synthetic cannabinoid exposure. I measure access to cannabis by treating operational medical cannabis dispensaries as a dichotomous variable as well as measuring the rate of medical cannabis patients in a given year as reported by state registries. In either approach, models

report significantly fewer calls to poison control centers for synthetic cannabinoids when access to medical cannabis increases.

This analysis is preliminary given current data limitations. Yet, early findings for the 102 observations data are promising. If future research with additional observations replicates a substitution effect, then perhaps regulating parent drugs, whose harms and risks are better understood, might have important impacts for the NPS phenomenon, particularly the synthetic cannabinoid market. This is important given that the majority of reported NPS mimic either cannabis or psychostimulants like ecstasy. However, regulation of substances for non-medical purposes requires society and politicians to recognize and accept the hedonic benefits (and risks) of their use. This conversation is undergoing with regard to cannabis in the United States.

Some of early findings or questions posed in this dissertation could be promising for future research. Using Ruhm's opioid overdose death count approach may improve measurement of several dependent variables of interest. Going forward, the United Kingdom plans to evaluate its total ban of all non-exempted psychoactives. Evaluations will be important as more jurisdictions consider blanket bans to deal with the NPS phenomenon. Work in Chapter 3 can help guide some of these evaluations or policy considerations. This dissertation has argued for a differentiated approach to new drugs and proposes some hypotheses as to why no NPS has become popular even though hundreds of new chemicals have appeared in the last ten years. Future work explaining how NPS markets evolve and how new chemicals become popular warrants further study. Additional research and observations from poison control data will help confirm the preliminary findings reported in Chapter 4. These ideas pave the way for additional research for years to come.

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