**Title**
Getting to Zero Overdoses: Exploring Patient's Opioid Using Experiences Amidst A National Overdose Crisis



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Getting to Zero Overdoses: Exploring Patient's Opioid Using Experiences Amidst A National Overdose Crisis

by
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**Contributions**

Portions of this manuscript are reprints of published materials. These sections can be cited as follows:

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**Abstract**

**Getting to Zero Overdoses:**

**Exploring Patients' Opioid Using Experiences amidst a National Overdose Crisis**

**Emily Behar**

Drug overdose is currently the leading cause of injury-related death in the United States, outpacing deaths from guns, motor vehicles, and HIV each in their respective peak-death years. In 2017, over 70,000 individuals died from drug overdose, the vast majority of which involved opioids. As a response, federal, state and local policies have been enacted to decrease opioid prescribing across the US. Unfortunately, research shows a likely association between decreases in the availability of prescription opioids and increases in illicit opioid use as individuals transition from prescription opioids to heroin and other street drugs as cheaper, more accessible alternatives to manage their pain and/or opioid use disorder.

Patients prescribed opioids for chronic pain are particularly vulnerable to changes in opioid prescribing policies, as these changes may substantially impact their pain management, illicit substance use and risk of overdose. In order for primary care providers to manage their patients' pain effectively and safely, providers must consider to the individual needs of patients instead of relying on one-size-fits all policy approaches. Additionally, the field would benefit from a deeper qualitative understanding of patients' experiences being offered opioid stewardship interventions in a clinical setting, shift from prescription to illicit opioids, and reflect on their overdose experiences.

The goal of my dissertation research is to qualitatively explore individuals in three distinct phases of their pain management. Specifically, I aim to: (1) explore the feasibility and acceptability of prescribing naloxone as an opioid stewardship intervention in primary care settings, (2) understand transitions from licit to illicit substance use among pain patients, and (3) to explore the way individuals at high-risk for opioid overdose conceptualize their overdose experiences compared to overdoses they have witnessed.

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# Chapter 1

## Introduction

The 1940s were an exciting time for aviation in the United States – with the advent of the jet-powered plane, we were on the frontier of revolutionizing air travel. However amidst the innovation, the United States Air Force faced a crisis: aviation mortality was at an all-time high. Air Force officials examined their planes' manufacturing and their pilots' skills searching for the cause. Eventually, and against their intuition, they discovered neither the planes nor pilots were to blame. The problem had been due to a design flaw: the cockpit was built as a fixed entity, aimed to serve the physical stature of the average pilot. The rigidity of the design prevented the cockpit from adapting to the unique needs of the individual pilots. Instead of thinking about planes and pilots in isolation, the Air Force instead needed to focus on the interaction between the two variables. Shortly after this discovery, they reconstructed their cockpits to allow for individualization by adding adjustable seats and modifiable control panels. Once the pilot-centered cockpit was introduced, aviation mortality decreased and this form of individualization remains standard practice in aircraft design today.[1]

Like the crisis endured in the early days of aviation, we are currently amidst a public health crisis of unprecedented proportion. Drug overdose is the leading cause of accidental death in the United States, accounting for over 70,000 deaths in 2017 and a 9.6% increase in the age-adjusted death rate from 2016.[2] Deaths from overdose have now outpaced deaths from guns,[3] motor vehicle accidents,[3] and HIV[4] each in their respective peak death years. The medical community is commonly viewed as a contributor to the epidemic due to the rapid escalation and frivolity of opioid prescribing in the 1990s and

the clear association between increased opioid prescribing and opioid overdose mortality.[5] Today physicians, researchers and policymakers are devoted to resolving this iatrogenic problem, but as overdose mortality continues to climb, our systemic failures become only more evident and our solutions only more polarizing.

One ideological camp argues that the opioid epidemic is driven by “risky drugs, not risky people”. This perspective focuses on the notable risks of prescribing long-term opioid analgesics for patients with chronic pain complaints. Indeed, there is significant evidence supporting this concern, including the fact that over 80% of young injectors who initiated heroin reported having first misused a prescription opioid.[6] Furthermore, long-term opioid therapy has no greater effect on managing chronic pain than acetaminophen or non-steroidal anti-inflammatory agents and may even cause opioid-induced hyperalgesia and increase nociceptive sensitization.[7]

Proponents on the other side of the debate emphasize a focus on “risky people, not risky drugs”. They note that 70-80% of patients who are sustained on long-term opioid analgesics do not abuse their prescription. Among individuals who report prescription opioid misuse, roughly five percent reported transitioning to heroin.[8–10] Based on retrospective research, patients with a history of substance use disorder, polysubstance use, or multiple pain complaints have an increased risk of opioid misuse, however, the field lacks reliable prospective risk assessments.[11–13] Advocates of this view profess that opioids are an essential human right, an indispensable component of pain management

for debilitating pain, and they fear that an overly-aggressive clamp down on opioid prescribing may jeopardize access for patients in need of opioid-based palliation.

But, just as neither the pilot nor the plane were to blame for aviation mortality, neither are we able to singularly blame the drug or the patient. This historical tendency towards binary oversimplification lacks the nuance required to resolve the opioid epidemic. In this dissertation, I argue that, like pilots and planes, the opioid epidemic is fueled neither by risky drugs nor people, but rather the interaction between the two variables which is driven by an era of risky policies; policies that foster a medical system that, like a fixed seat in a cockpit, is too inflexible to allow for the type of individualized patient-centered care we need to successfully reduce opioid mortality.

***Global Trends: At the Extremes***

The global opioid crisis is largely fixed at two extremes, resulting in the over- and under-utilization of opioids. The over-availability of opioids has resulted in significant increased mortality in many countries, while the under-utilization in other countries has left millions to suffer without pain relief.

Roughly 29.5 million people suffered from substance use disorders worldwide in 2015, and 70% of this global burden is attributed to opioids.[14] Illicit opioids (including heroin, synthetic opioids, and the misuse of opioid analgesics) are used by approximately 35 million persons and rates of opioid misuse and overdose continue to rise in numerous

regions of the world.[14] The global incidence of opioid dependence increased by 74% from 1994-2010.

Conversely, nearly 80% of the world's population currently lacks access to licit opioids for essential pain management.[15–17] Adequate access to opioids vary by country: in most low and middle income countries (LMICs) access is extremely insufficient.[18,19] In 2011, over 20 million people, largely concentrated in LMICs died from chronic illnesses without access to satisfactory palliative care treatment, including access to opioids.[20] Today, opioids are disproportionately distributed throughout the world, with North America and Europe accounting for the vast majority of consumption.[21]

In 1961, the United Nations' Single Convention on Narcotic Drugs was enacted to promote balanced drug control policies that ensure, the availability of opioids for medical necessity while managing opioid misuse.[22] Yet there is still tremendous variation among drug control policies, even within developed nations. "Progressive" policies tend to position opioid misuse as a public health challenge, focusing largely on "risky drugs", while more "conservative" policies situate drug use within the context of a criminal justice framework, focusing more on "risky people".

Policies that are written too far towards either extreme can create harmful drug control environments that effect opioid-related decision-making processes at the national, regional, and provider level. When access to opioids is too loose, providers risk over-

relying on opioids to manage patients' chronic pain complaints; when access is too restricted, providers may be unable to accommodate patients' pain relief requirements.

### *Domestic Trends: Across the Continuum*

Opioid overdose is among the most significant public health crises of our lifetime, resulting in over 47,000 opioid-related deaths in 2017.[2] There is a lineage of divisive opioid policies and political circumstances in the United States that have ushered in the current opioid epidemic, including welfare reform, the advent of pharmaceutical marketing, a constricting labor market, and a movement within the medical community to eradicate pain.

In the 1990s, the American Pain Society introduced the concept of pain as the "fifth vital sign", arguing that pain was a pervasive and undertreated problem that required increased medical attention. The Department of Veterans Affairs and the Joint Commission followed suit shortly after and developed their own guidelines to encourage providers to assess, manage and ultimately eliminate chronic pain.[23,24] This movement was not without merit – physicians, particularly in palliative care and oncology, noticed that pain was largely an invisible complaint falling outside the purview of standard and specialized care. Physicians believed they had an ethical obligation to recognize and decrease patient suffering, and managing patients' pain was part of their professional responsibility. This movement was supported by a seminal report demonstrating the non-addictive properties of long-term opioid use: out of a small cohort of 38 individuals, only

two patients developed substance use disorder, both of whom had histories of substance use.[25]

The desire to eradicate pain and results from this study fundamentally changed the discourse around pain management in the US. The rapid expansion of opioid prescribing was exacerbated by these factors, and in conjunction with a number of co-occurring external environmental factors, including a change in welfare reform in the mid-90s that increased patient demand, and the advent of the infamous pharmaceutical marketing campaigns that dramatically increased opioid visibility. While opioids were used almost exclusively for cancer and malignant pain prior to the 1990s, this decade would mark a major shift in the utilization and reliance on opioids to manage pain. Medical schools began instructing students to prescribe opioids as first-line treatment for pain management, insurance companies began reimbursing for opioids over alternative nonpharmacological therapies, and national guidelines promoted the use of long-term opioids for chronic pain. Between 1999 and 2011, consumption of oxycodone alone increased by nearly 500%.[26]

While the 1990s ushered in an era of opioid abundance, the 2010s have introduced policies that may result in an era of opioid scarcity. The national response to the overdose epidemic has focused primarily on reducing opioid prescribing, in an attempt to correct for liberal past prescribing trends. The 2016 Centers for Disease Control and Prevention (CDC) publication, *Guidelines for Prescribing Opioids for Chronic Pain,* aimed to improve the safety and effectiveness of pain treatment, reduce the development of opioid use

disorder, and reduce opioid diversion.[27] The CDC recommended against using opioids as first-line therapy for managing chronic pain, and instead endorsed nonpharmacological therapies such as behavioral, movement-based or integrative therapies. Additionally, the guidelines introduced a range of opioid stewardship interventions, such as urine drug screens, pain contracts, risk assessments, naloxone and prescription drug monitoring program (PDMPs). Unfortunately many of these interventions lack sufficient evidence demonstrating their effectiveness.[28] For instance, research shows that providers use of high quality PDMPs may be associated with a reduction in their opioid prescribing,[29] yet there is no clear evidence that PDMPs are associated with opioid mortality.[30]

Furthermore, the CDC guidelines are written primarily to target opioid naïve patients and do not address how to manage chronic pain among patients who have already been maintained on long-term opioid therapy. This is a considerable oversight, as in 2017 there were over 191 million opioid prescriptions dispensed in 2017 with a prescribing rate of 58.7 per 100 persons.[31] It is likely clinically inappropriate to treat patients with a history of opioid therapy according to the same guidelines as opioid-naïve patients. Thus, a significant number of adult Americans likely require pain management treatment plans that are more complex than recommended in the CDC guidelines. For these patients already maintained on long-term opioids, the CDC recommends tapering all patients below 50 morphine milligram equivalents (MMEs) daily.[27] However, the systematic and widespread effort to rapidly decrease opioid prescribing has not resulted in reducing opioid overdose and may, in fact, exacerbate the problem. Evidence shows a likely association between opioid prescribing reductions and an increase in illicit opioid use and

overdose. Today, while opioid prescribing is at its lowest point in 13 years,[31] opioid-related overdose mortality has reached a historic high, resulting in over 48,000 deaths in 2017.[2]

Since the 1990s, domestic opioid policies have swung on a pendulum from one extreme to the other. National guidelines provide a benchmark for clinical care decision-making, are time-saving, offer legal protection, and are simple to integrate into everyday practice. But a one-size-fits-all policy for managing pain is unlikely to succeed given the complexity, subjectivity and multidimensionality of pain. And, while policies written towards extremism have failed, centrist policies that eliminate the extremes are not the solution either. For some patients, maintaining a dose well-above the CDC recommendation of 50MMEs is essential to effectively manage pain and function; for other patients, a taper to below 50MMEs may take years to achieve. On the other hand, there are patients for whom opioids may never be appropriate in their pain management plan. In order to provide respectful, ethical and effective care, providers need to place patients at the center of the decision-making process; a task that can only be achieved with guidelines flexible enough to allow for individualized, patient-centered decision making across the pain management spectrum.

In my dissertation, I highlight the need to incorporate patient-centered care into everyday clinical practice. My research focuses on individuals at three distinct stages of their pain management, including those who are: (1) currently prescribed long-term opioids, (2) actively undergoing opioid reductions or discontinuations, and (3) using opioids illicitly and at high-risk of experiencing an opioid overdose.

***Brief Overview of Research***

**Acceptability and Feasibility of Naloxone Prescribing in Primary Care Settings: A Systematic Review.**

First, I present a systematic review assessing the acceptability and feasibility of co-prescribing naloxone to patients on long-term opioid therapy in primary care practice. Naloxone is a short acting opioid antagonist used to reverse the effects of opioid overdose. It has been utilized by street-based drug users for decades and naloxone distribution programs have proven to be widely successful: between 1996 and 2014, organizations across the US distributed over 152,000 naloxone kits to laypersons and received reports of over 26,000 overdose reversals.[32] Naloxone is associated with a reduction in heroin use among naloxone recipients[33] and a population-level reduction in overdose mortality.[34–39]

Nevertheless, it was not until the last 5 years that naloxone has been actively introduced to laypersons in clinic settings. In fact, the first naloxone device specifically targeting laypersons was only approved by the FDA in 2016. Expanding naloxone availability through diverse environments (such as primary care settings) is considered an important component of overdose prevention.

Many clinic-based opioid stewardship activities (e.g., pain contracts, urine drug screens etc.) are frequently viewed by patients as antagonistic and create a policing culture in the clinic.[40,41] However, unlike other stewardship interventions, preliminary research suggests that naloxone may have a positive effect on the patient-provider interaction because it is based not on punitive enforcement, but rather on providing patients with a potentially life-saving medication to protect themselves and their community. Furthermore, there is some evidence that naloxone can be used to improve patient-provider communication around difficult opioid-related topics.[42] In addition, early research suggests that naloxone may lead to positive behavior modification, such as improved knowledge around opioids, decrease concomitant substance use, and improved awareness around dose timing.[43] Finally, research demonstrates that receiving a naloxone prescription may result in a reduction in opioid-related emergency department visits.[44]

While naloxone is a patient-centered intervention with a growing body of supportive evidence, we should, nevertheless, be cautious of enacting overly-generalizable policies pertaining to its distribution. In January 2019, the Medical Board of California introduced Assembly Bill 2760 mandating that all providers must offer naloxone to patients with an opioid prescription above 50MMEs, concurrent benzodiazepines use, or a history of opioid use disorder or overdose.[45] Unfortunately, this bill applies a one-size-fits-all model to an intervention that may have varying degrees of utility in different circumstances. For example, a 70 year old woman prescribed a low dose of codeine as needed for joint pain may not be an ideal candidate for naloxone. Similarly, a patient who has accepted a prior

naloxone prescription does not need to receive the offer upon every visit, as is designated by the Bill. This lack of nuance results in a bill that not only targets patients for whom naloxone may not be appropriate, but may increase provider burnout and frustration around the growing requirements of opioid stewardship demands. The emphasis on rote standardization could negatively impact an intervention that otherwise has the potential to improve patient-provider relationships around opioid prescribing, increase patient safety, and decrease opioid-related mortality. In my systematic review, I evaluate various clinic-based naloxone prescribing programs throughout the US with the aim of assessing the feasibility and acceptability of different naloxone implementation strategies.

**"Chasing the Pain Relief, Not the High": Patients' Experiences Manage Pain after Opioid Reductions**

My second paper qualitatively examines patients' experiences in self-managing their pain after being reduced or discontinued from long-term opioid therapy. The national response to the opioid crisis, to date, has focused disproportionately on reducing opioid prescribing as exhibited by national guidelines to reduce prescribing to below 50MMEs.[27] This effort has resulted in many patients across the US receiving improper reductions or discontinuations of long-term opioid therapy. When patients are reduced/discontinued from opioids inappropriately or without adequate access to alternatives, patients are often left to manage their unresolved pain on their own. Not only may this increase patients' transition to illicit substance use, but according to recent VA data, patients who were discontinued from their opioid prescription may be more likely to die of suicide. Thus, this

is a particularly vulnerable time in a patient's life. In this study, I qualitatively explore patients' experiences during this transitional period, focusing specifically on the mechanics of utilizing illicit substances to manage pain after being reduced/discontinued from long-term opioid therapy.

**Perceived Causes of Personal versus Witnessed Overdoses among People who Inject Opioids**

In my third paper, I explore differences in patient perspectives around personal versus witnessed overdoses among people who inject drugs (PWID) in San Francisco. Extensive research has identified common opioid overdose risk factors, such as prior overdose,[46,47] polysubstance use (e.g., opioid use with alcohol or benzodiazepines),[48,49] change in tolerance,[50–52] and injection frequency.[53] Overdose risk reduction education is often provided to PWID through low-threshold services such as syringe exchanges which offer a package of overdose education and naloxone distribution (OEND). Research shows that PWID who receive OEND are knowledgeable around risk factors and are able to recognize and respond to an overdose, particularly with the use of naloxone.[32]

Notwithstanding PWID knowledge of overdose risks, several studies suggest that some opioid users may nonetheless present an optimistic bias, whereby even high-risk individuals may perceive their overdose risk to be significantly lower than their peers.[54–56] No study, however, has explored how this bias is operationalized, which may limit the effectiveness of current overdose prevention interventions. To further explore this, I

incorporated two theoretical frameworks – the actor-observer bias and intra-group stigma – into my analysis to enhance my exploration of PWIDs' overdose experiences and potential implications of participants' overdose narratives. Deeper understanding of differences in perceived causes of overdose may help inform the development of patient-centered, individualized, evidence-based behavioral interventions to reduce risky overdose behavior.

**Summary**

The research presented in this dissertation argues for the inclusion and emphasis of the patient experience when building policies, programs and research objectives. First, we note the importance of assessing the feasibility, acceptability and efficacy of opioid stewardship interventions (e.g. naloxone prescribing) prior to incorporating interventions into national recommendations and clinic guidelines. Next, we demonstrate the vulnerabilities, barriers and risks that opioid-experienced patients face during opioid tapers, and argue for the development of patient-centered pain management plans. Finally, we illustrate how behavioral interventions to reduce overdose risk can be improved by utilizing PWID's overdose experiences to promote safer using habits and increase empathy for using partners.

# Chapter 2

## Acceptability and Feasibility of Naloxone Prescribing in Primary Care Settings: A Systematic Review

### Background

The United States is amidst a drug overdose epidemic of unprecedented proportion. In 2016, there were an estimated 64,000 drug overdose fatalities, the majority of which involved opioids.[57] Naloxone, the short-acting opioid antagonist used to reverse the effects of opioid overdose, has been distributed to people who inject drugs through community based organizations and syringe exchanges for nearly two decades. In this context, naloxone is typically prescribed via a standing order, enabling non-physicians to furnish naloxone to individuals at risk for experiencing or witnessing an opioid overdose. Naloxone distribution programs have proven to be widely successful: people who use drugs can be trained to respond to overdoses effectively[58,59] and between 1996 and 2014, organizations across the US distributed over 152,000 naloxone kits to laypersons and received reports of over 26,000 overdose reversals.[32] Furthermore, naloxone is associated with a reduction in heroin use among naloxone recipients[33] and a population-level reduction in overdose mortality.[34–39,60,61] Every US state has some legislation supporting naloxone access.[62]

The demographics of individuals at risk for opioid overdose expanded since 2000 to include people who use prescription opioids who may not utilize community based services or syringe exchanges and thus may not have easy access to naloxone through standard means of distribution. Furthermore, syringe exchanges and harm reduction services may be difficult to access for individuals living in non-metropolitan areas. Thus,

expanding naloxone availability through diverse mechanisms is an essential component of overdose prevention, with primary care access a particularly valuable intervention. In fact, the Centers for Disease Control and Prevention now recommends that naloxone be co-prescribed to patients receiving opioids for chronic pain with risk factors such as receipt of more than 50 morphine milligram equivalents, concurrent benzodiazepine use, or a history of substance use disorder.[63] Despite this federal endorsement, naloxone prescribing is still a relatively nascent intervention in primary care. This systematic review aims to assess the acceptability and feasibility of prescribing naloxone to patients in primary care settings.

## Methods

*Search Methodology*

This review was conducted following PRISMA guidelines and was registered in PROSPERO prior to initiation. We queried PubMed, EmBase and CINAHL using the following Medical Subject Heading (MeSH) terms: (naloxone) AND (primary health care OR primary care nursing OR primary care physician). A complete list of database search terms can be found in Table 2.1.

**Table 2.1 Database Search Criteria**

| Database | Type of Search Term | Search Terms | Results |
|---|---|---|---|
| PubMed | MeSH terms | "Naloxone"[Mesh:NoExp] AND ("Primary Health Care"[Mesh] OR "Primary Care Nursing"[Mesh] OR "Physicians, Primary Care"[Mesh]) | 56 |
| PubMed | Keyword search | (naloxone OR narcan) AND (“primary health care” OR “primary care” OR “primary care nursing” OR “primary care physicians” OR "physicians, primary care") | 108 |
| EmBase | Index terms and keyword search | ('naloxone'/exp OR naloxone) AND ('primary health care'/exp OR 'primary health care') AND ('united states'/exp OR 'united states') | 153 |
| CINAHL | Index terms and keyword search | naloxone AND ( "primary care" OR "primary health care”) | 67 |

Database searches were conducted in October 2017, yielding 270 unduplicated articles. In addition to formal database searches, we hand searched citations from the eligible articles and consulted experts in the field to identify articles not found through our initial searches, adding one additional article to our results. Search results were exported to a reference manager, Mendeley Ltd., and then into Microsoft Excel (2013) for analysis. A PRISMA diagram illustrates the article selection process (Figure 2.1).

*Inclusion Criteria*

Articles were included in our analysis if they discussed the acceptability or feasibility of prescribing naloxone to patients in a primary care setting. The search was limited to US-only peer-reviewed, full-length articles that were written in English and based on original research. There was no restriction on publication date. Articles could include patient, provider or medical staff perspectives, could be evaluation or feasibility studies, and could use either qualitative or quantitative analytic methods. Articles were excluded if they focused on prescribing naloxone outside of a primary care setting (e.g. standing order or prescribing through an emergency department).

*Article Selection and Review*

One analyst (EB) reviewed the titles of all queried articles. Articles that clearly did not pertain to the topic of this systematic review were excluded immediately (e.g. articles referring to the co-formulation of buprenorphine/naloxone). We eliminated 218 articles based on title review. One reviewer (EB) then independently reviewed the remaining 52

abstracts for inclusion. If eligibility was unclear, the reviewer consulted a second reviewer (PC) for a final decision. After title and abstract review, 20 articles met inclusion criteria.

Two analysts (EB and RB) then independently read the full-text of the eligible articles and recorded general information such as date, location, study design, study sample, research question, and primary outcome. Additionally, reviewers also collected data relating to either the acceptability or feasibility of naloxone prescribing, depending on the study's primary purpose. Three articles were excluded during this phase; two did not meet inclusion criteria upon reading the complete text and one did not have full-text availability. We conducted a quality assessment of the eligible articles, however due to a high degree of heterogeneity in study design and inconsistencies in study metrics, we did not include the assessment in our results.

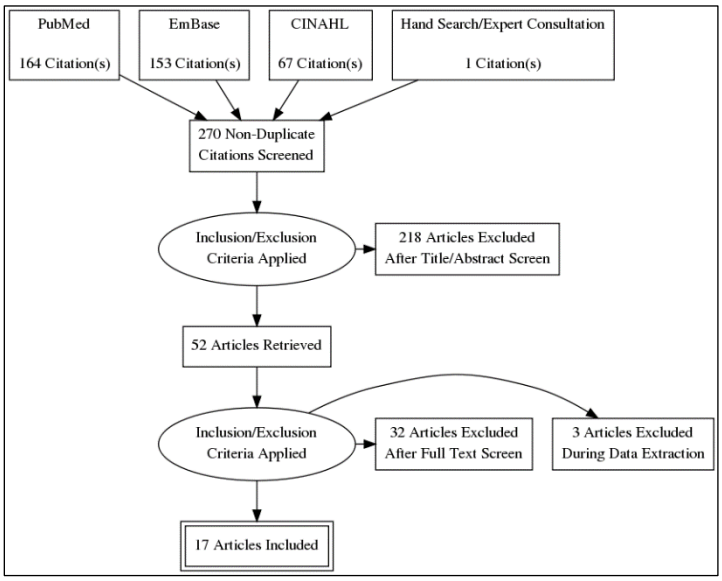


**Figure 2.1 PRISMA Study Selection Flow Diagram**

*Analysis*

To assess acceptability, we evaluated the articles for providers' awareness and willingness to prescribe naloxone, attitudes, and anticipated barriers/concerns. To assess feasibility, we evaluated the articles for descriptions of programmatic implementation (e.g. training process, patient identification, naloxone formulation, ordering and dispensing

processes, insurance and billing, and any streamlining or clinic based support), education (e.g. how were providers educated, was education provided to patients and by whom, and were educational materials distributed), attitudes, and experienced challenges. We report acceptability findings first, as many acceptability studies occurred prior to program implementation and feasibility results.

**Results**

Seventeen articles met our inclusion criteria and were included in this analysis (Table 2.2). Articles were categorized as either pertaining to naloxone prescribing acceptability (N=10),[42,43,64–71] feasibility (N=5),[72–76] or both (N=2),[77,78] and also categorized as including perspectives from prescribers (N=14),[42,64–68,70–77] patients (N=2),[43,69] or both (N=1).[78] The studies had broad geographic scope within the US, covering the Northeast (N=4), Midwest (N=1), Southwest (N=5), West (N=5), and national (N=2).

All studies assessing the acceptability of naloxone prescribing obtained data through surveys, interviews or focus groups. Analytic methodology varied and included quantitative, qualitative and mix-methods approaches. The time period for these studies ranged from 2001-2017. Feasibility studies focused largely on program evaluation studies and quantitative or mixed-methods analyses. The time period for these studies ranged from 2013-2017. Three papers explored the acceptability of naloxone prescribing from a patient perspective, using quantitative, qualitative and mixed-methods approaches.

| Table 2.2. Articles Included in Systematic Review (N=17) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Article** | **State** | **N** | **Study Sample** | **Study Design** | **Primary research question** | **Summary of Key Findings** |
| **Acceptability** | Behar 2017[42] | CA | 111 | Prescribers (MD, NP, PA) | Program evaluation | Is prescribing naloxone in primary care to patients on long-term opioids acceptable among primary care providers? | 79% of providers prescribed naloxone (mean 7.7 pts); 99% likely to prescribe in future; concerns were administrative related to pharmacy and payer logistics; internists and providers with more patients prescribed long-term opioids were significantly more likely to prescribe naloxone; providers did not think prescribing naloxone would affect their prescribing |
| | Behar 2016[43] | CA | 60 | Patients on long-term opioids (≥3 months) for chronic non-cancer pain | Program evaluation | Is receiving a naloxone prescription in primary care acceptable among patients on long-term opioids for chronic non-cancer pain? | 90% of patients had not previously received naloxone; 97% believe naloxone should be prescribed for pain patients; 79% had positive/neutral response to being prescribed naloxone; 37% reported beneficial behavior change due to prescribe; generally patients believe their risk of overdose is low; term "overdose" may be problematic and providers may want to use patient-centered language like "bad reaction" |
| | Beletsky 2007[64] | US – Nat'l | 588 | Physicians (MDs) | Postal surveys | What are primary care providers' knowledge and willingness to prescribe naloxone to people who inject drugs? | 23% of physicians were aware of naloxone prescribing; 54% never consider prescribing. Age, having more patients on panel who injected drugs, having better attitudes towards people who inject drugs, and having confidence in one's ability to help people who inject drugs were associated with a higher likelihood of prescribing naloxone. |
| | Binswanger 2015[65] | CO | 56 | Physicians, nurses, pharmacists and administrators | Focus groups | What are the knowledge, attitudes, and beliefs about overdose education and naloxone prescribing among staff in primary care? | Providers believed prescribing naloxone could save lives and result in safer opioid use**.** Providers noted knowledge gaps around naloxone in outpatient setting, concerns about identifying who to prescribe to, concerns about logistical barriers, fear of offending patients, and fear of risk compensation. |
| | Coffin 2003[66] | NY | 363 | Prescribers (MD, NP, PA) | Postal surveys | Are prescribers willing to prescribe naloxone to patients at risk of an overdose? | 33% prescribers said they would consider prescribing, 29% were unsure and 37% said they would not prescribe naloxone to patients at risk of an opioid overdose. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Gatewood 2016[67] | MD | 30 | Physicians and medical students | In-person interviews and focus groups | What are perceived barriers of third party naloxone prescribing among physicians and medical students? | Physicians and medical students identified three categories of concerns for prescribing naloxone to potential witnesses related to naloxone itself (e.g. duration of action, medical risks, route of administration etc.), providers (lack of knowledge or experience, medical community common practices and norms, insufficient provision of third-party education etc.), and patients (increased risk-taking behaviors, opioid withdrawal symptoms, decrease contact with medical staff etc.). |
| | Green 2013[68] | CT and RI | 24 | Emergency department, substance use treatment, and primary care providers | In-person interviews | What are barriers and facilitators to prescribing naloxone to patients and people who use drugs? | Overall support for prescribing naloxone**.** Three main categories of concern: risk compensation; identifying appropriate patients; and making sure naloxone is not a stand-alone approach. |
| | Mueller 2017[69] | CO | 24 | Patients prescribed high dose opioids for chronic non-cancer pain | In-person interviews | What are attitudes of naloxone prescribing among patients prescribed long-term opioids for non-cancer pain? | Positive narratives included patients receiving education around naloxone, and providers using empowering, non-judgmental language when discussing naloxone. Negative narratives included limited education around naloxone, medication costs, belief that overdose was caused by medication misuse, and fear that providers may think patient was misusing opioids if they accepted the naloxone prescription. |
| | Wilson 2016[70] | MD | 97 | Internal medicine resident physicians | Needs assessmen t | What are resident physicians' knowledge around overdose risk, naloxone prescribing, and barriers to overdose prevention? | Resident physicians are largely aware of naloxone and willing to prescribe it; barriers included needing more education around how to prescribe and support around identifying appropriate patients for a naloxone prescription. |
| | Winograd 2017[71] | MO | 45 | Prescribers (MD, NP, PA, and clinical pharmacists) | Surveys | What are prescribers' knowledge and concerns around prescribe? | Prescribers cited four categories of concern: lack of knowledge, concerns around iatrogenic effects, concerns about impressions of unsafe opioid prescribing, and concerns about risks of naloxone prescribing. Providers endorsed providing overdose education to patients. System-wide naloxone prescribing rates and sources increased over |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | 320% following the initiation of overdose education and naloxone distribution expansion efforts. |
| **Both** | Wilson 2017[77] | NC | 1297 | Patient electronic medical charts | Program evaluation and surveys | What is the process of designing and implementing a targeted naloxone coprescribing program for patients on long-term opioids in a primary care? | A chart abstraction prior to the implementation of a naloxone program showed that 49.4% of patients on chronic opioids met their criteria for naloxone, however only 3.4% had naloxone on their medication list. Pharmacists may be well-positioned to develop a targeted naloxone coprescribing program in primary care settings. |
| | | | 26 | Physicians and resident physicians | | | |
| | Han 2017[78] | PA | 16 | Patients | Program evaluation | Can a counseling intervention improve provider and patient awareness of naloxone, increase naloxone prescribing and prevent overdose? | 97 naloxone kits were dispensed, largely for illicit opioid use. Five patients reported successfully using naloxone to reverse an overdose. Physicians and resident physicians noted improved knowledge around naloxone prescribing, and increased professional satisfaction caring for patients requesting opioids. Patients endorsed high levels of comfort discussing opioid use with their primary care physician. |
| | | | 22 | Physicians and resident physicians | | | |
| **Feasibility** | Behar 2017[72] | CA | 40 | Prescribers (MD, NP, PA) | Program evaluation | Is academic detailing an effective intervention to increase naloxone prescribing among primary care providers? | Academic detailing addressing opioid safety and naloxone prescribing was well-received by primary care providers and associated with an 11-fold increase in naloxone prescriptions filled by Medi-Cal patients among providers who received academic detailing compared to those who did not. |
| | Coffin 2016[73] | CA | 1,985 | Patients receiving long-term opioids (≥3 months) for chronic non-cancer pain | Nonrandomized intervention study | Is implementing a naloxone coprescribing program in primary care settings feasible and effective? | Naloxone can be co-prescribed to primary care patients on long-term opioids for chronic non-cancer pain. 38.2% of 1,985 patients receiving opioids were prescribed naloxone. Patients who received a naloxone prescription had 47% fewer opioid-related ED visits in the 6 months after receipt of the prescription (incidence rate ratio [IRR], 0.53 [95% CI, 0.34 to 0.83]; P = 0.005) and 63% fewer visits after 1 year (IRR, 0.37 [CI, 0.22 to 0.64]; P < 0.001) compared with patients who did not receive a naloxone prescription. When advised to offer naloxone to all patients |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | receiving opioids, providers may prioritize those with established risk factors. Providing naloxone in primary care settings may have ancillary benefits, such as reducing opioid related adverse events. |
| | Devries 2017[74] | CA | 252 | Prescribers (MD, NP, PA, and pharmacist) | Program evaluation | Is implementing a naloxone coprescribing program in primary care settings feasible and effective? | 252 physicians, pharmacists and nurses were trained in overdose education and take-home naloxone. Naloxone prescribing increased from a baseline of 4.5 per month to an average of 46 per month during the 3 months following implementation of the program. |
| | Oliva 2017[75] | US – Nat'l | 142 | Veterans Health Administration Medical Facilities | Quality improvement project | Is implementing a naloxone coprescribing program in primary care settings feasible and effective? | The Veterans Health Administration dispensed 45,178 naloxone prescriptions written by 5,693 prescribers to 39,328 patients who were primarily prescribed opioids or had opioid use disorder. There were 172 reported opioid overdose reversals using the prescribed naloxone at the time of reporting. |
| | Takeda 2016[76] | NM | 164 | Patients on long-term opioids for chronic non-cancer pain | Observational study | Can naloxone prescribing be implemented in primary care settings using a universal precautions model? | 164 patients were enrolled in the study; all subjects were educated around opioid overdose risks and provided naloxone. No overdoses occurred in the study population. 57% of the cohort had depressive disorder, the median MED was 90mg/day, and the median Current Opioid Misuse Measure score was 5.0. The ambulatory co-prescribing of naloxone in a Universal Precautions model for all patients prescribed chronic opioid therapy can be adopted as a useful public health intervention. |

## ACCEPTABILITY OF NALOXONE PRESCRIBING

### *Willingness to prescribe naloxone (N=6)*

Six articles directly assessed providers' willingness to prescribe naloxone.[42,64,66,68,70,77] The two earliest published articles reported the highest degree of provider resistance to naloxone prescribing. One study, published in 2003, stated that 37% of respondents would not be willing to prescribe naloxone[66] while another study, published in 2006, stated that 54% of respondents would not prescribe naloxone.[64] In contrast, the two most recent studies, published in 2016 and 2017, indicated that 90% and 99% of prescribers were willing to prescribe naloxone, respectively.[42,70]

Study results demonstrate that providers are willing to receiving education around naloxone prescribing and once education is delivered, providers are largely willing and capable of prescribing. Han et al., for example, reported a statistically significant increase in providers' comfort prescribing naloxone after receiving education.[78] Results from another study showed that providers who had received naloxone education were 11 times more likely to prescribe naloxone to their patients compared to providers who had not received education.[72] Not only are providers willing to receive education, but Wilson et al. showed that most resident physicians in their sample (88%) believed it was their responsibility to education their patients on overdose and naloxone utilization.[70]

### *Concerns related to naloxone prescribing (N=9)*

While results suggest a secular trend of increasing willingness to prescribe naloxone in primary care settings, there remain a number of barriers. Concerns referenced by seven

of the nine studies[42,65,67,68,70,71,77] include: lack of knowledge around prescribing naloxone, lack of knowledge around educating patients, and inability to identify patients eligible for naloxone (Table 2.3). Additional concerns included fear of risk compensation, fear of offending patients, and fear that prescribing may take too long. Yet while many studies cited barriers, other studies in this sample directly refuted many of the same barriers. For instance, Wilson et al. reported that 86% of resident physicians did not believe naloxone enabled risky behavior[70] and Behar et al. reported that the majority of providers did not believe their patients would react poorly if offered a naloxone prescription.[42]

| **Table 2.3 Barriers to Naloxone Prescribing (N=9 articles)** | N | % |
|---|---|---|
| **Patient concerns** | | |
| Risk compensation | 4 | 44% |
| Naloxone alone not adequate overdose response | 2 | 22% |
| Fear of decreased contact with medical providers/less likely to seek treatment | 2 | 22% |
| **Provider concerns** | | |
| Fear of offending patients | 3 | 33% |
| Fear of appearing to condone opioid misuse | 2 | 22% |
| Introspection on prescribing practices | 1 | 11% |
| Liability in naloxone prescribing | 1 | 11% |
| **Logistical concerns** | | |
| Lacking knowledge to prescribing naloxone | 6 | 67% |
| Identifying patient eligibility for naloxone | 5 | 56% |
| Educating patients | 6 | 67% |
| Prescribing takes too much time | 3 | 33% |
| Prescribing should be done by someone else | 1 | 11% |
| Privacy and confidentiality concerns | 1 | 11% |
| Remembering to prescribe and follow up | 1 | 11% |
| Lack of awareness around prescribing | 1 | 11% |
| Billing/cost issues | 1 | 11% |
| Limited availability of naloxone | 1 | 11% |
| **Naloxone concerns** | | |
| Route of administration | 2 | 22% |
| Difficult assembling device | 2 | 22% |
| Duration of action | 1 | 11% |
| Medical risks | 1 | 11% |
| Expiration date | 1 | 11% |

## FEASIBILITY OF IMPLEMENTING A NALOXONE PRESCRIBING PROGRAM

Seven studies provided information around the implementation process of their naloxone prescribing program. There were four main components of program implementation noted throughout the studies, including: training providers to prescribe naloxone, indications for naloxone prescribing, training providers to educate patients on naloxone, and logistics of filling the prescription.

### *Overall feasibility of naloxone prescribing (N=6)*

Studies assessing feasibility demonstrated that naloxone prescribing in primary care practice is feasible. A combined total of 46,453 naloxone prescriptions were written among the studies. After training physicians, pharmacists, and nurses, one study saw the number of prescriptions for naloxone increase from a baseline of 4.5 prescriptions per month to 46 per month during the three-month follow up.[74] Oliva et al. reported significant uptake in naloxone prescribing, with over 45,000 naloxone prescriptions written by over 5,600 providers to 39,328 patients who were prescribed opioids or who had an opioid use disorder.[75] In addition to being feasible, naloxone prescribing may also be effective at reducing opioid-related adverse events, as Coffin et al. demonstrated that patients who had received naloxone had 63% fewer opioid-related emergency department visits one year after receiving a naloxone prescription compared to those who did not receive naloxone.[73]

In a number of papers, providers noted ancillary benefits of prescribing naloxone to patients. In one paper, a provider stated:

> "I expected the decreases in death from overdose – but I hadn't thought about how this simple act of prescribing potentially lifesaving treatment has opened up other important conversations that have allowed me to provide better, safer and more compassionate care to my patients."[42]

Another provider suggested that naloxone prescribing may help to re-set the culture around opioids and overdose:

> "I was sort of hoping that if we implement a good program where even at initiation [of opioids], we talk about overdose prevention and naloxone, that it will bring, you know, the safety concerns to the forefront, and then it might actually help people understand that these are potentially lethal medications, and I feel like that might be one of the things that might be most beneficial from it… just re-setting of, like, the culture around [opioids] as much as, you know, potentially saving someone's life from overdose."[79]

*Training providers to prescribe naloxone (N=5)*

All five studies reported at least some in-person training, while a few studies also reported supplemental electronic[74] or video-based[75] education. Trainings were offered to prescribers in all studies, with some also offering trainings to pharmacists, resident physicians, medical students, and other clinic staff. The majority of trainings were conducted by pharmacists followed by prescribers and staff from local health departments. All studies trained prescribers on how to educate patients on naloxone and opioid overdose. The majority reported also training prescribers on how to write a naloxone prescription, indications for prescribing, and method of naloxone

| **Table 2.4 Content of Provider Education (N=6 articles) (all that apply)** | **N** | **%** |
|---|---|---|
| How to educate patients on naloxone and opioid overdoses | 6 | 100% |
| Instructions for how to write a naloxone prescription | 5 | 83% |
| Indications for prescribing naloxone | 4 | 67% |
| Method of naloxone administration | 4 | 67% |
| Rationale for furnishing naloxone | 3 | 50% |
| Naloxone prescribing laws | 3 | 50% |
| Patient-level opioid overdose risk factors | 3 | 50% |
| Background on overdose | 2 | 33% |
| Background on naloxone (pharmacokinetics, effectiveness etc) | 2 | 33% |
| Payer/pharmacy coverage | 2 | 33% |

administration (Table 2.4). Only three studies documented training length, which together, ranged from 5-60 minutes.[72–74] Two studies used an approach called academic detailing to provide education.[72,75] Some studies discussed soliciting support from a "clinic champion" to help raise awareness and garner support for naloxone prescribing.[44,78]

*Indications for prescribing naloxone (N=7)*

While we can identify certain risk factors for overdose (e.g. having previously experienced an overdose,[46,47] periods of abstinence,[50–52] and concomitant benzodiazepine use[48,49]), there is limited research suggesting that we can adequately predict risk factors for developing an opioid use disorder or experiencing an opioid overdose among patients on chronic opioids; to date the only studies aimed to validate risk assessment tools are retrospective.[80–82] As a result, the majority of studies recommended a simple universal naloxone prescribing model for patient on long-term opioids (≥3 months) for chronic non-cancer pain or otherwise at risk of experiencing an overdose.[44,72,75,76] In one paper, a pharmacist advocated for universal prescribing for patients on long-term opioids stating, "logistically it's hard to reach out to every patient, but if the goal is to save lives, you have to bring it up to everybody."[79] Similarly, a provider from the same study grappled with determining naloxone eligibility, ultimately suggesting universal prescribing may be the best approach:

> "I had a patient whose daughter accidentally overdosed on her meds, so, I'm wondering, shouldn't we be offering [naloxone] more broadly? Do we have to discuss this with everybody and then offer to write the prescription for those who are accepting of it?"[79]

Three studies provided additional guidance around patient eligibility, including indications of primary risk factors (such as concomitant benzodiazepine use, recent period of abstinence etc.) but ultimately also noted that the decision could be based on provider discretion or at a patient's request.[74,77,78]

*Patient education (N=7)*

While all seven studies provided some component of patient education around naloxone prescribing, the content and duration varied. There was only one study in which prescribers themselves did not provide education directly to patients.[76] Some studies also employed additional clinic staff to conduct education, including pharmacists, medical and pharmacy students, medical assistants, and research associates. Five studies[44,72,74,75,78] offered patients the same or an adapted version of a tri-fold brochure around overdose and naloxone (Appendix 2), while the remaining two used different materials with similar messaging. Four studies[44,72,76,78] explicitly advised that patients' caregivers, family, or friends be included in the naloxone training if possible, though none required that such persons be present.

*Filling the naloxone prescription (N=7)*

Naloxone formulation was largely determined by medication availability and payer coverage at the time studies took place. All studies provided an option to prescribe an off-label intranasal naloxone device, four studies also offered the intramuscular device,[44,72,74,75] three offered the auto-injector[72,74,75] and one offered the nasal spray.[75] Two studies systematically implemented an alert in their electronic health record (EHR)

system to assist providers in naloxone prescribing,[74,78] one of which also included a link in their EHR to patient educational materials. Two studies dispensed naloxone to patients onsite,[76,78] while all other studies relied on pharmacy pick-up. All studies billed patients' insurance for the naloxone.

## PATIENT PERSPECTIVES

Of the three studies focused on patient perspectives, two presented results from patients who had received a naloxone prescription;[43,78] the remaining study solicited perspectives from patients who were on long-term opioids but did not include data on whether patients had been offered a naloxone prescription.[22]

### *Naloxone acceptability and utilization (N=3)*

Overall, study results suggest that patients had little prior knowledge of naloxone. One paper from a metropolitan area with high rates of lay naloxone distribution reported that 36 of 60 interviewees (60%) had never heard of naloxone prior to being offered a prescription, though 95% were willing to receive the prescription again in the future and 97% believed it should be prescribed to some/all patients on long-term opioids in a primary care setting.[43] Two studies[43,78] reported that the majority of patients felt an increased sense of security after receiving naloxone, and one noted that 37% of patients reported beneficial behavior changes after receiving the prescription with no harmful behavior changes reported.[43] Studies also confirmed that the majority of patients were comfortable and willing to administer naloxone if needed.[43,78] One study reported that 5 patients (5%) who received naloxone had used it,[78] and another reported that 3 of 60

patients (5%) stated that the naloxone they were prescribed by their provider was used on them.[43]

*Facilitators/benefits and barriers/concerns (N=3)*

Two papers presented facilitators and perceived benefits around naloxone prescribing. In Behar et al., patients discussed benefits of receiving naloxone, including: benefits to the community; appreciating it was offered; and improving their relationship with their provider.[43] Mueller et al. noted facilitators, including: providers' using empowering, non-judgmental communication; framing naloxone for use in "worse case scenarios"; and providing education and training around opioids and naloxone.[69] Framing naloxone as a safety precaution for an unexpected situation resonated with patients in Mueller et al, as one patient stated:

> "It's like a seatbelt. You don't plan on getting in an accident but if you do it's good to have the seat belt. I can see the fire extinguisher analogy…it doesn't mean you're going to go set a fire, but [naloxone is] there just in case so it could save lives."[69]

Similarly, in Behar et al., a patient shared positive sentiments about receiving naloxone:

> "I thought [naloxone] was a wonderful idea…I have been on a reasonably high dose for many years and have never overdosed, but there have been at least 1 or 2 times where I've [said], 'Oh, wait, I just took a pill 20 minutes ago and I just took another…oops!' It can happen to anybody."[43]

Mueller also noted barriers to naloxone receipt, including: fear of exacerbating providers' concerns of opioid misuse if the naloxone prescription was accepted; fear of loss of opioids for pain management; and concerns around medication costs.[69] Because Mueller et al. did not report how many patients, if any, had been offered a naloxone prescription,

it's unclear if these barriers are based on patients' real experiences or expectations. Behar et al. reported that a minority of patients had negative reactions to being offered a naloxone prescription, most commonly due to: feeling the prescription was unnecessary, feeling judged, or being scared.[43] An additional barrier presented in the studies may be that patients believed they were at low risk for overdose, commonly attributing this to the fact that their opioids were prescribed by their physician.

*Framing an educational message (N=2)*

Messaging around overdose and naloxone may influence patients' interpretation and willingness to accept a naloxone prescription and understand its utility. In Mueller et al. one patient offered two different explanations for naloxone prescribing, stating:

> "Well, I guess you could look at it two ways. You could look at it as well, you know, if [an overdose] should accidentally happen, [naloxone] would be a good thing, or you could think, 'Well, do they think I'm at risk for [misusing my medications]...or are they doing this more out for my protection?'"[69]

When framed positively, patients may be very willing to accept naloxone. A patient from the same study, after learning about naloxone, said: "If I had not heard what your description [of naloxone] was, I would probably almost be offended or something. I might be like you think I'm abusing [my medications]."[69] Another patient from Mueller et al. agreed: "[Naloxone] would be very helpful…just in the event that it may happen, it'd be nice to know I have that preventive…medicine there for me."[69]

Using strategic educational messaging was also considered important by authors of one paper that found 37% of interviewees had personally experienced an opioid-poisoning

event, yet 45% of these respondents described the event as a “bad reaction” not overdose.[43] Based on this, authors suggested replacing the term “overdose” with patient-centered language such as “bad reaction” or “accidental overdose” to increase patient comprehension. Results from these studies suggest that if proper language is used, naloxone may be a useful tool to enhance a provider-patient relationship, increase patients’ understanding of overdose events, open dialogue around opioids, and increase patients’ sense of security.

## Discussion

Current literature finds that prescribing naloxone in primary care settings is an acceptable and feasible intervention among both providers and patients. Over 46,000 naloxone prescriptions were written among the studies presented in this review, and it is likely that many of those prescriptions reached patients who did not otherwise have easy access to naloxone.

Providers’ willingness to prescribe naloxone to patients appears to have increased over time from the early 2000s to today, suggesting that, as the overdose epidemic worsened, providers became more amenable to the intervention. This may be due to increased awareness around naloxone prescribing, increased empowerment among providers to participate in prevention efforts, and/or the advent of simpler naloxone formulations intended for lay use.

Most program evaluation studies reported on formal clinic-wide naloxone prescribing programs, as opposed to passive recommendations to prescribe naloxone. Rationales for implementing a structured program include: (1) naloxone prescribing is still novel in many primary care settings and there are currently no formal, national guidelines on how to integrate naloxone into primary care practice, (2) historically there have been logistical barriers to prescribing such as obtaining atomizers for the off-label intranasal naloxone device, and (3) a formal program links naloxone prescribing to broader opioid stewardship efforts enacted on a clinic-wide scale. As clinic-based naloxone prescribing becomes more widespread, it may allow the intervention to become an integrated part of panel management without the need for formal programming. In the meantime, such as with other preventative interventions like vaccinations and cancer screenings, clinic-wide programs can offer essential reminders, support, and instruction for providers for whom it is not yet part of standard care. Overall, there was considerable diversity between the training models represented in the studies, suggesting that programs can adapt and modify training approaches to best fit clinic needs.

Implementing a universal prescribing model – as used in many studies in this review – could be useful for integrating naloxone into standard clinical practice as it may alleviate complicated decision making processes for providers and quell concerns around evaluating patients' risk for overdose, remembering who to prescribe to, and fear of singling out or offending patients. Furthermore, a universal model may help decrease stigma and initiate communication between providers and patients around opioid use, overdose risk, and pain management. Naloxone prescribing may benefit from being

paired with an educational, counseling or interpersonal intervention, as results suggest that the act of prescribing naloxone itself could have ancillary benefits related to safer opioid use behaviors. Further research is needed to determine both the optimal indications for naloxone and the efficacy of naloxone prescribing in decreasing overdose among patients prescribed opioids and their immediate social networks.

**Limitations**

This systematic review has limitations. First, the sample size is relatively small and is limited only to US published studies. Methodological limitations of the studies (e.g. most were descriptive or observational) prevented us from assessing the efficacy of naloxone prescribing in primary care, although assessing naloxone prescribing with more rigorous study designs such as randomized-controlled trials is challenged by substantial logistical and ethical barriers. Finally, this review may not be comprehensive of all clinic-based naloxone interventions as it only includes published studies, thereby excluding naloxone prescribing interventions that have not been published.

**Conclusions**

Naloxone prescribing in a primary care setting is an acceptable and feasible intervention. Primary care is a strategic point of naloxone distribution as it may help destigmatize the medication, connect it to larger opioid stewardship efforts, and expand access to individuals who otherwise may lack awareness or access.

# Chapter 3

## "Chasing the Pain Relief, Not the High": Experiences Managing Pain after Opioid Reductions among Patients with HIV and a History of Substance Use

### Background

Opioid overdose mortality continues to increase in the United States despite significant investments to reverse the epidemic. The national response to-date has focused primarily on reducing prescribing of opioid pain relievers (OPRs), justified by evidence that long-term OPR therapy has no greater effect on chronic non-cancer pain than acetaminophen or non-steroidal anti-inflammatory agents, and carries greater risks.[63,83] However, reductions in prescribing also carry risks: barriers to accessing opioids may have led to increased pain and decreased function in some patients,[84] and evidence suggests that reductions in OPR prescribing may result in increased illicit opioid use.[84,85] Most importantly, mortality has paradoxically increased concordant with reductions in prescribing.[84–86]

The Centers for Disease Control and Prevention (CDC) Opioid Prescribing Guidelines recommend against using OPRs as first line therapy for managing chronic pain, and instead endorses nonpharmacological therapies such as behavioral, movement-based or integrative therapies.[63] While evidence about the effectiveness of these modalities is limited, a systematic review of noninvasive nonpharmacological treatments for chronic pain suggests that exercise, multidisciplinary rehabilitation, acupuncture, cognitive behavioral therapy, and mind-body practices were associated with improvements in pain and function among patients with selected chronic pain conditions.[87] However, there are a multitude of barriers to accessing these therapies, such as insufficient insurance

coverage, limited referral options, and logistical challenges. Moreover, the CDC guidelines are focused on opioid-naïve patients and authors recently clarified that the dose limitations and related recommendations were never intended to apply to patients already maintained on long-term OPRs

When OPRs are reduced or discontinued, patients may experience uncontrolled pain, psychological distress, and transitions to illicit substances.[75,88] Veterans' Administration data suggest that patients discontinued from OPRs may have been more likely to die of suicide than those not discontinued.[89] Retrospective research has found that patients with a history of substance use,[11,12,90] on a high daily dose of opioids,[63] and with multiple pain complaints may be at heightened risk of transitioning to illicit opioids.[13]

People living with HIV (PLWH) may be at particularly high-risk in the context of changing prescribing practices, as they suffer from high rates of multiple medical disorders that increase the likelihood of chronic pain, the risks associated with OPR therapy, and social and environmental challenges.[91] PLWH also have unique causes of pain, such as HIV-associated neuropathy, and higher prevalence of substance use disorders.[92] Moreover, early HIV care was associated with palliative care medicine, thus many patients have already been provided OPRs long-term.[93,94]

There is little research documenting PLHW's lived experiences managing their pain after losing access to prescribed opioids. It is critical to gain greater insight into patients' pain management experiences during this transitional period in order to develop appropriate,

patient-centered opioid prescribing recommendations. In this study we qualitatively explored PLWH's chronic pain management attempts after long-term opioid therapy reductions or discontinuations. We focus specifically on the patients' rationales for and description of barriers and facilitators to non-clinical pain management modalities.

## Methods

### Study Sample

Participants were recruited in 2018 from a longitudinal cohort study to assess the impact of prescribing changes among patients with chronic pain (N=300) in San Francisco (COPING Study). Participants in COPING were recruited from safety-net clinics, had been prescribed long-term opioids (≥3 months) for chronic non-cancer pain for at least three of the 12 months prior to enrollment, and had a history of illicit opioid, cocaine, or methamphetamine use. Participants for this nested qualitative study were also HIV-positive and had been reduced or discontinued from OPRs in preceding 12 months.

### Data collection and analysis

We qualitatively analyzed 18 interviews, stopping once theoretical saturation was reached.[95,96] An interviewer trained in qualitative methods (EB) conducted the interviews which lasted approximately 45 minutes and took place at the San Francisco Department of Public Health. Participants were compensated $30.

Interviews were audio-recorded and transcribed verbatim, after which data were entered into Atlas.ti (Version 8). We used content analysis to expose emergent data through

descriptive summaries. This method of qualitative description, rooted in phenomenology, is best suited for moments of early exploration when outcomes are focused on exposition instead of hypothesis or theory generation.[97,98] Two analysts (EB, RB) independently reviewed the interviews and extracted emergent themes to inform the development of a master codebook. *A priori* and inductively-generated codes were compared and discrepancies discussed until consensus was formed and the codebook finalized. Analysts then coded the interviews and measured interrater reliability. Upon completion of the process, results were organized into thematic findings.

## Results

### Demographics

Sixty-one percent of participants were male with a mean age of 55; 44% were African American and 44% were White. All participants were HIV-positive, actively engaged in primary care, and had a lifetime history of illicit substance use. Sixty-seven percent reported using illicit substances within the past year, including non-prescription opioids/heroin (75%), and stimulant use (83%) (Table 3.1).

**Table 3.1. Demographics and Substance Use (N=18)**

| | **N** | **%** |
|---|---|---|
| **Gender** | | |
| Male | 11 | 61% |
| Female | 6 | 33% |
| Transfemale | 1 | 6% |
| **Race** | | |
| Black | 8 | 44% |
| White | 8 | 44% |
| Other | 1 | 6% |
| N/A | 1 | 6% |
| **Age, mean** | 55.4 | |
| **Substance use, lifetime** | 18 | 100% |
| Opioids | 11 | 61% |
| Stimulants | 14 | 78% |
| **Substance use, prior 12 months** | 12 | 67% |
| Opioids | 11 | 61% |
| Stimulants | 10 | 56% |

Overall, the vast majority of participants neither connected their pain to their HIV, nor reported that their HIV was affected by changes in OPR prescriptions. Because of this, even though the population was comprised of PLWH, our analysis does not focus on HIV specifically. In the results below, we describe four strategies that participants reported using to manage their pain after being reduced/discontinued from opioids: (1) nonpharmacological therapies, (2) illicit opioid analgesics, (3) heroin, and (4) stimulants.

## Nonpharmacological therapies

*Rationale*

Participants reported utilizing a range of nonpharmacological therapies to manage their pain, including physical therapy, acupuncture, massage, yoga, prayer, reading, writing, using marijuana, and attending social support groups. Some participants reported using these therapies because of prior exposure in a clinical setting, as Participant A, a white transfemale in her early-50s, described:

| | |
|---|---|
| Interviewer (I): | Is there anything else you're doing for your pain? |
| Respondent (R): | Just my physical and occupational therapy. |
| I: | Okay. And how often do you do those? |
| R: | They gave me…I don't have the therapist come visit anymore but I still do the exercises every day. |

Other participants described using nonpharmacological therapies because they were legal. For instance, Participant B, a black male in his early-60s, reported refraining from illicit opioid use for fear of jeopardizing his active prescription:

> I tried to do everything right [to manage pain]. I didn't go to the street to cop some, even though I wanted to. I wanted to go to the street so bad and cop me some, try to get me some pills…I said, "I'm not gonna do nothing wrong."

In lieu of illicit opioids, Participant B reported exercising, weight lifting, and attending physical therapy to manage his pain.

*Barriers*

Many participants encountered barriers when using nonpharmacological therapies including issues related to accessibility and availability. For instance, Participant C, a black male in his late-40s, benefited from physical therapy, but ultimately lost access to the service because of payer coverage limitations:

> R: While I was on codeine we did physical therapy, and after eight sessions we noticed that the [prescribed opioid] dosage was going backwards. So instead of six or eight [codeine pills per day], I was back to three…you know, it's lower… [But] right after that, the sessions stopped. They only gave me eight [sessions]…
> I: And why did they only give you eight physical therapy sessions?
> R: They said Medi-Cal only covers eight sessions.

Similar to Participant C's experience with physical therapy, Participant D, a white male in his late-30s, described benefiting from acupuncture but ultimately discontinuing the therapy because of the out-of-pocket expenses:

> R: It [acupuncture] really fucking helped. They wanted me to pay money…There was this sliding scale thing, but I can't afford even what they were asking. Even as beneficial as I felt it was, and I don't care if it's placebo effect or what, but in my world, if I'm not hurting, and I'm taking a least amount of opiates, then I'm doing something right.
> I: Have you talked to your doctor about being able to get the acupuncture prescribed?
> R: Medi-Cal will not pay for that.

In both examples, participants reported that nonpharmacological therapies such as physical therapy and acupuncture decreased both pain and OPR consumption. These pain management modalities, however, were unsustainable due to administrative barriers related to payer coverage.

Participants also noted logistical barriers to accessing nonpharmacological therapies such as availability and accessibility. Participant E, a white female in her early-50s, explained that, while acupuncture had been beneficial, its availability was limited:

> [Acupuncture] was helping in the beginning…but…I can't have acupuncture any time I want it…I can't call somebody up and go, 'Well, I'm really in pain, it's two o'clock in the morning, can you come over and do this for me?' …So it works, but it doesn't work all the time.

Similarly, Participant F, a black male in his mid-50s, reported the geographic distance to pain management services as a barrier:

> I met with these pain management people…about how to basically control it and the steps. "But we're gonna do that for you and you have to come here." It's like, "You know, you lost your mind. [Laugh.] I'm not going through all of that. Are you crazy? …It's not like going on…a freaking bus ride across the city to go to [location of pain management services] every so many hours.

These narratives are illustrative of the range of barriers participants encountered when attempting to access and sustain nonpharmacological pain management services.

*Facilitators/Benefits*

Many participants found that nonpharmacological therapies reduced both pain and opioid intake. In addition, participants noted ancillary benefits, such as general enjoyment of the intervention and psychological improvements. Participant F explained his positive experience using exercise as a means of pain management: “Exercise and stretching and walking. I walk a lot. I do like to walk…it also helps this little body of mine keep moving…I love that part.”

Participant G, a black woman in her late-60s, described the benefits of passive nonpharmacological approaches that she discovered on her own: “I read, yeah, I read, I listen to music, and sometimes I just walk. Whenever I’m in pain, I just get up and walk around the block, take my mind off of it or whatever.” In addition, she reported benefiting from an HIV support group even though it was not focused on pain management:

> I go to these support groups...And they’re not really about pain, you know, but it... helps me…It don’t need me to just sit around and think about my pain, you know… I don’t know about how it would help somebody else, but it helps me to take my mind off my pain.

Similarly, Participant F described prayer as an approach to manage his pain: “I pray a lot… Gets your mind off what the hell you doing… I’m just a religious individual. I love God and God loves me, and he keeps me moving, honey.”

The diversity of nonpharmacological approaches (from physical to passive therapies) suggests that participants are managing different elements of their pain with different coping mechanisms.

**Overview of illicit substance use**

The majority of participants reported using illicit substances to decrease physical pain, while some reported also using to decrease psychosocial pain and increase function. As such, many participants described their substance use as an emotionally charged experience. Participant H, a white male in his late-40s, explained this phenomenon: “I’m not looking at it recreationally…I just don’t wanna suffer.”

Many participants described a similar feeling of desperation. Participant J, a black woman in her early-60s, describes this sensation by saying she would do, “anything [to] stop the pain, I don’t care, you know.”

In fact, many participants indicated that their ideal pain management regimen was reverting back to their prior prescription. Participant K, a black woman in her mid-60s, stated:

> I: What’s your ideal [pain management regimen]?
> R: Where my medication was a year and a half ago…That’s when I was really ideal…I mean, the difference in the pain that I experience now…even my body is broke down.

These sentiments illustrate that, for many participants, self-managing their pain illicitly was not a preferred solution but rather one of last resort.

## Illicit Opioid Analgesics

*Rationale*

Many participants reported their rationale for using illicit opioids was to replicate their prior opioid prescription after having been reduced or discontinued. For instance, Participant L, a black female in her late-50s, explained that after being reduced from methadone prescribed for pain, she "would use the same that…the same thing [to] what I use[d]. I would use [the same] pills".

Another participant (Participant M – a white male in his mid-50s) described trying to replicate his prior methadone prescription after it was reduced:

> R: I'm used to the feeling that [methadone pills] gives me when I take them…But any other pills, no, I can't do it…I don't like the way it makes me feel...I ran out [of my prescription] a couple times. I went to the street and asked certain people and they would give them to me...Sometimes [I buy] three at a time, so this way I'll be able to have them…And never other than that [methadone pills]. Other than that, none.
> I: And when you were getting eight pills a day from your doctor [previous dose], at that point, were you buying pills from the street as well?
> R: No I wasn't... [I started buying] ever since he's [my provider] started lowering them [prescribed methadone], lowering, lowering them.

Here, Participant M described experimenting with other pills to identify his ideal pain management regimen, but reported ultimately seeking out methadone, the same medication he was prescribed by his provider. Participant N, a mixed-raced woman in her

early-50s, also reported seeking an approximation for her prescription from the street when she was unable to access timely refills:

> She [her provider] gives me my pain killers according to her schedule. And if you miss an appointment, they don't give you your pain killers, and they don't care if you [go into] withdrawal. I had to buy oxycodone on the street sometimes at a dollar a [milli]gram.

*Barriers*

Accessing illicit opioid analgesics was complicated and participants reported a number of barriers to navigating the underground system, including logistical (unpredictable purity, cost, and insufficient options), and knowledge-based (lack of experience and lack of risk reduction education).

One participant (Participant K) described managing logistical barriers by transitioning from illicit prescription opioids to heroin due to fear of impurities and unreliability in the illicit prescription opioid supply:

> R: They started making [fake prescription] pills…And I won't go for that…They got more loyalty in the illicit than they do in the licit. I mean, in the real prescribed medication, they got more cheating going on in that.

Other participants noted cost as a barrier to obtaining illicit opioids. For instance, Participant L bought methadone from the street after her prescription was reduced, but cost ultimately became a barrier: "There's still pain, but I just can't afford to go out and pay ten dollars for a pill. I can't afford that." Instead, Participant L reported replacing

methadone with alternative modalities that were more affordable including writing, coloring, reading, prayer and using crack cocaine.

Participants who lacked experience using illicit substances identified knowledge-based barriers when using illicit opioids to manage pain. For instance, Participant H described relying on peers to access his supply because he was unfamiliar with the black market:

> I got [methadone] from my friend who would go get it for me; 'cause I don't know how to buy drugs. I know how to pay for them but I don't know how to walk on the street and say, 'You, you...' You know, like 'Who has the crack? Who has the speed?' You know what I mean? Like I don't know how to do that.

Similarly, Participant N reported never using illicit opioids prior to being prescribed opioids and relied on others to procure illicit opioids when she would run out of her prescription early:

> I: You said that three months into being at [clinic] was the first time you bought pills [oxycodone] from the street. Can you tell me how you knew where to go, how you knew what to buy, what that experience was like?
> R: Actually I didn't. My home care provider [informal caregiver] saw me and he went and got them for me.
> I: Okay. Can you tell me more about that?
> R: I was screaming. I was going up on my third day and he started crying too, "You can't stay this way, when are the pills coming?" I told him probably Tuesday and this was on Sunday night and he said, "You can't stay this way." And so he went and got them.

In addition to being unable to access illicit opioids herself because of lack of experience, Participant N also reported a substantial financial burden of purchasing oxycodone from the street: "Since I've been at [clinic], I've probably spent $7,000…Since I've been at

[clinic] I haven't seen my kids. You know, it's all about the oxycodone. I can't save money to go visit my kids when I'm buying street drugs."

When Participant N had insufficient funds to access illicit oxycodone, she reported going through withdrawal which, in one instance, led to an overdose event:

> I: Had you been using any oxycodone the days prior [to the overdose]?
> R: No, there was no money.
> R: I'm like going, "I can handle this." And I was taking Excedrin…and I told myself I had the flu…So I was just vomiting…And then finally my medication came in and like I told you I took it and I dozed off. So when I woke up I took another. And that was it. About a few minutes later I thought I was going to vomit and then boom, everything started dimming out for me. And that's weird, I've never done that before…It's like the lights started going out slowly, it started turning black.

*Facilitators/Benefits*

Some participants benefited from their knowledge about street-drug use and were able to manage the transition with greater ease than others. Participant D, for instance, reported understanding how to navigate the black market:

> I'm a gay man in San Francisco and I have an internet connection. So there's websites and apps that within five minutes of logging on you can have relations, you can have sex, and you can have whatever drug you want; five, ten minutes.

Similarly, Participant J expressed easily accessing illicit opioids when she needed to supplement her prescription after reduction:

> I have to go buy some down in the [neighborhood], wholesale. They charge like $2, $3 a pill…Oh, I don't have a problem. I'm a diva! I go in all neighborhoods, I don't care how rough it is, when I go through they open up.

Participant H explained the benefit of having a "safety net" supply of illicit opioids in case he encountered delays or gaps in his prescription:

> I: What have you been doing for the last month [during an opioid prescription gap]?
> R: Buying them from my friend…I buy two pills a week and that's eight doses, and I take one a day. I'm very good at having a back-up or the net under the wire…So if I fall off the wire I'll hit the net. I plan ahead. I don't wanna suffer ever.

In having a "back-up" plan, Participant H ensured that he was able to maintain his pain management regimen even amidst prescription breaks.

**Heroin**

*Rationale*

While many participants described a desire to replicate their prior opioid prescription, some reported managing their pain with heroin instead. For some participants this was because they had a history of heroin use, while for others, it was a response to the barriers they encountered when attempting to access illicit opioid pills.

Participant K had a prior history of heroin use and described increasing her use to ensure her pain relief was sustained after her opioid prescription was reduced:

R: I kind of like substitute my medicine [with heroin] so it lasts…I make it up by doing the right dose for three days, and for two days I'll substitute the other missing portion with the heroin and it brings it up to that same level.
I: So before your opiates were reduced, how often would you say, just roughly, were you using heroin?
R: Maybe once every two or three months.
I: And then once your opiates were reduced, how often would you say you were using heroin?
R: Once every two or three days.

While some participants increased their current heroin use, others initiated heroin for the first time. Participant E, for instance, had a history of stimulant use, yet reported never having used heroin prior to when her prescription opioids were reduced, and described the transition as a last resort:

> I mean, I've done pills; I've taken some because they were the thing that was there. 'Cause basically, I'm doing it for pain management. It wasn't like it, "I prefer heroin over this." But heroin's just easy to get, and not as expensive as everything else.

In addition to the ease and cost benefits, Participant E began using heroin because she was "chasing the pain relief":

> Heroin was really not the appealing thing. The appealing thing was when…someone said, "Well, this will help your hands. This will help your knees." And…I did it, and it did. You know, I was nauseous and stuff but the pain was relieved really well. And unfortunately, the pain relief was almost like getting high would be to somebody else. That's what got me wanting to use it more, more, more because it wasn't getting high from it. It was because I wasn't hurting anymore...So that's what made me wanna do it, even though I knew that this is not a good road to go down…It was chasing the pain relief, not the high.

Similarly, Participant O, a white male in his mid-40s, expressed his rationale for using was because of a desire to be pain-free. Here he described watching someone fall into a heavy nod after injecting heroin:

R: It just looked like they were like really, really, excuse my language, fucked up, you know what I mean? And it looked very, very, very comfortable...You know what I mean? And very pain-free…And I wanted that, you know.
I: When you say people were…pain-free, what do you mean by that?
R: They were comfortably numb…Not numb and the feelings of like, emotionally, which I'm sure they were too, man, but…I just wanted not to, you know, feel pain. I mean, I've been living with pain all my life, man.

*Barriers*

Participants described a number of barriers around heroin use including lack of education about the drug, negative health effects, inaccessibility, and social stigma.

Participant P, a mixed-race male in his mid-50s, transitioned from methamphetamines to heroin and described his lack of education as a barrier to safe use:

> About four months ago I almost OD'ed...I decided to change my drug of choice, and I didn't know the right amount to do. I did too much… They had to give me a shot of Narcan [to reverse the overdose].

Participant D had a history of injection stimulant use but had never used heroin prior to his prescription reduction and described his lack of knowledge around heroin injection as a barrier:

> I couldn't find any pills anywhere to make up for what she [his provider] had taken away. All of a sudden, I mean, I was sick. I'd… never shot up. I didn't know how to cook it [heroin] up or nothing. And believe it or not, the person that I went to ask about it, they didn't want to do it, but they were behind in rent and I had cash, and I said, "I'll pay your rent if you'll teach me how to do this. I just want to know how

> to do it right and not hurt myself."…He said, "The things that you look out for is when you have trouble breathing, Narcan yourself. If you are getting too sleepy too quickly, Narcan yourself. If you feel odd after you do a shot, Narcan yourself. If you still feel odd, and another dose does nothing, call 911." He was like, "You've been doing drugs for many years. There's no reason that you have to die because a doctor's not taking care of you.

While Participant D had access to risk reduction and overdose education, he still identified barriers around his heroin use, including social stigma:

> At the time I started having to use heroin, I had not used a syringe in almost a year. And I'd been shooting crystal meth since I was thirteen…It's sad that she [provider] has decided to mess with my pain medication, where [previously] I could just take a pill and things were fine, to [now] sticking myself. Heroin in the gay community [is] looked down on by other users. And no matter what your background, your education or how your life is going, you could be perfect, but they see it [heroin] is not clear like meth [and] immediately, you're not trusted anymore. There's this very bad stigma that goes along with it.

*Facilitators/Benefits*

Some participants' experiences were facilitated by their comfort accessing heroin, and their ability to independently manage and monitor their use, as Participant K described:

> I knew what to do, and I knew where to go…And I ingested [heroin] just like I ingested with my medication to arrive at the comfort zone on legal medicine. I had to learn that same approach with my illicit drug usage.

Here Participant K illustrated that even knowledgeable users may undergo a process to learn their ideal pain management regimen. Participant K explained employing risk reduction techniques, like cautious dosing and consistent suppliers, to ensure her safety:

> They [her provider] started dropping me because of the state regulatory crap. But the state don't regulate my body and it don't regulate my pain, so I regulate it…I do what I have to. …I know better than to hurt me. I know when I've reached the level and I have sense enough to find the right individual to purchase my illicit products from…They have the same thing, and when they change [my supply], they let me know honestly. We have that kind of rapport. It's like [my dealer is] my pharmacist and we keep it like that.

Participant K described a shadow-medical system in which she is her own advocate and pain specialist. By referring to her dealer as her pharmacist, she further emphasizes the medicalization of her heroin use.

Another reported benefit of heroin was improvement to participants' function/productivity that had declined due to unmanaged pain. Participant E described:

> R: And then at about forty milligrams [of prescribed methadone, reduced from previous dose] a day I couldn't take it anymore. I couldn't do it anymore... Things…weren't getting done because I couldn't do them. I couldn't get on my knees to…wash the kitchen floor well.
> I: And is that because the pain was not being managed?
> R: Correct…So then I started using so that I could get things done. So I could get to the grocery store…Things like that.
> I: So when you say you started using then, what were you using?
> R: Heroin.

Heroin was able to suppress Participant E's pain to allow her to accomplish household chores like cleaning and grocery shopping.

## Stimulants

*Rationale*

Many participants identified pain management as their primary rationale for using stimulants, as Participant M explained:

> I: When was the last time that you used cocaine?
> R: Maybe last week…Because I had no opiates to help the pain. No methadone. So I sniffed it [cocaine]…the pain went away.

Similarly, Participant P reported using methamphetamines recreationally however also noted that he increased his use when feeling pain:

> I: Does it [methamphetamines] have any effect on your pain in any way?
> R: It gets rid of the pain.
> I: Did you change…the amount of meth that you used once you started feeling more pain in your hands and feet?
> R: I'd do a lot. [A] whole syringe full.

Participant O also expressed feeling pain relief after using methamphetamines:

> I: So you use it [methamphetamines] sometimes but not consistently.
> R: Yeah. And I only use it when like... I miss going to the [methadone] clinic that day to actually dose, right?
> I: Uh-huh.
> R: For me…a shot of methamphetamine will sometimes be better than...like a pain pill to take the pain away.
> I: So sometimes you'll use meth when you've missed a dose and you need to control your pain?
> R: And I'm starting to feel sick. And the pain's coming... Yeah, yeah, I'll do it like that, and it'll work better than if I took, you know, some type of pain medication to substitute; and not all doctors understand that.

Most participants who reported using stimulants had a history of stimulant use and did not seek it out explicitly to manage their pain. Nevertheless, many still identified it as a tool they used to manage their pain.

*Barriers*

Counter to the descriptions above, some participants reported that stimulants were inadequate at managing pain, as described by Participant E:

> Speed did some good, it helped with my pain. Back in the day, it would help with the pain, but then it would make more pain when I'd come down.

Similarly, Participant L explained that crack cocaine increased his pain:

> R: If I smoke too much crack, then it's [my current opioid prescription] not enough, no.
> I: So what happens when you smoke crack?
> R: When you smoke too much crack? It take the methadone out of your system and make the pain, you know, makes it more painful.

While many participants used stimulants to manage pain, its success varied, and for many, feeling increased pain as stimulants wore off was a significant barrier.

*Facilitators/Benefits*

While participants' narratives around stimulant use for pain management varied, a number of participants identified alternative benefits to their stimulant use, including managing psychosocial challenges and increasing productivity.

For instance, Participant L reported that crack was a facilitator to cope with the emotional burden of his life, connecting his use to difficulties around managing loss:

> Every month it's a struggle, 'cause somebody's… I'll have my whole family is deceased, so each month it's a struggle; it's somebody's death anniversary. It's my birthday and everybody gone, so that's harder alone. And that's hard itself, you know.

Participant L continued to describe also using crack to increase productivity: "When I buy a piece of crack, I'm buying false energy…I'm trying to get something done, I use it. Just to be buying it for the hell of it? No, I buy it for a reason."

Participants identified productivity and psychosocial management as non-physical benefits of using stimulants.

## Discussion

After being reduced/discontinued from prescribed OPRs, many participants reported being left out of the traditional medical system and tasked with becoming their own pain management specialists: independently assessing their pain and developing informal pain management solutions including nonpharmacological therapies and illicit opioids, heroin and stimulant use. Most participants described embarking on thoughtful and intentional journeys of self-managing pain that included multimodal experimentation. Cost, payer coverage and the geo-location of nonpharmacological interventions served as structural barriers that hindered initiation and ongoing access to nonpharmacological

treatments. Most participants who turned to illicit substances did so after exhausting other options.

In the absence of clear medical guidance, participants described utilizing a range of approaches, often without a clear understanding about the appropriateness or effectiveness of the interventions. Current evidence suggests that the effectiveness of nonpharmacological therapies varies by type and duration of intervention and pain complaint.[87] When patients experiment with therapies outside a medical setting, they do so in the absence of clinical scientific evidence, thus hindering their ability to target and optimize treatment. Provided outside the context of coordinated medical care, the therapeutic benefits of nonpharmacological options may be reduced and may increase reliance on illicit substances.[87,99]

OPR reductions/discontinuations may be particularly traumatizing and physically taxing for patients who have been maintained on opioids for long periods of time, due to significant and difficult-to-reverse changes in body function, neuroplasticity, and the physical and psychological perception of pain.[88] This may be particularly relevant for PLWH who may be likely to have a history of receiving long-term opioid therapy. Among many barriers to safely tapering opioid-experienced patients is protracted abstinence syndrome, which is caused by allostatic changes due to opioid tolerance and/or dependence, and can result in extended withdrawal symptoms (e.g. anxiety, depression, fatigue, increased pain etc.) that last for years and may have substantial negative consequences on patients' physical, psychological, and psychiatric wellbeing.[84,88,89,100]

The therapeutic and clinical complexities that make opioid-experienced patients distinct from their opioid-naïve counterparts must be accounted for in the development of opioid stewardship guidelines.[84,88,101] This may have contributed to our participant populations' high rates of reported illicit substance use. The FDA has recognized the dangerous and potentially life-threatening consequences of overly-simplified tapering guidelines for opioid-experienced patients and now recommends gradual, individualized tapering plans built in conjunction with patients to modulate risk of serious withdrawal symptoms, uncontrolled pain, psychological distress, emergence or reemergence of substance use disorder, violence, or suicide.[84]

Patient's experiences of pain and capacity to access therapies are multifaceted and complex. Recognizing the various issues that may affect how a patient is able to manage physical and psychological pain may help providers manage long-term opioid therapy. Considering opioid experience, substance use, and social and psychosocial supports are essential prior to discussing a taper of prescribed OPRs. Providers should recognize the significant impact that any reduction in OPR prescriptions may have on a patients, as some may begin supplementing prescriptions with street drugs during prescription gaps or during a taper, which complicates pain management efforts and clinical evaluation. To manage opioid-experienced patients, it is critical for providers to develop a patient-centered pain management and, if indicated, opioid reduction plan, in conjunction with the patients, and to pay close attention to patients' well-being during this vulnerable period.

## Limitations

Our study has several limitations. First, these data were collected via self-report during in-person interviews, which may lead to social-desirability or recall biases. Second, participants were HIV-positive and had a history of some substance use, thus their experiences may not be generalizable to a wider audience. Finally, our analysis was driven by a small sample size which did not include provider perspectives.

## Conclusions

When losing access to opioid therapy for chronic non-cancer pain, patients pro-actively self-manage symptoms outside of the traditional medical system. Patients experiment with a range of pain management modalities including nonpharmacological therapies and illicit substance use. For patients with a history of substance use, illicit drugs are a common remedy, including both opioids and stimulants, with a range of noted barriers and benefits. When providers make any changes to patients' long-term opioid therapy, a holistic and patient-centered approach should be considered.

# Chapter 4

## Perceived Causes of Personal versus Witnessed Overdoses among People who Inject Opioids

### Background

Drug overdose is the leading cause of injury-related death in the United States, outpacing deaths from guns, motor vehicles, and HIV each in their respective peak-death years (National Institute on Drug Abuse [NIDA], 2019). In 2017, more than 70,200 individuals died from drug overdose, the vast majority of which involved opioids (NIDA, 2019). As synthetic opiates such as fentanyl penetrate the street drug market in the US, people who inject drugs (PWID) remain at heightened risk of experiencing and witnessing overdose events [103].

Extensive research has identified common opioid overdose risk factors such as prior overdose [46,47], polysubstance use (e.g. opioid use with alcohol or benzodiazepines) [48,49], change in tolerance [50–52], and injection frequency [53]. Risk reduction education is often provided to PWID through low-threshold services such as syringe exchanges. Research shows that PWID who receive overdose education are knowledgeable around risk factors and are able to recognize and respond to an overdose, particularly with the use of naloxone, the opioid antagonist used to reverse the effects of an opioid overdose [104–107].

Notwithstanding PWID knowledge of overdose risks, several studies suggest that some opioid users may nonetheless present an optimistic bias, whereby even high-risk individuals may perceive their overdose risk to be significantly lower than their peers [54–

[56]. No study, however, has explored how this bias is operationalized, which may limit the effectiveness of current overdose prevention interventions. To further explore this, we sought to assess the way individuals attribute causation of personal versus witnessed overdose experiences. Deeper understanding of differences in perceived causes of overdose may help explain the presented optimism and inform the development of patient-centered, evidence-based behavioral interventions to reduce risky overdose behavior.

## Theoretical frameworks

### *The actor observer bias*

The actor observer bias (AOB) is a concept drawn from social psychology that posits that individuals may be more likely to assign responsibility for their own actions to situational causes (e.g. external/environmental factors), while ascribing responsibility for others' actions to dispositional causes (e.g. internal/personal characteristics) [108–113]. For example, imagine a car accident caused by a driver who does not stop at a red traffic light. When asked what led to the event, the driver of the car responsible for the accident may attribute blame to a fallen tree branch blocking his ability to see the traffic light. Conversely, the person whose car was struck may be more likely to attribute blame to the drivers' inexperience or reckless driving. In this example, the driver (the actor) has attributed blame to situational causes, while the witness (the observer) has attributed blame to dispositional factors.

The AOB is particularly salient when applied to events with negative outcomes [114]. The AOB, however, has not frequently been applied in public health, and to our knowledge has never been applied to risky drug using behavior. In our analysis, we explore how the AOB can elucidate the different explanatory models used by participants to describe their personal overdose experiences versus those they have witnessed.

*Intragroup stigma*

Stigma is a complex and dynamic concept that exists when individuals experience structured status loss or discrimination due to specific societally-constructed "negative" characteristic attributed to him/her [115]. Stigma can have significant health consequences on a person and has been linked to increased risk in stress, hypertension and other significant health problems [115]. Stigma is also enduring - there are often long-term ramifications of stigma even after someone has left their stigmatized group [116]. The concept of stigma is important to consider in our analysis because it is widely noted that PWID experience significantly higher rates of stigma than the general population [117–120].

Intragroup stigma is a concept that describes the process by which people from within a stigmatized group perpetuate the principles of stigma within their own group. Goffman explains that people have a tendency to develop a hierarchy within their own marginalized group and stigmatize the most vulnerable within that population [121]. Consequently, intragroup stigma is most commonly applied to people in a group that exhibit the most extreme version of the negative characteristic being stigmatized. Intragroup stigma may

be more likely to appear when stigmatized groups are highly heterogeneous or easily stratified [122].

Researchers have demonstrated numerous examples of intragroup stigma within the PWID community. For example: heroin users may stigmatize other heroin users who are perceived as lacking control of their substance use [123]; PWID may stigmatize other PWID who contract Hepatitis C [124]; and female substance users may stigmatize other women based on their substance of choice [125]. In our analysis, we explore how intragroup stigma may be applied to PWID who have experienced an opioid overdose.

## Methods

### *Study sample*

Participants were enrolled in REBOOT, a randomized-controlled behavioral intervention to reduce overdose among opioid users in San Francisco (N=63), conducted from 2014-2016 (REBOOT Study; ClinicalTrials.gov #NCT02093559). Subjects were aged 18 and older, current injectors of illicit opioids with opioid use disorder, had received take-home naloxone, lived in San Francisco, and had overdosed within the past 5 years. Participants were recruited through street-outreach and print advertisement at syringe access programs in San Francisco and through snowball sampling. The study was approved by the Institutional Review Board at the University of California, San Francisco (CHR 13-11168).

### *Data collection and analysis*

We qualitatively analyzed the first 41 interviews from REBOOT, stopping once theoretical saturation was reached. We excluded one participant for reporting no injection drug use, making our sample 40 participants. Interviews lasted approximately 45 minutes to one hour, were conducted by research associates, and took place at the San Francisco Department of Public Health. Participants were compensated $25 for their time. The interviews occurred during participants' first (baseline) visits, which included additional study activities such as randomization, HCV and HIV testing, a urine drug screen, and a computer-assisted personal interview. The motivational-interviewing (MI)-based counseling intervention consisted of two components: the first half was an MI-based interview about participants' personal and witnessed overdose experiences; the second half was an MI-based counseling session which included information around overdose risk reduction techniques. We analyzed data from the first segment of the REBOOT counseling intervention during which participants were asked open-ended questions about what factors contributed to their most recent personal overdose event and the most recent overdose event they witnessed. Our analysis is based on participants' responses to these questions.

Interviews were audio-recorded and transcribed verbatim, after which data were entered into ATLAS.ti (Version 7.5). Three independent researchers analyzed the data to ensure interrater reliability. We used thematic content analysis to conduct the analysis [126]. The analysts developed a codebook, consisting of both *a priori* codes and codes generated inductively from the data. The codebook was applied to all interviews. New concepts that

emerged during the coding process were discussed and added to the code list. Coding discrepancies were discussed with the entire research team. Upon completion of the coding process, results were organized into thematic findings.

## Results

### *Demographics and overdose experiences*

The study sample of 40 participants was mostly male (73%), white (63%), used heroin in the past four months (98%), and had a mean age of 43 years (SD 11.5). The majority (95%) had experienced homelessness at some point in their life. Eighty percent of participants were sero-positive for hepatitis C virus and 10% for HIV.

**Table 4.1. Demographics, Substance Use and Overdose History (N=40)**

| **Characteristics** | **N** | **%** |
|---|---|---|
| Gender, male | 29 | 73% |
| **Race** | | |
| White | 25 | 63% |
| African American | 6 | 15% |
| Hispanic | 8 | 20% |
| Mixed or other | 1 | 3% |
| Age, mean (SD, range, IQR) | 43 (11.5, 21-60, 34-52) | |
| HIV status, positive | 4 | 10% |
| HCV status, positive | 33 | 83% |
| Ever homeless | 39 | 98% |
| Years of illicit opioid use, lifetime, mean (SD, range, IQR) | 24.5 (11.7, 4-52, 17-33.5) | |
| Heroin use, prior 4 months | 39 | 98% |
| Ever enrolled in substance use treatment program | 35 | 88% |
| Personal ODs, lifetime, mean (SD, range, IQR) | 6.4 (15.9, 1-100, 1-4) | |
| **Personal ODs prior 12 months** | | |
| Zero | 19 | 48% |
| One | 14 | 35% |
| ≥Two | 7 | 18% |
| Witnessed ODs, lifetime, mean (SD, range, IQR) | 14.6 (22.6, 1-100, 3.5-14) | |
| **Witnessed ODs, prior 12 months** | | |
| Zero | 11 | 28% |
| 1-5 | 22 | 55% |
| >5 | 7 | 18% |
| Somewhat/very likely to witness an OD in next 4 months | 25 | 63% |
| Somewhat/very likely to experience an OD in next 4 months | 14 | 35% |

All participants had experienced an opioid overdose in the past five years, with a mean of 6.2 (SD 15.7) overdoses and over half (53%) had overdosed

at least once in the preceding 12 months. All participants had witnessed at least one overdose in their lifetime, with a mean of 14.6 (SD 22.6) witnessed overdoses, and nearly three-quarters (73%) had witnessed at least one overdose in the preceding 12 months. Participants reported believing they were significantly more likely to witness an overdose in the upcoming four months (63%) compared to experiencing an overdose themselves (35%). Most (88%) reported enrolling in a substance use disorder treatment program at least once (Table 4.1).

### ***Personal Overdoses - Contributing Factors***

When participants described the factors leading to their most recent personal overdose experiences, they frequently cited situational, external attributes such as (1) drug volatility and (2) ascribing blame to others.

#### *Drug volatility*

Most participants cited volatility in drug potency, batch or source as the primary contributing factor to their overdose. The majority of participants focused specifically on the strength of the substance, indicating that they were not able to predict when a batch was stronger or weaker than expected. Participant A, a white male in his late 50s, explained that sometimes this is due to inconsistencies in batch preparation. When asked what contributed to his overdose, he stated: “The heroin was better than I…was used to. Yeah. Well, sometimes if they don’t mix it well, there’s a little hot spot.”

Participant B, a Hispanic male in his late 20s, also noted heroin strength as a primary contributing factor:

I: What do you think led up to the OD? Like what was different that time than other times?
R: It was just stronger. It was different stuff. Same thing as his [using partner]. It was just... I don't know. That's the only thing I can think of, which is...it's the luck of the draw.

By alluding to "luck", this participant highlights the unpredictability and irregularity of heroin strength. Change in drug strength, however, is perhaps not always a mystery. In fact, Participant C indicated that she was warned about the strength of the batch, but dismissed the warning due to ongoing overstatements about good drug quality:

I: What was different about that circumstance that led to an overdose? What do you think was the circumstances? Like what was different than the other time?
R: I didn't… I didn't realize how strong the heroin was.
I: That's what it was. Okay.
R: That's it, and all it was… I wasn't trying to OD or anything.
I: Okay. So looking about it aside from not knowing how strong it was, was there anything else that contributed to the overdose?
R: No.
I: Okay. Was it new, a new source, so you didn't know that the dope was that strong?
R: No, no. It was… They were saying, "Oh, it's really strong." But like, you know, everybody says that.

A change in strength could be attributed to either a change in batch, as noted in the examples above, or a change in source, as noted by Participant D, a Hispanic female in her mid-40s:

I: Was there anything different about that time than other times?
R: No.
I: So, what do you think contributed to your own overdose?
R: The person who sold me the dope.

Finally, Participant E, a white male in his mid-30s, outlined a series of evidence-based precautions he took to reduce overdose risk, yet was still unable to prevent his overdose event:

I: Let's switch gears. Talk to me about your experience of overdosing.
R: It only happened once.
I: Okay.
R: I was with a friend, so I wasn't by myself, and I wasn't drinking. I wasn't… I didn't take any benzos or anything like that. I just did, I guess, a stronger batch of dope.

While the situations varied, these participants all identified drug volatility – an external factor – as being the primary contributor to their overdose event.

*Ascribing blame to others*

Some participants cited other individuals as contributing to their most recent overdose event, with explanations ranging from innocent error to malicious intent.

A white female in her late-50s (Participant F) noted that low tolerance due to a period of abstinence contributed to her overdose. Yet when describing the situation, she also noted her friend's role in the event:

I: What else do you think contributed to that overdose?
R: Just the strength. It was just…I hate to say this but my friend, like fixed it for

me.
I: Okay.
R: So, and I kept saying, you know, "Just a tiny, tiny bit." But that probably meant something different to him.

Here, the participant identified herself as taking protective action against an overdose by asking her friend to use only a small amount. However Participant F ceded at least some control of the overdose experience by stating that her friend's interpretation of a small amount may have varied from her definition, thereby also linking attribution of blame to her friend.

Another participant (G), a white male in his mid-50s, described a situation in which he believed others acted with malice. He describes being given a "hot shot" – an impure shot of heroin, either intentionally or unintentionally cut with other substances:

R: We were shooting the same damned dope all day long, and that's what was weird. That one got me, you know, and they don't... I think I was set up. I think I was set up with a hot shot.
I: Had someone made your shot?
R: Well, they handed me a chunk.
I: Uh... hum.
R: It was different than what we were doing.

The examples above, demonstrating participants' tendency to attribute all or partial blame to external forces, supports the first component of the actor observer bias which states that individuals have a tendency to ascribe responsibility for suboptimal events to external/environmental factors.

### *Witnessed Overdoses - Contributing Factors*

When discussing the factors that contributed to witnessed overdoses, many participants cited evidence-based overdose risk factors such as polysubstance use and fluctuations in tolerance. However, in addition to these risk factors, and in contrast to personal overdose descriptions, participants also cited dispositional factors such as personal shortcomings as contributing to witnessed overdose events. These factors fell into two primary categories: (1) greed and (2) inexperience/foolishness. The use of personal characteristics in this section may also represent an expression of intragroup stigma among our participant population.

#### *Greed*

Greed was the most commonly cited personal shortcoming that participants used to describe contributions to witnessed overdoses. By referencing "greed", participants seemed to imply a situation in which someone may have willfully overused, often despite warnings or potential negative consequences. Greed was often not the sole contributor, but rather, was mentioned in conjunction with other high-risk behaviors, as demonstrated by Participant H, a white female in her mid-40s:

I: So you mentioned this a little bit but tell me, what do you think was S's…? Like what caused the overdose?
R: It was the heroin he had (O/V)…
I: Just it was a lot, it was strong? What was that?
R: It was a strong heroin and he did more than he should've. He just got out of jail two days before. He thought he could do as much as I can.
I: Okay.
R: And look at him… He's just… He's a greedy little fucker. That's what's wrong with him.

By mentioning greed in addition to traditional risk factors such as drug strength and reduced tolerance, the participant suggests that personal shortcomings also contributed to this overdose event. Similarly, when Participant J, a male in his late-50s, was asked what led to the overdose he witnessed, he explained: “He just used too much. He had been greedy…That’s the thing; he was being greedy.” Yet another participant (K), a white female in her early-60s shared a similar description:

I: Let me ask you; what do you think were the factors that caused her overdose?
R: Fresh out of jail, fresh out of drugs...
I: Got you...
R: And greed.
I: Explain that. What do you mean?
R: [Imitating person who overdosed] I'm not gonna do half the bag; I'm doing the whole God damned thing.

These examples illustrate participants’ ability to identify evidence-based risk factors (e.g. using after periods of abstinence), yet nonetheless these examples all still include greed as a contributing factor.

*Inexperience/Foolishness*

Participants also identified inexperience and foolishness as primary contributors in many witnessed overdose events. A white male in his late-20s (Participant L) explained how inexperience could contribute to an overdose:

I: Okay… And so, looking back on that event, what… what do you think contributed to this person’s OD?
R: Just the lack of experience, I guess…Lack of tolerance…Kind of silly now that I look at it…Because it’s… ‘Cause it’s just that how silly the person was that hadn’t… you know, that that [overdose] happens to…‘Cause… I guess

they didn't have any experience with what they were doing or something.

Similar to the descriptions of greed in the section above, this participant successfully identified an evidence-based risk factor (reduced tolerance) yet also included a personal shortcoming (inexperience) in his description of the event.

Some participants expressed more overt labels of personal shortcomings, such as foolishness, as noted here by Participant M, a white male in his mid-40s:

I: What do you think led to that incident?
R: Him being stupid and not paying attention to his habit.

Participant N, a male in his mid-20s, articulated a similar sentiment when describing an overdose he witnessed:

R: This was before I would ever think I would ever shoot up, you know, so I just like, "What a dumb girl" like "Why would she do that?" you know. Like I don't know; it was kind of like... it was kind of messed up but like me and a friend were like laughing at her like, "Oh, who's this dumb girl," like, you know, like I don't know. I was young. I was like 18 or 17 or 19; I don't know, somewhere around there. But I just found it kind of like not like funny but like, you know, "What is this girl thinking?" you know.

**Discussion**

All study participants had experienced at least one overdose, making this a particularly high-risk population, but also had previously received take-home naloxone and thus represented a population educated on overdose risk factors. Thus, it is not surprising that participants often cited evidence-based risk factors when describing both personal and

witnessed overdose events. The difference in the explanatory models, therefore, is based on the additional, non-evidence based factors that were frequently included in the descriptions of overdose experiences, which was particularly salient in the descriptions of witnessed overdose events.

Participants described the differences between personal and witnessed overdose events in a manner consistent with intragroup stigma and/or the actor-observer bias. The presence of the AOB and intragroup stigma create an environment whereby PWID may negatively judge other PWID for experiencing an overdose, even when they, themselves, have also experienced an overdose. This could lead to negative health consequences that practitioners should consider addressing in counseling interventions with PWIDs. Below we present two potential theoretical explanations for our findings and suggest how these findings could be incorporated into risk reduction interventions.

First, we identified persistent actor observer bias. PWID often share situational factors (e.g. individuals often buy and use drugs together), thus the actor and observer may have shared insight into the joint external factors present at the time of an overdose event. If someone overdoses in this context, the observer may attribute causation to dispositional/personal factors because the external circumstances are seemingly equivalent for both users, yet only one experienced an overdose. In this case, we found that the observer may discount external, situational factors, and instead focus on the internal characteristics of the individual who overdosed.

Furthermore, the AOB may relate to a self-protection bias, particularly in a time of drug market volatility, heightened overdose risk, and nationwide stigma related to injection drug use. The belief that personal shortcomings contribute to witnessed overdoses may engender a sense of greater agency over one's own overdose risk and may provide a false sense of security.

The AOB helps explain why individuals may be more likely to discount their own overdose risk factors by distinguishing themselves from the persons whose overdoses they witness. This is useful to inform public health interventions. To address this issue, an interventionist could point out the differences between the causal factors noted for personal and witnessed overdose events, suggesting that the witnessed overdose may have actually occurred for similar, difficult to control, reasons as well. Such an exercise could (a) help PWIDs develop a more nuanced explanation of their own overdose events, (b) validate witnessed overdoses by suggesting they may also be influenced by external factors, and (c) promote the universal use of evidence-based safety precautions during episodes of substance use (e.g. "tester shots" to ensure the dose is not too strong, using in the presence of others, and staggered use to ensure someone is not high when each person uses, etc.).

Second, intragroup stigma may also play an important role in shaping PWID's overdose narratives. When participants attribute the cause of witnessed overdoses to personal shortcomings not only do they employ the AOB, but they also propagate intragroup stigma among their peers. When our study participants use negative, emotionally-charged

language such as “greed” and “foolishness” to refer to people who have overdosed, they are harnessing the very stigma often cast on them by the general public and redirecting it to those deemed lower in the PWID hierarchy. While this is a common, often subconscious, occurrence among stigmatized groups [114], it can have harmful effects on relationships, social structures, and drug using practices. Similar to the AOB, this may also produce a false sense of security among PWID who believe they do not embody the negative characteristics of those they stigmatize.

Practitioners should consider integrating the concept of intragroup stigma into counseling interventions. For instance, it is well established that stigma is associated with social isolation [127–129], and social isolation is a recognized risk factor for fatal overdose [130–132]. Thus, casting stigma onto this subpopulation of PWID may further exacerbate their already high risk for overdose. Working with PWID to improve peer and social support and reduce intragroup stigma may be an important tool for promoting safer drug using behavior, such as avoiding drug use in isolated settings.

**Limitations**

Our study has several limitations. First, trial eligibility criteria required that participants had experienced at least one overdose in the past 5 years and had received naloxone, thus making this a particularly high-risk population, but also a population with some baseline knowledge about risk factors and overdose, which may not be generalizable. Second, these data were collected via self-report during in-person interviews, which may lead to social-desirability or recall biases. Finally, our analysis was based on information

captured during the initial section of a counseling session and was not based on a traditional semi-structured qualitative interview guide. The narratives analyzed in this paper occurred prior to counseling, however this context could exacerbate social-desirability bias.

## Conclusion

Among people who inject opioids and are at high-risk for overdose, differences in perceived causes of personal versus witnessed overdose align with the actor observer bias and intragroup stigma. Leveraging these theories in counseling interventions may help to improve peer-based support programs and encourage PWIDs to employ evidence-based safety precautions when using opioids.

# Chapter 5

## Recommendations for Future Policy, Programmatic and Research Development

This dissertation outlines three distinct phases in individuals' opioid-using life-cycles, including when being prescribed opioids, during an opioid taper/discontinuation, and while using illicit opioids. First, we outlined the importance of evaluating the acceptability, feasibility and efficacy of opioid stewardship interventions (e.g., naloxone prescribing) when developing national recommendations and clinical guidelines. Next, we demonstrated the vulnerabilities, barriers and risks that opioid-experienced patients face during opioid tapers, and argued for the development of national guidelines aimed at managing chronic pain and opioid prescribing for opioid-experienced patients. Finally, we illustrated the importance of integrating the overdose experiences of people who inject drugs (PWIDs) into behavioral interventions to reduce overdose risk, promote safer drug use, and improve PWID social support networks. Based on this research, we propose recommendations and implications for future policy creation, programmatic development and expansion, and novel research interventions.

### Acceptability and Feasibility of Naloxone Prescribing in Primary Care Settings: A Systematic Review

#### Policy Recommendations

***Conduct rigorous research on the feasibility, acceptability and efficacy of opioid stewardship interventions prior to inclusion in guidelines.***

- Opioid stewardship activities should be rigorously assessed for feasibility, acceptability and, when possible, effectiveness, before being included in national recommendations. The cadre of opioid stewardship interventions (including but not

limited to: pain agreements, risk assessments, urine drug screens, prescription drug monitoring programs, and naloxone prescribing) are promoted in recommendations at the national, state and clinic-level, yet there is a dearth of data on their feasibility, acceptability or efficacy.[133,134] There is mounting evidence suggesting that many of these interventions may create an environment of clinical policing, strain the patient-provider relationship, and result in patient drop out.[41,135–137]

- Naloxone prescribing has been incorporated into clinical care as a response to the opioid crisis. Our systematic review is a critical first step towards comprehensively assessing the feasibility and acceptability of naloxone prescribing. There was considerable diversity among implementation models represented in our systematic review, suggesting that clinics can adapt naloxone prescribing approaches to best fit clinic needs. Further research is needed to determine both the optimal indications for naloxone prescribing and the efficacy of naloxone prescribing on overdose outcomes. Furthermore, considerable more research is needed around the feasibility, acceptability and efficacy of other opioid stewardship interventions such as prescription drug monitoring programs, risk assessments, and urine drug screens.

***Revise California Naloxone Prescribing Law requiring all prescribers to offer naloxone to qualifying patients.***

- Primary care is a strategic point of naloxone distribution as it may expand access to individuals who otherwise may lack awareness or access, destigmatize the medication, and connect it to larger opioid stewardship efforts.[43] In January 2019, CA Assembly Bill 2760 was signed into law, mandating that all prescribers must offer

naloxone to patients with an opioid prescription above 50MMEs, concurrent benzodiazepines use, or a history of opioid use disorder or overdose. Unfortunately, this law applies a one-size-fits-all model to an intervention that may have varying degrees of utility in different circumstances. Current interpretation implies that all eligible prescribers must comply, even if a prescriber is not the opioid-prescribing provider; a naloxone prescription must be offered at every visit; and naloxone should be prescribed to patients with any substance use disorder, which could include patients with tobacco use disorders with no history of illicit substance use. (Note: given the increased fentanyl contamination in stimulants, naloxone should be accessible to persons who use illicit substances. We argue that the legislation should be explicit about which SUD are included in its mandate). This lack of nuance results in a law that not only targets patients for whom naloxone may not be appropriate, but may increase provider burnout and frustration around the growing requirements of opioid stewardship demands.

- Findings from our systematic review demonstrate the feasibility and acceptability of different clinic-based naloxone prescribing programs throughout the US. Based on our findings, we hypothesize that this law is likely infeasible given the scope of the intervention. Refining the legislation would make naloxone prescribing a more feasible and acceptable intervention. As it stands, the law's emphasis on rote standardization could negatively impact an intervention that otherwise has the potential to improve patient-provider relationships around opioid prescribing, increase patient safety, and decrease opioid-related mortality. Based on our systematic review, we suggest that the State consider modifying the legislation to encourage primary care providers to

offer a naloxone prescription approximately every two years to patients with: ≥50 daily MMEs, concomitant benzodiazepine use, a history of opioid overdose and/or opioid/stimulant use disorder, at risk of witnessing an overdose, or otherwise at risk of experiencing an overdose.

## Research Recommendations

***Evaluate the effects of the Naloxone Prescribing Law in a pre-post analysis of naloxone prescribing.***

- We are well-timed to conduct an effectiveness analysis of the naloxone prescribing law, using a difference-in-difference model to evaluate naloxone prescribing rates before and after the law went into effect, in addition to secondary outcomes such as opioid-related hospital admissions, patient retention in care, and qualitative interviews with patients and providers around the acceptability and feasibility of the naloxone prescribing law.
- As stated above, findings from our systematic review illustrated a range of clinic-based naloxone prescribing implementation strategies. An ideal next step based on these findings would be to evaluate the effectiveness of this state-wide naloxone prescribing initiative to determine the best strategies for integrating policy change into clinical practice.

## Policy Recommendations

***Modify the CDC Guidelines, Prescribing Opioids for Chronic Pain”, to include explicit guidance on managing chronic pain and opioid prescribing among opioid-experienced patients.***

- The CDC Guidelines were formulated with consultation from expert leadership in the field and intended to improve pain management, decrease opioid diversion, and reduce opioid dependence and addiction. During policy formulation the CDC neglected to include sufficient recommendation for pain management among opioid “experienced” patients, however, evidence shows distinct physiological differences between these two populations.[88] Furthermore, the CDC Guidelines’ recommendation to universally limit opioid dosing to below 50/90 daily MMEs may be clinically inappropriate or take years to achieve for many opioid-experienced patients.[84,138]
- Our research illustrates the devastating effects that reducing/discontinuing long-term opioids can have on the health, wellbeing and quality of life for chronic pain patients with a history of substance use. Patients described challenges in managing their pain outside of the medical system, including using illicit substances as a result of their opioid taper, and a number of patients reported using heroin for the first time. Our research supports modifying the CDC Guidelines to provide explicit recommendations on how to manage opioid “experienced” patients, including establishing patient-centered pain management tapering plans, eliminating maximum dosing thresholds, and expanding treatment options, like buprenorphine, for opioid use disorder.

***Demand insurance/payer plans reimburse for nonpharmacological alternatives for pain management as first-line treatment for chronic pain.***

- Most national guidelines now recommend nonpharmacological pain management modalities as first-line therapy for chronic pain patients. However, nonpharmacological treatment options are often not covered by insurance companies, or have limitations on the duration of service. Until insurance companies add nonpharmacological therapies to their formularies, these alternatives will remain inaccessible and unavailable for many patients.
- Our research suggests that patients may benefit from nonpharmacological and noninvasive pain management therapies. In fact, many patients reported improved pain and function and reduced opioid use while using nonpharmacological pain management modalities. Unfortunately, patients were overwhelmingly unable to sustain these treatments due to lack of payer coverage and steep out-of-pocket expenses. Findings from our study should be leveraged as an advocacy tool to demand that insurance companies include sustainable nonpharmacological pain management therapies for patients experiencing chronic pain as first-line treatment options on their formularies.

***Terminate the California Medical Board "Death Certificate Project" which investigates prescribers of overdose descendants.***

- The California Medical Board enacted the "Death Certificate Project" in 2018 – an initiative aimed to identify risky opioid prescribers by cross-referencing opioid-related

death certificates with prescription drug monitoring program data and initiate investigations on providers when appropriate. Identifying “pill mills” and inappropriate opioid prescribing is an important initiative in reducing OUD and overdose. However this project may also put providers practicing “above-board” at risk for investigation as well. Furthermore, the Death Certificate Project is retrospectively evaluating overdose deaths as early as 2012, when opioid prescribing guidelines were significantly more lenient. Punitive initiatives like the Death Certificate Project are becoming more common across the US and can have substantial negative consequences, as threatening disciplinary action (including revoking medical licenses), may incited fear of medicolegal reproductions for many providers.[139] Based on anecdotal evidence from providers across California, this legislation has resulted in rapid opioid tapers and, in some cases, outright patient abandonment.

- Results from our paper “Chasing the Pain Relief” demonstrate the unintended consequences that opioid tapers may have on chronic pain patients, including the physical, emotional, financial, and psychological burden. The California Medical Board should not focus so singularly on penalizing opioid prescribing, and instead focus efforts on measures to support patients with chronic pain and OUD, including increasing the number of providers waivered to prescribe buprenorphine, investigating the accessibility and availability of alternative non-pharmacological pain management, and providing opioid stewardship educational support and guidance for providers through education programs like academic detailing.

## Programmatic Recommendations

***Develop and expand multimodal pain clinics for chronic pain management.***

- Managing chronic pain is complex. Integrative, multimodal pain management approaches may be optimal to manage the challenging and multidimensional aspects of chronic pain. The Integrative Pain Management Program (IPMP) was established in San Francisco as multimodal pain management clinic serving safety-net patients in a resource-limited environment. The IPMP offered education about the biopsychosocial model of pain, mindfulness training, physical movement exercises, acupuncture, massage and health coaching. Patients who participated in the IPMP were significantly more likely to report improvements in pain interference, pain intensity, social satisfaction, global mental health, and pain self-efficacy during 3 and 6 month follow-up.[140]
- Our research suggests that patients with a history of opioid prescribing and substance use may benefit from multimodal approaches to pain management, especially during an era of reduced opioid prescribing. An integrative pain clinic would allow patients to access concurrent, non-opioid, specialized care. Furthermore, our research demonstrates notable barriers to initiating and sustaining access to nonpharmacological pain management therapies, even though patients reported improved physical pain and decreased opioid use when using nonpharmacological therapies. We recommend States and Counties consider adapting the San Francisco IPMP model of multimodal pain clinics in resource-limited settings.

**Research Recommendations**

***Evaluate the effect that changing prescribing practices have on patients' pain, function, quality of life, and illicit substance use.***

- As cited above, emerging research suggests that shifting pain management and opioid prescribing policies may have considerable effects on patients' pain, function, quality of life and illicit substance use. In April 2019, the CDC published a press release calling attention to the noted misinterpretations of their recommendations around enforce opioid prescribing thresholds and abrupt tapers/discontinuations.[141] However a significant population of patients have already experienced consequences of restrictive opioid prescribing policies. It is essential to assess the effects that opioid tapers/discontinuations have had on patients' pain, function, quality of life, and illicit substance use.
- Our research offers preliminary data that opioid-experienced patients may face significant challenges during opioid tapers. Results from this study, however, are based on a small qualitative sample of pain patients with a history of illicit substance use and thus may not be generalizable. Expanding research efforts to evaluate the effect that opioid reductions/discontinuations have on chronic pain patients is critical. Particularly, we need to identify predictors for chronic pain patients to transition to illicit substances. The Substance Use Research Unit is currently conducting two studies (a longitudinal cohort study and a cross sectional study) aimed to rigorously assess the effects that changes in opioid prescribing have on patients' pain, function, quality of life, and illicit substance use.

## Policy Recommendations

***Pass legislation approving the establishment of safe consumption sites.***

- Safe consumption sites (SCS) currently exist in 11 countries and have been shown to reduce drug-related morbidity and mortality.[142] The legality of establishing SCS in the US, however, remains is uncertain,[143] although public advocacy efforts are gaining traction in a few progressive cities (e.g. San Francisco, Philadelphia and New York City). Without SCS, people who use drugs (PWUD) often use drugs in suboptimal conditions that can lead to negative health consequences and heightened overdose risk. SCSs offer PWUDs access to safe physical environments, clean equipment, and medically-trained staff who can respond to medical emergencies.
- Our research demonstrated intragroup stigma among PWIDs. Research has shown that stigma is associated with social isolation and isolation is a recognized risk factor for fatal overdose.[115] Thus, casting stigma onto a high-risk subpopulation of PWID may further exacerbate their already high risk for fatal overdose. Using drugs in the presence of others is a well-established harm reduction technique to reduce risk of fatal overdose.[38] This, however, relies on PWID developing and maintaining reliable social networks. PWID who are isolated, therefore, may be at greater risk for fatal overdose. SCS would provide an environment by which PWID could use drugs in the presence of others who can intervene if a health emergency arises and removes the responsibility from PWID to establish and maintain their own social networks. Given the potential prevalence of intragroup stigma among high-risk users, a service

provision like a SCS is a critical public health intervention to decrease overdose mortality.

## Research Recommendations

***Develop and test a partner-based intervention to reduce real-time risky overdose behavior.***

- Behavioral interventions to reduce opioid overdose can work. For instance, the REBOOT study demonstrated that a motivational-interviewing counseling intervention significantly reduced both the occurrence of any opioid overdose and the number of overdoses among participants who received the intervention compared to those who received treatment as usual.[144] Given the high rate of opioid overdose and the increased prevalence of fentanyl, it is particularly important to continue to develop novel behavioral interventions that target overdose risk behavior *prior* to the overdose occurrence.
- Results from our research may help to inform a novel behavioral intervention to reduce overdose events. Many participants reported an awareness of their peers' risky overdose behavior prior to overdose events, however, they were unable to effectively communicate the risk to their using partners. Participant narratives also suggested patterns of stigma around overdose events within the PWID community. These findings support the development of a peer-based communication-based behavioral intervention to encourage using partners to intervene in real-time moments of high risk drug use. This study would aim to decrease overdose events, increase recognition of

risk factors among using partners, and create an environment of support instead of stigma among PWID.

**Summary of Recommendations**

Overall, findings from this dissertation can be strategically utilized to inform novel policy, programmatic and research efforts to improve the current national opioid and overdose crisis. In an era of shifting opioid policies, there are increasing risks for people who use opioids, including those prescribed or reduced from long-term opioid therapy and those who use opioids illicitly. In order to protect these vulnerable populations, we must develop a system that allows providers to provide comprehensive, humane and patient-centered care for their patients. Furthermore, it is critical that we support patients during high-risk times in their opioid use, particularly for those individuals transitioning to illicit opioids and those at-risk for opioid overdose. Findings from this dissertation can be used to evaluate opioid stewardship activities, promote balanced, more nuanced opioid-prescribing policies, and develop behavioral interventions to reduce the opioid overdose mortality.

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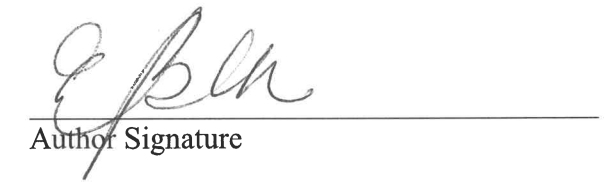

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