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Pharmacists' Role in Opioid Use Disorder and Overdose Prevention and Treatment and Their Attitudes and Perceptions Towards Distributing Naloxone Under a Standing Order.

A Thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Pharmaceutical Sciences with a concentration in pharmacoeconomics and health outcomes at Virginia Commonwealth University

By

Stephen C. Ijioma, PharmD
VCU School of Pharmacy

Director: Julie Patterson, PharmD, PhD
Assistant Professor
Department of Pharmacotherapy and Outcomes Science

Virginia Commonwealth University
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LIST OF ABBREVIATIONS

ART	Antiretroviral therapy
BZD	Benzodiazepine
CARA	Comprehensive Addiction and Recovery Act
CBT	Cognitive behavioral therapy
CDC	Centers for Disease Control and Prevention
CE	Continuing education
COREQ	Consolidated Criteria for Reporting Qualitative Research
CP	Clinical pharmacist
CPI	Consumer Price Index
CT	Connecticut
DATA	Drug Addiction Treatment Act
ER	Extended-release
GDP	Gross domestic product
HCV	Hepatitis C virus
HEOR	Health Economics and Outcomes Research
HIV	Human immunodeficiency virus
ICER	Incremental cost-effectiveness ratio
ID	Idaho
IDU	Injection drug user
IHS	Indian Health Service
IN	Intranasal
JCDH	Jefferson County Department of Health
KBP	Kentucky Board of Pharmacy
LA	Long-acting
MAT	Medication-Assisted Treatment
MOUD	Medications for opioid use disorder
MRI	Magnetic resonance imaging
ND	North Dakota
NM	New Mexico
OE	Opioid epidemic
OR	Oregon
ORA	Opioid receptor antagonists
OST	Opioid substitution therapy
OUD	Opioid use disorder
PCHC	Penobscot Community Health Care
PMP	Prescription monitoring program
PONI	Preventing Overdose and Naloxone Intervention
PRRP	Pharmacy-Only Patient Review and Restriction Program
REMS	Risk Evaluation and Mitigation Strategy
RI	Rhode Island
SAMHSA	Substance Abuse and Mental Health Services Administration
SEP	Syringe exchange programs
SSP	Syringe service programs

SUPPORT	Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment
TASC	Treatment Alternative for Safer Communities
TPB	Theory of planned behavior
UAB	University of Alabama at Birmingham
UK	United Kingdom

ABSTRACT

Pharmacists' Role in Opioid Use Disorder and Overdose Prevention and Treatment and Their Attitudes and Perceptions Towards Distributing Naloxone Under a Standing Order.

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Virginia Commonwealth University, 2022

Advisor: Julie A. Patterson, PharmD, PhD
Assistant Professor, Department of Pharmacotherapy and Outcomes Science

Background: Opioids are a class of drugs that bind to opioid receptors (mu, delta, and kappa), located in the central and peripheral nervous systems, to exert responses such as analgesia, respiratory depression, euphoria, and miosis. The opioid epidemic is characterized in large part by an increase in opioid overdose deaths. Community pharmacists are one of the most accessible healthcare professionals who frequently interact with patients and can implement OUD and opioid overdose prevention strategies. Treatment for opioid overdose and OUD include naloxone for overdose deaths as well as medication-assisted treatment for OUD.

Objective: The specific aims of this thesis include i) to explore community pharmacists' attitudes, subjective norm, perceived behavioral control, and behavioral intention towards dispensing opioid receptor antagonists (ORAs) under a standing order in Virginia and ii) to evaluate the cost-effectiveness of SSP alone, MOUD alone, and SSP+MOUD combination in preventing HCV cases among opioid IDUs in the US.

Methods: A broad search strategy of terms relevant to OUD was used to find evidence of pharmacist involvement in OUD management from PubMed/MEDLINE. Articles were excluded if not related to pharmacist OUD management, including pain management, not related to pharmacy practice, not involving OUD, or not relating to the opioid epidemic. The first aim was

assessed by conducting semi-structured interviews of community pharmacists across Virginia between June 2018 – October 2019. The interview guide was based on the Theory of Planned Behavior. Interviews were recorded, transcribed *verbatim*, and thematically analyzed. The second aim assessed cost-effectiveness from a public payer perspective over a one-year time horizon by using a decision-tree analysis model based on published literature and publicly available data.

Results: Pharmacists were confused about the specifics and the processes involved with dispensing naloxone under the standing order. Furthermore, many recognized the underuse of the standing order. Community pharmacists in Virginia expressed mixed intentions toward dispensing ORAs under the standing order. The incremental cost savings per HCV case avoided per 100 opioid IDUs compared to "no intervention" were as follows: SSP+MOUD combination = $347,573; SSP alone = $363,821; MOUD alone = $317,428. The ICER for the combined strategy was $4,699 compared to SSP group. Sensitivity analysis showed that the results of the base case cost-effectiveness analysis were sensitive to variations in the probabilities of injection-risk behavior for the SSP and SSP+MOUD combination groups, probability of NO HCV with "no intervention", and costs of MOUD and HCV antiviral.

Conclusions: Pharmacists expressed mixed behavioral intention toward dispensing ORAs under the standing order. Future research should focus on quantifying the uptake of the standing order at the state level. The SSP+MOUD combination and SSP alone strategies dominate MOUD alone and "no intervention" strategies. Pharmacists may incorporate a combination strategy as it is shown to be cost-effective if payers were willing to pay $4,699 or more per case of HCV avoided. Although these harm reduction programs will provide benefits in a one-year time frame, the largest benefit may become evident in the years ahead.

CHAPTER 1: INTRODUCTION

Introduction to Opioids

Opioids are a class of drugs that bind to opioid receptors (mu, delta, and kappa), located in the central and peripheral nervous systems, to exert responses such as analgesia, respiratory depression, euphoria, and miosis.[1] The Centers for Disease Control and Prevention (CDC) Injury Center examines deaths and nonfatal overdoses related to opioids into four categories: i) natural opioids (e.g., morphine and codeine) and semi-synthetic opioids (e.g., oxycodone and hydrocodone); ii) methadone, a synthetic opioid; iii) synthetic opioids other than methadone (e.g., tramadol); and iv) heroin.[2] Opioids can be legally prescribed for pain or illegally manufactured for illicit use.

Increases in opioid prescribing have generated concerns about over prescribing as well as opioid abuse and misuse, and this has contributed to an opioid epidemic which is characterized by increased incidence of opioid use disorder and opioid overdose.[3-6] By 2015, opioids were overprescribed in the US at 640 morphine milligram equivalents (MME) per capita compared to 180 MME per capita in 1999. However, there was a reduction in opioid usage following the CDC's 2016 guidance to reduce the overprescribing of opioids.[7,8] There has also been a growing concern of opioid misuse and abuse. In 2020, an estimated 9.5 million people aged 12 or older misused opioids, with 9.3 million and 902,000 people misusing prescription pain relievers and heroin, respectively.[9] Beyond the misuse and abuse of opioids, overdose is a serious concern. The presentation of opioid overdose may include pinpoint pupils and loss of consciousness and may be fatal given respiratory depression.[10]

The Rise in Opioid Overdose Deaths

The opioid epidemic is characterized in large part by an increase in opioid overdose deaths. The rise in opioid overdose deaths is noted to have occurred in three distinct waves. The first wave was characterized by increased prescribing of opioids in the 1990s attributed to the approval and marketing of OxyContin and pain as the fifth vital sign; the second wave attributed to physicians decreasing opioid prescriptions and patients turning to heroin to help with cravings and withdrawal symptoms, led to rapid increases in overdose deaths involving heroin in 2010; and the third wave beginning 2013 resulted in increased overdose deaths involving synthetic opioids, reflecting increased fentanyl trafficking.[11-16] Throughout these waves (1999-2020), more than 564,000 people have died from an overdose involving prescription and/or illicit opioids.[2,15] During this time, opioid-involved death rates increased by 38%, driven by increases in rates of death involving synthetic opioids excluding methadone (56% increase), prescription opioids (17%) and heroin (7%).[17,18] Synthetic opioids are now the leading cause of opioid overdose deaths, accounting for over 82% of all opioid-involved deaths in 2020; rates of synthetic opioid-related overdose deaths was more than 18 times higher in 2020 than in 2013.[17,19] The increased availability of illicitly manufactured synthetic opioids, especially fentanyl and its combination with heroin, counterfeit pills, and cocaine has contributed to these rising rates of overdose deaths.[20,21] Drug overdose deaths involving psychostimulants such as methamphetamine are also increasing with and without synthetic opioid involvement.[22,23]

The opioid epidemic has been further exacerbated by the COVID pandemic. In 2021, an estimated 107,622 individuals died due to drug overdose in the United States (US), equating to more than 294 deaths per day and nearly 15% increase from 2020. Prior to 2021, there was a 30% increase in overdose deaths from 2019 to 2020.[24] These trends have continued beyond the

initial stages of the pandemic, with recent data suggesting that there was a reported 3.9% increase in drug overdose deaths between April 2021 to April 2022.[25]

Opioid Use Disorder and Associated Risks

Opioid use disorder (OUD) is a major contributing factor to opioid overdose deaths. OUD is defined in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) as a "problematic pattern of opioid use leading to clinically significant impairment or distress".[26] To date, various studies have shown that between 0.10% to 34% of patients develop prescription OUD symptoms following an opioid prescription.[27-29] Patients with OUD are at increased risk of overdose and death from overdose; one study reported that, among patients with OUD who were discharged from a hospital, about 58% died of drug-related causes within 12 months, including 13.6% who died of an overdose during this time.[30] Beyond overdoses, opioid injection drug users (IDUs) often share injection equipment with one another and are at an increased risk of acquiring human immunodeficiency virus (HIV), hepatitis C virus (HCV), infective endocarditis, and soft tissue infections.[31]

Treatments for Opioid Overdose and OUD

Naloxone for Overdose Deaths

Naloxone, an opioid antagonist, is used to reverse an overdose from both prescription and illicit opioids. Naloxone can be given by intramuscular, intravenous injection, or intranasal every 2 to 3 minutes, with a duration of effect of about 30 to 90 minutes to quickly restore normal breathing in the case of an opioid overdose.[32,33]

Naloxone can be dispensed by pharmacists to be administered quickly and effectively by trained professionals or lay individuals who observe the initial signs of an opioid overdose. The

Commonwealth of Virginia could serve as a case-study on pharmacists dispensing naloxone. In Virginia, an average of 4 Virginians died of an opioid overdose daily in 2020. From 2019 to 2020, overdose-related emergency department visits increased by 33% to 9,901 while overdose deaths increased by 17% to 1,478.[34] Virginia first passed the statewide naloxone standing order on November 11, 2016, allowing pharmacists with an active license to dispense naloxone in accordance with the Virginia Drug Control Act §54.1-3408, Code of Virginia's Good Samaritan Act, and the current Board of Pharmacy-approved protocol. It requires pharmacists to provide counseling whenever naloxone is dispensed.[35] The standing order also allows naloxone to be dispensed to a person to administer to another person believed to be experiencing or about to experience a life-threatening opioid overdose.[36]

Medication-Assisted Treatment for OUD

Medication-assisted treatment (MAT), sometimes used interchangeably with medications for opioid use disorder (MOUD), involves using medications in combination with counseling and behavioral therapy to treat patients with substance use disorder. Food and Drug Administration (FDA)-approved medications used to treat OUD include buprenorphine, methadone, and naltrexone. Buprenorphine is a partial agonist at the mu opioid receptor and an antagonist at the kappa and delta opioid receptors.[37-45] Methadone is a synthetic opioid agonist that binds and activates mu opioid receptors centrally and in the periphery.[46] while naltrexone is an opioid antagonist that binds and blocks opioid receptors.[47] Per the Substance Abuse and Mental Health Services Administration (SAMHSA), the MAT treatment approach is effective in decreasing illicit behaviors while improving patient survival, treatment retention, patients' ability to gain and maintain employment, and birth outcomes among women with substance use disorders who are pregnant.[48,49] For example, buprenorphine resulted in high levels of abstinence

and psychosocial functioning, fewer withdrawal symptoms, lower pain, positive health-related quality of life, minimal depression, and higher employment versus pre-trial visit.[50,51]

Expanding Treatment Options and Accessibility

Various federal statutes have been implemented to expand access to MAT. The Drug Addiction Treatment Act (DATA) of 2000 permits physicians to obtain a waiver to treat opioid dependency with FDA-approved narcotic medications, such as buprenorphine, in treatment settings other than opioid treatment programs.[52] The Comprehensive Addiction and Recovery Act (CARA) of 2016 raised the maximum number of patients treated by a single physician from 30 to 100, and the Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities (SUPPORT Act) further raised this limit to 275 patients. Under the SUPPORT Act, other qualified practitioners were permitted to treat opioid dependency to expand access to treatment; of note, the SUPPORT Act does not include pharmacists.[53,54] The number of DATA waivered prescribers doubled to over 70,000 from 2016 to 2019; however, only approximately 50% of all waivered prescribers were actively prescribing from February 2017 to April 2019.[55,56]

Despite these legislative efforts to expand patient access to MOUD, several challenges persist. Among people aged 12 or older in 2020 with a past year substance use disorder, only 6.5% (or 2.6 million people) received any substance use treatment in the past year.[9] As a result, reducing barriers to treatment by expanding treatment options and accessibility is of utmost importance.

Increased Pharmacist Roles in OUD and Overdose Prevention and Treatment

Community pharmacists are one of the most accessible healthcare professionals who frequently interact with patients and can implement OUD and opioid overdose prevention

strategies.[57,58] Specifically, pharmacists are able to promote safe opioid use by identifying patients at risk of overdose, dispensing naloxone, and counseling patients on appropriate opioid and naloxone use. Despite the effectiveness of naloxone, there is a low uptake of naloxone dispensing. In 2019, for example, only 3 naloxone prescriptions were dispensed per 100 high-dose opioid prescriptions on average.[59] Hence, there is a need for clear understanding of pharmacist roles and barriers and facilitators to naloxone dispensing to expand its accessibility and uptake. Beyond safe prescription opioid use, community pharmacists can play a role in promoting safer conditions for those who abuse opioids by providing syringe exchange programs and resources for safe syringe disposal.[60-62]

Syringe Service Programs

Syringe service programs (SSPs) involve the distribution of sterile syringes and other injecting equipment to patients to increase the number of clean syringes in circulation.[63] SSPs work by reducing the number of contaminated syringes and consequently reducing the risk of acquisition of hepatitis C virus (HCV) and other diseases acquired by needle-sharing. Some of the most common barriers to SSPs include lack of awareness and stigma.[64] SSPs are associated with an estimated 50% reduction in human immunodeficiency virus (HIV) and HCV incidence.[65] The risk of HCV and HIV transmission is further reduced when SSPs are used in combination with MOUDs.[65,66] As a result, there is a need to understand the economic value of SSPs in OUD and overdose deaths.

Aims

The goal of this thesis was to address barriers to two ways of expanding treatment accessibility for opioid overdose and OUD: naloxone standing order protocols and harm-reduction strategies such as SSPs and MOUDs. Understanding pharmacists' behaviors towards

distributing naloxone under a standing order and estimating the cost-effectiveness of harm-reduction strategies such as SSPs and MOUDs will help future efforts to expand the uptake and accessibility of these programs. Specifically, the specific aims of this thesis include:

Specific Aim 1: To explore community pharmacists' attitudes, subjective norm, perceived behavioral control, and behavioral intention towards dispensing opioid receptor antagonists (ORAs) under a standing order in Virginia.

Specific Aim 2: To evaluate the cost-effectiveness of SSP alone, MOUD alone, and SSP+MOUD combination in preventing HCV cases among opioid IDUs in the US.

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CHAPTER 2: NARRATIVE REVIEW OF PHARMACIST INVOLVEMENT IN OPIOID USE DISORDER TREATMENT

Abstract

Pharmacists have training and increasing opportunities to provide services to patients that suffer from opioid use disorders (OUD). To assess the landscape of services that pharmacists provide to patients with OUD, a narrative review that evaluated the programs and activities pharmacists provide or are directly involved in for patients with OUD undergoing treatment was conducted. Thirty-five articles were evaluated for pharmacist type and level of involvement. Pharmacists were found to be involved in direct patient OUD management (including participating in collaborative practice agreements, training patients in naloxone administration, naloxone distribution, and leading opioid substitution and methadone programs) as well as providing necessary ancillary services (including receiving OUD related training, controlled substance stewardship and participation in prescription monitoring programs). Pharmacists have a long-standing role in OUD management, although the extent and aspects of the role is highly variable, particularly when comparing the US to other countries. Pharmacists have unique training that allows them to provide harm-reduction services, be readily accessible, and to establish relationships with patients. However, many pharmacists require more training in order to provide these services with confidence. Pharmacists have shown willingness and ability to implement several harm-reduction strategies for patients with OUD. Pharmacist roles in OUD should be tailored towards direct-patient management given they are the most accessible and frequently visited health care professional.

Introduction

The opioid epidemic has received increasing attention in the last few years. Per the Substance Abuse and Mental Health Services Administration (SAMHSA) in 2020, 9.5 million Americans reported misusing prescription opioids.[1] Additionally, there has been a surge of opioid related deaths from 4,200 in 1999 to 15,300 in 2013 and over 64,000 in 2016.[2,3] There was an estimated 9.3% change increase in opioid drug overdose deaths in the US from January 2021 to January 2022.[4] OUD is "characterized by intense and, at times, uncontrollable drug craving, along with compulsive drug seeking and use that persist even in the face of devastating consequences."[5] OUD is a complex disease of the brain as "addiction affects multiple brain circuits, including those involved in reward and motivation, learning and memory, and inhibitory control over behavior."[5] Development of OUD is multifactorial because differences in genetic makeup, age of exposure to drugs, and other environmental influences vary from person to person. Therefore, some individuals are more vulnerable to addiction, compromising their ability to choose abstinence and eluding their self-control or willpower.[5]

OUD has far-reaching health and social consequences due to dysfunctional behaviors that "can interfere with a person's normal functioning in the family, the workplace, and the broader community."[5] Therefore, OUD has a significant psychosocial component. Cognitive behavioral therapy (CBT) and psychotherapy are regular components of treatment to promote adoption of healthier non-drug-using lifestyles along with medications for symptomatic support.[6] Use of counseling and behavioral therapies, in addition to medications, is known as Medication-Assisted Treatment (MAT).[7]

OUD has been managed medically for over 50 years but is multidimensional and complex.[6] Treatment of OUD is time intensive and requires close follow-up. Additionally,

"Because addiction is a disease, most people cannot simply stop using drugs for a few days and be cured. Patients typically require long-term or repeated episodes of care to achieve the ultimate goal of sustained abstinence and recovery of their lives."[5] A health screening survey of 333 patients showed that rural respondents had increased risk for opioid misuse if they had previous illicit drug use (14 times more likely), post-traumatic stress disorder (5.44 times more likely), and less than high school education (6.68 times more likely).[8] All FDA approved opioid substitution therapies (ORT/OST) for OUD are listed in Table 1.

MAT is highly individualized, and patients are offered access to all three available options (i.e., methadone, buprenorphine, naltrexone) to allow patients and providers to work collaboratively to select the treatment best suited to an individual's needs.[7,9] Because of methadone's addictive properties, patients are required to receive their daily medication at a licensed methadone clinic under the supervision of a physician. The logistics of regular methadone administration at designated clinics can be too difficult for some patients for reasons such as limited clinic locations, difficulty arranging transportation or taking time away from work, as well as the stigma associated with visiting the clinic. Therefore, many patients prefer other ORT/OST therapy options that can be taken at home or once a month to improve adherence and success of therapy.

Pharmacists have the training and increasing opportunity to provide services to patients with OUD. It has been suggested that pharmacists should have a role in OUD management by decreasing opioid diversion through utilization of prescription monitoring programs, proper storage and disposal of unused or expired opioid prescriptions, increasing access to naloxone for patients at high risk and for bystander administration to prevent opioid overdose deaths, providing immunizations for diseases associated with OUD such as hepatitis B, screening for co-

morbid diseases such as hepatitis C and human immunodeficiency virus (HIV), screening for persons who may be at risk for OUD, conducting opioid related research, and advancing patient education.[10–13] However, barriers to these suggested roles exist, for example, barriers to guideline recommended naloxone distribution include cost and remuneration for community pharmacists' time and difficulty identifying and training naloxone recipients.[13] Pharmacists play an important role in targeting at-risk individuals as well as other third-parties that could assist in the case of an overdose.

While reviews have been written suggesting the role of pharmacists in addressing opioid misuse and the opioid epidemic, there has not been a narrative literature review that evaluated the programs and activities pharmacists provide or are directly involved in for patients with opioid use disorders undergoing treatment.[11,12,14,15] In order to assess the landscape of services pharmacists provide to patients with opioid use disorders, a narrative review was conducted. Pharmacists can be proactively involved in identifying patients at risk of developing OUD and providing guideline-based naloxone distribution to patients with OUD.[16] The research question for this narrative review is: What services do pharmacists actively provide related to OUD and what are their outcomes?

Table 1: FDA Approved Medications for OUD

		Brand	Generic	Formulation
FDA-approved buprenorphine products				
	Bunavail		buprenorphine and naloxone	buccal film
	Cassipa		buprenorphine and naloxone	sublingual film
	Probuphine		buprenorphine	implant for subdermal administration
	Sublocade		buprenorphine extended-release	injection for subcutaneous use
	Suboxone		buprenorphine and naloxone	sublingual film for sublingual or buccal use, or sublingual tablet
	Subutex		buprenorphine	sublingual tablet
	Zubsolv		buprenorphine and naloxone	sublingual tablets
FDA-approved methadone products				
	Dolophine		methadone hydrochloride	tablets

	Methadose	methadone hydrochloride	oral concentrate
FDA-approved naltrexone products			
	Vivitrol	naltrexone for extended-release injectable suspension	intramuscular

Direct Patient Management

Pharmacist and Physician Collaboration

Some of the more novel programs developed to improve OUD management for patients involve collaboration between pharmacists and physicians to allow pharmacists to take on a larger role in OUD management. In 2015, a pilot program composed of a physician-pharmacist collaborative practice for 12 opioid dependent patients in the US Patients in this study were monitored weekly by the pharmacist at an independent pharmacy and physicians confirmed the history and treatment plan. Patient retention rates (in continuous months in treatment) ranged from 39 to 59% at six months and about 50% after the first year prior to the program initiation. After initiation of this pilot program, 100% of patients remained in treatment at six months and 73% continued at one year and generated an estimated $22,000 in savings.[17] The pilot also demonstrated "enhanced communication, reduced physician burden, regular access to urine toxicology results, increased buprenorphine/naloxone treatment, and enhanced monitoring of diversion with cost savings."[17]

A survey of 345 general practitioners in France investigated participation in guideline recommended collaboration with pharmacists in high-dosage buprenorphine patient management.[18] The study reported that only 54% of general practitioners reported using pharmacists for management of patients on high-dosage buprenorphine treatment, despite guidelines encouraging physician-pharmacist management in this patient population. Pharmacist training in addiction treatment was associated with collaboration.[18]

A Canadian large cohort study of 3,743 patients at 43 clinics determined that patients receiving methadone at a clinic with physicians and other health services versus a community pharmacy alone had higher retention - 57% compared to 12% - at one year.[19] Patients were 77% less likely to remain under treatment at one year following initiation of therapy at an off-site community pharmacy.[19]

A sample of 242 pharmacies from the rural Appalachian areas of Tennessee, Kentucky, Virginia, and West Virginia were contacted to determine their willingness to participate in buprenorphine pill counts in collaboration with physicians and reporting results to physicians.[20] Seventy-four percent of pharmacies were willing to participate, and five pharmacies reported that they were already conducting pill counts for their patients. The study reported that "pharmacy willingness to partner with physicians and engage in activities aimed at prevention and detection of drug diversion/misuse to improve safety and treatment outcomes may have broader applicability to other medications with abuse potential."[20]

An American Journal of Health System Pharmacy news brief described two pharmacist-physician collaborative clinics to treat opioid dependence.[21] A California clinic based on a successful collaborative care model from Massachusetts provided office-based treatment of opioid dependence to homeless people led by a pharmacist managing assessment, induction, and stabilization.[21] The Boston Medical Center program was implemented at 14 community health centers and had 51% of opioid dependence patients remain in treatment or had undergone buprenorphine taper treatment at 12 months.[21]

The Indian Health Service (IHS) created the Prescription Drug Abuse Workgroup to develop effective pharmacy-based harm reduction programs within the Indian population.[22] Pharmacists collaborated with multidisciplinary chronic pain management teams through the

patient-centered model and CPA. The CPA allowed pharmacists "to assess overdose risk, prescribe naloxone, provide patient and caregiver education, and offer referral to local treatment resources". IHS pharmacists were involved with dose escalation or de-escalation recommendations, functional status assessment, and prescription monitoring program (PMP) queries. They also developed a comprehensive training program to train 350 officers across 6 different districts and expanded the naloxone coprescribing initiatives. These initiatives resulted in an increase in patient access to naloxone.[22]

A physician-pharmacist naloxone prescription program protocol in Alabama was established through a collaborative practice agreement between the Jefferson County Department of Health (JCDH) medical director, pharmacists, resident pharmacists, and clinical professors from the McWhorter School of Pharmacy at Samford University.[23] Pharmacists were responsible for ordering, allocating, maintaining inventory, and managing the naloxone program with physicians at JCDH in-charge. One hundred and nine appointments, in which participants visited the clinic within the Health Department, were scheduled from November 2015 to August 2016. The majority of appointments (76%) were for law enforcement officers, religious leaders, and University of Alabama at Birmingham (UAB) Treatment Alternative for Safer Communities (TASC) employees. The remaining 24% of appointments were for individual clients, half of which were receiving naloxone for a friend or family member at risk. Eighty-three clients received training, and 150 naloxone (Evzio) kits were distributed to opioid and heroin users (n=13), concerned family members or friends (n=13), and UAB TASC employees (n=55). This physician-pharmacist collaborative program addressed the need for naloxone education and access among heroin and opioid users, concerned family members or friends, and those who work closely with users.[23]

Pharmacist-Led Opioid Substitution Services

Stigma related to OUD treatment can be a major barrier preventing patients from seeking or maintaining care. These barriers can extend to the pharmacies from which patients with OUD receive their medications. A qualitative study from Scotland, United Kingdom (UK) involving seven focus groups with 41 participants found that participants experienced stigma and discriminatory practices at pharmacies from which they received ORT.[24] Despite this, some patients reported positive perceptions of received care. The study also noted that pharmacists may still be less-than-optimally prepared to manage patients exhibiting drug-seeking behaviors.[24]

Matheson et al. surveyed 709 pharmacists in the United Kingdom, and it revealed improving attitudes towards treatment of drug misuse.[25] Being male and having training in drug misuse significantly predicted better attitudes. Specifically, "Pharmacists with training in drug misuse were 1.6 times more likely to dispense any drug for drug misuse."[25] Additionally, pharmacists with blood-borne pathogen training were 1.8 times more likely to participate in needle-syringe exchange programs. Pharmacists in the UK can prescribe controlled medications, but only nine of the pharmacists questioned dispensed controlled medications for drug misuse. While most the pharmacists felt included in the addiction treatment team, more than a quarter did not feel their role was valued.[25]

A 2011 Finnish survey of 64 pharmacies dispensing buprenorphine-naloxone reported a need for more education and financial remuneration to increase buprenorphine-naloxone dispensing.[26] Eighty percent of those questioned perceived that supervision of buprenorphine-naloxone dosing was not a suitable task for pharmacists alone due to lack of resources and the task falling outside of the pharmacist's scope of practice.[26]

Pharmacists delivering opioid substitution treatment at almost one thousand pharmacies in Australia were surveyed about their experiences with opioid substitution therapy.[27] While

nearly all pharmacies (96%) provided methadone treatment, only 59% provided buprenorphine or buprenorphine-naloxone.[27] Pharmacies often reported services to improve treatment accessibility and acceptability, including offering credit for patients unable to pay (79%), having a separate dosing area for OST patients (71%), and providing syringes (63%).[27] The most commonly reported OST-related problems included difficulty in contacting the prescriber, prescribing of take-away doses to patients that the pharmacist deemed to be unstable, and a lack of perceived competence in identifying opioid toxicity and withdrawal.[27] Eighty percent of pharmacists had refused to dispense an OST dose to the patient in the last year, most commonly due to expired prescriptions and missing three or more consecutive doses; of those, 74% reported notifying the clients prescriber when they refused a dose to the patient.[27]

Also in Australia, Lea et al. investigated consumer satisfaction in 508 patients and experience with OST at community pharmacies.[28] Sixty-one percent of participants reported being satisfied and expressed a high-level of satisfaction with OST delivery at their pharmacy, but participants were least satisfied with privacy at the pharmacy.[28]

In the US, MAT involves the use of FDA-approved drugs such as buprenorphine and naltrexone in combination with behavioral and counseling therapies to manage patients with OUD. IHS pharmacists have also contributed in increasing access to MAT for American Indians and Alaska Natives. Indian Health Service (IHS) pharmacists have been involved in patient care coordination with behavioral health resources, appropriate laboratory monitoring, and dose adjustments to ensure appropriate buprenorphine taper due to limited number of available buprenorphine providers.[22] Pharmacy-led clinics for patients interested in opioid antagonists or opioid abstinence also involved depot naloxone injections.[22]

Pharmacist-Led Methadone Programs

Jaffray et al. investigated by cluster randomized controlled clinical trial if motivational interviewing from community pharmacists in the UK improved outcomes for 542 patients receiving methadone.[29] This study determined that patients demonstrated a reduction in illicit heroin use and improved treatment satisfaction from baseline, but there was no difference in treatment retention or treatment satisfaction between the two groups indicating that motivational interviewing may not have an effect.[29]

Pharmacists Providing Training

A program instituted in a single urban community pharmacy, Kelley-Ross Pharmacy Group, in Seattle, Washington allowed pharmacists to provide community and group training to various organizations on how to properly respond to an opioid overdose and administer take-home naloxone to potentially save a life. This resulted in about 1400 people receiving training to recognize and respond to opioid overdose and 234 take-home naloxone kits (97% intranasal (IN) route) dispensed between August 2012 and August 2016.[30] One organization, which typically worked with a higher-risk population, reported 20 successful overdose rescues from 99 kits dispensed by the pharmacy (20.2% rescue rate). The training increased awareness of opioid overdose recognition and response.[30]

The Indian Health Service has implemented several initiatives in which pharmacists provide overdose-related training. IHS pharmacists trained first responders on recognizing the signs and symptoms of opioid overdose, emergency response activation, expectations regarding withdrawal adverse effects, scene safety, various available formulations of naloxone, and resupply steps when a naloxone kit is used in the field or expired. This effort, combined with training pharmacists and expanding naloxone co-prescribing, was associated with a 195% increase in the purchasing of naloxone from the second half of 2015 to the first half of 2016.[22]

Naloxone Distribution

Naloxone distribution seems to be the largest area for pharmacist involvement in OUD management. Results from a scoping review show that most pharmacists support having a naloxone standing order but are uneasy with the idea of dispensing naloxone without a prescription or physician's authority.[31] Most pharmacists are willing to have an expanded role in managing patients at risk of an opioid overdose or OUD, but adequate training, education, and support is needed to increase pharmacists' role in OUD.

Davis et al. investigated the scope of naloxone dispensing laws and subsequent practices in the US.[32] Today, all 50 states in the US allow naloxone to be prescribed for administration to patients with whom the prescriber has no prescriber-patient relationship. Some states allow naloxone to be distributed via non-patient specific mechanisms such as standing orders and protocol orders while others (CT, ID, ND, NM, and OR) granted pharmacists a prescriptive authority to allow for patient-specific naloxone prescriptions by some or all licensed pharmacists. Some states also permit pharmacists to dispense naloxone under a protocol order, which differs from standing orders such that dispensed pursuant to a "protocol promulgated by 1 or more professional boards or government agencies"; thus, the prescriber of record varies by state to state since it is passed by an organization(s).[32]

A 2013 qualitative study involving 21 injection-drug users (IDUs) and 21 pharmacy staff in Rhode Island (RI) assessed barriers and facilitators of pharmacy-based interventions.[33] All injection drug users (IDUs) reported witnessing or experiencing an overdose, and some reported trying to reverse an overdose with unapproved methods.[33] There was an overall support for pharmacy-based intervention from both IDUs and pharmacy staff, but both expressed doubts about each other's ability to participate in the intervention. Pharmacists approved of 3

implementation mechanisms: 1) dispensing naloxone without a prescription and on-site training for participants, 2) pharmacists fill naloxone prescription upon provider's approval, and 3) off-site training for participants by a certified community-based organization and then participants provide certificate to pharmacist to obtain naloxone.[33]

Morton et al. evaluated a multifaceted New Mexico pharmacist naloxone distribution program from Medicaid claims.[34] From 2014 to June 2016, there was a 9-fold increase in outpatient pharmacy naloxone Medicaid claims. Outpatient naloxone Medicaid claims expanded from roughly 8 out of 33 counties in New Mexico in 2014 to 24 counties in 2016. A peer-to-peer questionnaire data revealed that the top 3 perceived barriers to pharmacy-based naloxone distribution were pharmacy reimbursement challenges, affordability for patients, and lack of patient interest.[34]

Six pharmacists in community- and clinic-based settings in large metropolitan cities, including Boston, Seattle, and Pittsburgh, who collaborated with physician specialists in opioid abuse and overdose prevention were interviewed over a 3-month period. The goal was to describe outpatient naloxone dispensing practices.[35] The results showed that 50% of pharmacies targeted patients on high-dose opioids for chronic pain management while 83% of these pharmacies targeted patients at high risk of overdose secondary to abusing opioids, whether prescription or illicit. Five pharmacies required a prescription prior to dispensing naloxone, and only 1 pharmacy was exercising pharmacist prescriptive authority.[35]

Puzantian et al. surveyed about 20% of mostly urban community pharmacies in California to determine if pharmacists were aware of information such as available naloxone formulations, cash price, and whether naloxone could be billed to insurance 2 years after implementation of pharmacist-furnished naloxone legislation in 2016.[36] The survey had a 95%

response rate and estimated that pharmacist-furnished naloxone with a physician prescription was available at 23.5% of pharmacies, with significantly more chain pharmacies (31.6%) furnishing naloxone in this way than independent pharmacies (7.5%). About 83.6% of the pharmacies offered the nasal formulation and only 5.2% offered buprenorphine-naloxone combination. Only half of the pharmacies surveyed kept naloxone in stock, with chain pharmacies more likely to do so.[36]

Another study in RI evaluated naloxone distribution through the Preventing Overdose and Naloxone Intervention (PONI) program, which is the opioid overdose prevention program in Rhode Island.[37] Participants from high-risk communities were recruited, completed a short medical history, and trained on common causes of opioid overdose, techniques for prevention, proper and improper responses, and administration of intramuscular naloxone. Participants completed a short quiz after the training, and prescribed naloxone was dispensed upon physician's approval. Due to the limited pattern of data collection in this study, only 10 out of 120 participants returned for follow-up. Half reported utilizing their overdose response training but did not find it necessary to administer naloxone. The other five successfully administered IM naloxone to reverse an opioid overdose. Despite the limited data, PONI helped with naloxone distribution, saved lives, and demonstrated feasibility in Rhode Island.[37]

A cross-sectional census of Indiana community pharmacists showed that numerous pharmacy- and pharmacist-level characteristics related to structural capacity impacted the likelihood of stocking naloxone. Specifically, pharmacies with more than one full-time pharmacist (OR: 1.6) and chain pharmacies (OR: 3.2) were more likely to stock naloxone, as were pharmacists who had received continuing education on naloxone (OR: 1.3).[38]

Do et al. surveyed 58 pharmacists in San Francisco to evaluate pharmacists' acceptability of naloxone dispensing to patients prescribed opioids in clinics participating in a naloxone intervention. A slight majority of pharmacists (55.2%) reported experiencing no problems with dispensing naloxone, and the most cited problem was insufficient naloxone knowledge.[39] Another survey assessing 157 pharmacists' readiness to dispense naloxone across community pharmacies in West Virginia reported that only 20.4% of pharmacists felt comfortable selling naloxone without a prescription.[40]

Ancillary Services

Pharmacists seem to play a larger role in OUD management by provision of ancillary services in conjunction with MAT. Such ancillary services include naloxone distribution, MAT programs, prescription monitoring programs/restriction programs, pharmacists receiving OUD related training, controlled substance stewardship programs, and syringe exchange programs. Naloxone standing orders involve a physician issuing a written order for pharmacists to distribute naloxone to patients who meet predetermined criteria such as risk of opioid overdose. Syringe exchange programs involve providing injection drug users with new syringes and safely disposing of used syringes.

Pharmacist Receiving Training

Stewart et al. surveyed Michigan pharmacists to identify gaps in knowledge regarding naloxone and found that only 64% of pharmacists could identify the signs of an opioid overdose. About 74% agreed that a CE or training is important prior to dispensing naloxone; however, only 20% had completed one.[41] Another survey of North Carolina pharmacists examined barriers to naloxone dispensing, finding that only 30% of pharmacists scored greater than 90% on the naloxone knowledge assessment portion of the survey. Lack of training was the most cited

barrier to dispensing naloxone in a community pharmacy, and there was a correlation between pharmacists' knowledge on naloxone and opioid overdose and willingness to dispense naloxone.[42]

Palmer et al. Investigated the impact of a 90-minute Kentucky Board of Pharmacy training program covering naloxone access, opioid overdoses, the pharmacology and use of naloxone, protocol development, patient identification, and resources.[43] The training program offered an opportunity for pharmacists to receive the required education to apply to the Board of Pharmacy for certification be able to dispense naloxone under a physician-approved protocol in preventing opioid overdose deaths in Kentucky. Specifically, it covered the safe dispensing of opioids and the use of naloxone as rescue therapy for opioid overdose.[43] A total of 1320 pharmacists and 348 student pharmacists successfully completed the naloxone training. The article notes that while training pharmacists may be the first step towards expanding pharmacist involvement in naloxone dispensing, pharmacists still need to enter into physician-approved naloxone protocol.[43]

Controlled substance stewardship

Pharmacists can be involved in thorough patient chart review programs to prevent patients from obtaining excessive or beyond guideline recommended amounts of controlled substances. These programs thus reduce unnecessary risk associated with controlled substances and potential development of OUD.

A patient-centered medical home at a small health-system implemented a controlled substance stewardship program to promote appropriate use of controlled substance, reduce misuse and abuse, decrease morbidity and mortality, and improve patient outcomes.[44] Pharmacy residents performed initial and subsequent reviews at 1 and 3 months for over 1300 patients. The

number of patients receiving opioids decreased by 67.2%, and there was a 65.6% decrease in the number of patients receiving benzodiazepines. Subsequent premature deaths declined by 50% between 2013 and 2015.[44]

A survey of pharmacists in Texas and Utah with low response rate (19%) investigated prescription opioid misuse screening and discussion with patients.[45] Pharmacists who reported currently screening patients for opioid misuse had more than 4 times greater odds of engaging in discussions with patients on misuse. Pharmacists who wanted to help their patients who misuse were more than 3 times as likely to discuss current misuse. Pharmacists commonly indicated that too little training on working with individuals who misuse prescription medications presented a barrier to engaging in screening efforts but "possessing quick and easy screening questionnaires would motivate them to work with patients who misuse".[45]

PMP/Restriction Programs

Pharmacists can further engage in promoting safe opioid use by continued monitoring of state PMP and restriction programs. Most pharmacists seemed to have more favorable opinion towards PMP, but regular utilization of the state-run programs could improve.[46] Another form of restriction in the US includes the class-wide risk evaluation and mitigation strategy (REMS) for extended-release (ER) and long-acting (LA) opioids.[47] The goal of REMS is to address the risks of the entire medication class of ER/LA opioids, and has 3 components: 1) medication guide, 2) elements to ensure safe use, 3) timetable for submission of assessments. Prescriber and pharmacist participation in REMS is voluntary, but to compensate for lost times and resources, manufacturers are suggested to provide reimbursement for REMS participation.[47]

Keast et al. evaluated the incremental effect of prescriber restrictions to a Pharmacy-Only Patient Review and Restriction Program (PRRP) on pharmacy and resource utilization (such as

medical and pharmacy costs, prescription counts, and opioid use per member per month) from administrative claims data of enrolled members.[48] The PRRP resulted in a reduction in opioid use per member per month for both groups for short-acting opioids but no differences in daily morphine equivalents, benzodiazepine (BZD) prescriptions, or maintenance prescriptions.[48]

Green et al. also surveyed 294 pharmacists in two states, Connecticut (CT) and RI, with different PMP accessibilities explored use of PMPs in pharmacy practice and examined associations between PMP use and pharmacists' responses to suspected diversion or "doctor shopping."[49] The CT PMP is readily accessible and provides a report within seconds to providers. The RI PMP requires inquiries to be called in, faxed, or mailed to the RI Board of Pharmacy, who oversees the RI PMP. The proportion of respondents who had ever used the PMP was 770% higher among CT pharmacists than those in RT. PMP users were less likely to address concerns on suspicious medication use behavior and state they were out of stock of the drug than non PMP users, but as likely to contact the provider, refer the patient back to the prescriber, refuse to fill the prescription.[49]

Syringe Exchange Programs

Pharmacists can also be involved in Syringe Exchange Programs (SEP) to promote harm reduction patients with OUD. A survey of community pharmacists and coordinators participating in syringe exchange programs (SEP) in England showed that the SEP program reached many IDUs. Commonly reported policies and protocols implemented by SEPs included: disposal of contaminated waste; supply of swabs, filters and ascorbic acids; and referrals. Eighty-three percent (83%) of SEP pharmacies provided pre-packaged injecting equipment, while 12.1% provided it as a "pick-and-mix". There was a return rate of 30% of the injection units, although not all pharmacists provided data on this.[50]

A study in Portugal found that 59.4% of pharmacies were actively participating in SEP, 24.8% were former participants, and 15.7% had never participated in SEP. A strict "one-for-one" policy was implemented by 64.3% of active SEP participants, and only 21.6% had a limit to the number of syringes distributed to IDUs. About 62.4% of respondents provided at least one kit to IDUs without a syringe to exchange, and 20.9% had refused offering SEP in the previous year due to concerns like lack of used syringes to return and 22.0% due to violent behavior.[51]

Tesoriero et al. surveyed New York pharmacists registered in a SEP in 2002 and 2006 showed that more than 90% of pharmacists reported "no problems" or "very few problems" when asked about their experience with SEP. Most of the pharmacists (91.6% in 2002 and 89.7% in 2006) believed that a limit of 10 syringes per transaction was "just right." The proportion of pharmacists selling sharps containers significantly increased from 2002 (85.2%) to 2006 (92.8%), as did the number of pharmacists distributing literature on syringe disposal 25.1% in 2002 to 38.3% in 2006.[52]

Table 2a: Summary of Direct Pharmacist Management Authors and Titles of Articles

	Authors	Title	Study Design	N	Major Results	Limitations
Pharmacist / community pharmacy and physician collaboration						
1	DiPaula et al. (2015)[17]	Physician-pharmacist collaborative care model for buprenorphine-maintained opioid-dependent patients	Physician-pharmacist collaborative practice description	12 patients	Increase in retention rate from 40-60% to 100% at 6 months and 50% to 73% at one year	Single pilot study with low sample size
2	Feroni et al. (2005)[18]	Collaboration between general practitioners and pharmacists in the management of patients on high-dosage buprenorphine treatment	Telephone survey	345 general practitioners	54% of general practitioners reported using pharmacists for guideline recommended high-dosage buprenorphine management	Majority of the study in French
3	Gauthier et al. (2018)[19]	Improved treatment-retention for patients receiving methadone dosing within the clinic providing physician and other health services (onsite) versus dosing at community (offsite) pharmacies	Cohort	3,743 patients	Patients filling methadone prescriptions at an onsite (rather than offsite) pharmacy with physicians and other health services were 77% less likely to withdraw from treatment before 1 year	Not able to discern what aspects of onsite pharmacy led to this result including patient choice of pharmacy
4	Lofwall et al. (2010)[20]	Pharmacy willingness to partner with office-based opioid dependence treatment providers in conducting random buprenorphine pill counts	Telephone survey	242 pharmacies	74% of pharmacies willing to participate in pill counts	Rural region of US, only asked about participation in pill counts
5	Thompson et al. (2016)[21]	Pharmacist, physician collaborate at clinic to treat opioid dependence	Physician-pharmacist collaborative practice description	14 community health centers	51% of opioid dependence patients remain in treatment at 12 months	Descriptive article
6	Duvivier et al. (2017)[22]	Indian Health Service pharmacists engaged in opioid safety initiatives and expanding access to naloxone	Evaluation Study	N/A	Pharmacists assessed overdose risk, prescribed naloxone, provided patient and caregiver education, and provided referral to specialists	Less generalizable since the study examined the program within the Indian Health Service population
Pharmacist-Led Opioid Substitution Services						
1	Radley et al. (2017)[24]	'Standing Outside the Junkie Door'- service users' experiences of using community pharmacies to access treatment for opioid dependency	Qualitative focus groups	41 participants in 7 focus groups	Participants experienced stigma and discriminatory practices at pharmacies from which they received ORT	Focus group and small sample size
2	Matheson et al. (2016)[25]	Community pharmacy services for people with drug problems over two decades in Scotland: Implications for future development	Survey	709 pharmacists	Pharmacists' attitudes towards drug misuse have improved over time and having training and being male are associated positive attitudes	Limited to Scotland

3	Uosukainen et al. (2013)[26]	First insights into community pharmacy based buprenorphine-naloxone dispensing in Finland	Survey	64 pharmacies	80% questioned reported need for more education and financial renumeration and perceived buprenorphine-naloxone dosing was outside of the pharmacist's scope of practice	Limited to Finnish pharmacies and did not conduct multivariate analyses
4	Winstock et al. (2010)[27]	Problems experienced by community pharmacists delivering opioid substitution treatment in New South Wales and Victoria, Australia	Cross-sectional Survey	593 New South Wales pharmacies, 393 Victoria pharmacies	41% of pharmacies refused a dose to a client for any reason in the last month and had a low level of perceived confidence in identifying opioid withdrawal or toxicity	Pharmacists asked about presence of experience, not number of experiences Only pharmacists in charge were questioned. Risk of social desirability and affirmative response bias
5	Lea et al. (2008)[28]	Consumer satisfaction with opioid treatment services at community pharmacies in Australia	Survey	508 clients at 50 community pharmacies	61% reported satisfaction with treatment program, less satisfied with privacy, but most felt welcomed by pharmacy staff	Selection bias possible Underrepresentation of buprenorphine to methadone clients Reluctance of patients to provide negative appraisal to pharmacy treatment
6	Duvivier et al. (2017)[22]	Indian Health Service pharmacists engaged in opioid safety initiatives and expanding access to naloxone	Evaluation Study	N/A	IHS pharmacists support expanded access to MAT therapies, including buprenorphine and naltrexone	Less generalizable since the study examined the program within the Indian Health Service population
Pharmacist- led methadone programs						
1	Jaffray et al. (2013)[29]	Does training in motivational interviewing for community pharmacists improve outcomes for methadone patients? A cluster randomized controlled trial	Cluster randomized controlled trial	542 patients at 76 pharmacies	Patients demonstrated a reduction in illicit heroin use and improved treatment satisfaction from baseline, but no difference in treatment retention or treatment satisfaction	Lower-than-expected patient follow-up Inability to determine if intervention was delivered as intended Inconsistent motivational interview training with difficulty in assessing motivational interviewing competency
Pharmacists Providing Training						
1	Akers et al. (2017)[30]	Implementing take-home naloxone in an urban community pharmacy	Evaluation study	1400 trainees	THN programs were successfully implemented into community pharmacies to increase awareness and access to naloxone, and led to a decrease in overdose deaths	One limitation is that there is no mandatory reporting requirement regarding naloxone use. There is also no information as to the client receiving naloxone (i.e.

						patient, family/friends, or community worker).
2	Duvivier et al. (2017)[22]	Indian Health Service pharmacists engaged in opioid safety initiatives and expanding access to naloxone	Evaluation Study	N/A	IHS pharmacists have successfully completed advanced training on responsible opioid prescribing, increased access to MAT, and increased access to naloxone for opioid overdose reversal. Pharmacists developed a comprehensive training program and program measurement tool for law enforcement officers. 350 law enforcement officers in 6 districts were successfully trained by the tools developed by IHS pharmacists	Less generalizable since the study examined the program within the Indian Health Service population
Naloxone Distribution						
1	Davis et al. (2017)[32]	State legal innovations to encourage naloxone dispensing.	Commentary	N/A	Forty-four states permit naloxone to be prescribed to non-patients. Forty-two states permit naloxone to be dispensed via none patient-specific mechanisms. Liability risks related to naloxone dispensing are low to very low.	Descriptive article
2	Zaller et al. (2013)[33]	The feasibility of pharmacy-based naloxone distribution interventions: a qualitative study with injection drug users and pharmacy staff in Rhode Island	Qualitative interviews	21 injection drug users (IDUs) and 21 pharmacy staff (pharmacists and technicians)	Most participants supported the initiation of pharmacy-based naloxone intervention, but identified barriers such as misinformation about naloxone, interpersonal relationships between IDUs and pharmacy staff, and costs of such an intervention	Small sample size, not generalizable since interview was only conducted in Providence, RI. Possibility of recall bias with respect to trends of IDU-pharmacy staff interactions
3	Morton et al. (2017)[34]	Pharmacy-based statewide naloxone distribution: A novel "top-down, bottom-up" approach	Descriptive study	N/A	There was a significant increase in the number of pharmacies dispensing naloxone, number of naloxone doses dispensed, and the number of counties in which naloxone was available through pharmacies. There was a 9-fold increase in naloxone Medicaid	Inability to effectively evaluate distribution, proper use, and overdoses reversed among patients receiving naloxone. Extracting data from a claims database poses some challenges, and there could be an underestimation of the impact of the programs implemented in this

					claims in the first half of 2016 when compared to 2014	study. Inability to differentiate between naloxone dispensed under the statewide standing order from those dispensed by other prescribers
4	Wulz et al. (2017)[23]	The pharmacist role in the development and implementation of a naloxone prescription program in Alabama	Descriptive report	N/A	83 clients were trained and 150 naloxone kits were distributed among heroin and opioid users, family members, friends, and other third-parties involved with users.	Most of the advertisements came in early February 2016, well after the initial launch of the naloxone prescription program in November 2015. Poor attendance upon initiation of the trial as participants mistakenly thought they would be receiving a combination buprenorphine-naloxone hydrochloride but were only receiving naloxone only product.
5	Bailey et al. (2014)[35]	Naloxone for opioid overdose prevention: pharmacists' role in community-based practice settings	Qualitative study	6 pharmacists	33% of pharmacists practiced in a community setting and 67% practiced in outpatient clinic-based settings. 5 of 6 pharmacies required a provider's prescription to dispense naloxone, and only 1 pharmacy was able to exercise pharmacist prescriptive authority.	Small sample size. Lack of generalization given the providers interviewed work in large metropolitan cities
6	Puzantian et al. (2018)[36]	Provision of Naloxone Without a Prescription by California Pharmacists 2 Years After Legislation Implementation	Telephone survey	1147 pharmacies	Pharmacist-furnished naloxone, without a physician prescription, was available in 23.5% of pharmacies with 31.6% of them being chain pharmacies and 7.5% being independent pharmacies. 83.6% offered a nasal formulation and 5.2% offered combination buprenorphine and naloxone tablets for OUD. Only 50.6% of pharmacies stocked nasal naloxone	Under-representation of rural pharmacies, inclusion of non-pharmacist respondents, restriction to only the state of California
7	Muzyk et al. (2019)[53]	Pharmacists' attitudes toward dispensing naloxone and medications for opioid use disorder: A scoping review of the literature	Scoping review	N/A	80% of pharmacists had no negative concerns with filling a buprenorphine/naloxone prescription. Most pharmacists	The studies included lacked generalizability and comparator groups, and response rates were low

					supported having a naloxone standing order but are uneasy with the idea of dispensing naloxone without a prescription or physician's authority.	
8	Meyerson et al. (2018)[38]	Predicting pharmacy naloxone stocking and dispensing following a statewide standing order, Indiana 2016.	Cross-section census	284 pharmacists	Pharmacies with the structural capacity were more likely to stock naloxone: more than one full-time pharmacist (1.6 times as likely); pharmacists receiving continuing education on naloxone (1.3 times as likely); chain pharmacies (3.2 times as likely).	Low response rate (33.4%)
9	Do et al. (2018)[39]	Acceptability of Naloxone Dispensing Among Pharmacists.	Survey	58 pharmacists	55.2% of pharmacists had no problems with dispensing naloxone. Inadequate training to educate patients on naloxone was the most cited problem. 43.4% wanted authority to dispense without a prescription	Convenience sampling method. Survey was self-administered resulting in incomplete and missing data
10	Thornton et al. (2017)[54]	Pharmacists' readiness to provide naloxone in community pharmacies in West Virginia.	Cross-sectional survey	157 pharmacists	Only 20.4% of pharmacists feel comfortable dispensing naloxone without a prescription	Low generalizability and convenience sampling since the survey was only done in West Virginia
11	Yokell et al. (2011)[37]	Opioid overdose prevention and naloxone distribution in Rhode Island	Survey	120 participants	Out of 120 participants, 10 participants that returned for follow-up with PONI staff. Only 5 used their overdose response training and did not find it necessary to administer naloxone and the other 5 successfully administered intramuscular naloxone to reverse an opioid overdose	The lack of significant follow-up from patients due to the passive nature of PONI's reporting system is a limitation.

Table 2b: Summary of Ancillary Pharmacist Services Authors and Titles of Articles

	Authors	Title	Study Design	N	Major Results	Limitations
Pharmacists Receiving Training						
1	Palmer et al. (2017)[43]	Development and delivery of a pharmacist training program to increase naloxone access in Kentucky	Descriptive study	N/A	1254 pharmacists and 348 student-pharmacists completed training for naloxone certification, and 646 (52%) and received naloxone-certified status.	Not all pharmacists that obtained a naloxone-certification were trained under the program.
2	Stewart et al. (2018)[41]	Pharmacists' knowledge, support, and perceived roles associated with providing naloxone in the community.	Survey (email)	211 pharmacists	Only 64% of pharmacists could identify an opioid overdose. 74% highlighted the importance of naloxone training, but only 20% had actually received training or education on naloxone	Low generalizability and small sample size
3	Rudolph et al. (2018)[42]	Identifying barriers to dispensing naloxone: A survey of community pharmacists in North Carolina.	Cross-sectional survey	423 pharmacists	Only 30% of pharmacists scored over 90% on the naloxone knowledge assessment. There was a correlation between lack of training and willingness to dispense naloxone	Low response rate (7.4%) and lack of generalizability
Controlled Substance Stewardship						
1	Homsted et al. (2017)[44]	Population health management in a small health system: Impact of controlled substance stewardship in a patient-centered medical home	Chart review	1,300 patient reviews	There was a 67.2% decrease in the number of Penobscot Community Health Care (PCHC) patients receiving chronic opioids and a 65.6% decrease in the number of patients receiving benzodiazepines. Premature deaths were reviewed to identify associations with opioids prescribed at the time of death, which revealed a decline of 50%	This study only looked at certain high-risk medications such as opioids, BZDs, and carisoprodol. The study was also performed in a small health-system.
2	Cochran et al. (2015)[45]	Pharmacists Who Screen and Discuss Opioid Misuse With Patients: Future Directions for Research and Practice.	Cross-sectional Web-based survey	739 (360 from Texas pharmacists and 379 from Utah pharmacists)	62,2% of PO abuse with patients also screened. Chain pharmacists were the largest group to engage in discussions regarding misuse (38.3%) while hospital pharmacists were the smallest group (43.1%). Screening increased the odds of	This study had a low response rate by pharmacists. These results may only be representative of a portion of pharmacists' perspectives in either state.

					engaging in discussions on PO misuse by more than 4-fold.	
PMP/Restriction Programs						
1	Keast et al. (2017)[48]	Incremental Effect of the Addition of Prescriber Restrictions on a State Medicaid's Pharmacy-Only Patient Review and Restriction Program	Case Control Study	504 (378 controls and 126 cases)	There was a reduction in mean PMP use for both groups for short-acting opioid claims, overall opioid claims, prescribers. Cases had significantly larger decrease in short acting opioids, number of prescribers and number of pharmacies relative to controls. No differences in daily morphine equivalents, BZD prescriptions, or maintenance prescriptions.	Errors with administrative claims data such as billing and coding. The analysis did not account for patients who were members of the MOK pharmacy-only PRRPs who received opioids which were not covered by Medicaid.
2	Green et al. (2012)[49]	How does use of a prescription monitoring program change pharmacy practice?	Survey	294 pharmacists (198 in CT and 96 in RI)	Respondents in CT who had ever used PMP was 770% higher than those in RT. PMP users were less likely to address concerns on suspicious medication use behavior and state they were out of stock of the drug than non PMP users, but as likely to contact the provider, refer the patient back to the prescriber, refuse to fill the prescription	Low sample size in the RI group. Low external validity since other states could have different PMP systems
Syringe Exchange Programs						
1	Torre et al. (2010)[51]	Syringe exchange in community pharmacies—The Portuguese experience	Cross-sectional survey	1538 pharmacies	59.4% of pharmacies were actively participating in SEP, 24.8% were former participants, and 15.7% had never participated in SEP. 76.2% of pharmacies implemented a policy of selling syringes. A strict "one-for-one" policy was implemented by 64.3% of active SEP participants, and only 21.6% had a limit to the number of syringes distributed to IDUs.	Limited to Portuguese pharmacies
2	Sheridan et al. (2000)[50]	Pharmacy-based needle exchange schemes in South East England: a survey of service providers	Survey (mail)	381 pharmacists and 32 coordinators	83% of SEP pharmacies provided pre-packaged injecting equipment while 12.1% provided as a "pick-	Not all pharmacist provided data on the number of injection units returned for an exchange.

					and-mix". There was a return rate of 30% of the injection units.	
3	Tesoriero et al. (2009)[52]	Expanding access to sterile syringes through pharmacies: Assessment of New York's Expanded Syringe Access Program	Survey (mail)	506 pharmacists (2002); 346 pharmacists (2006)	Decrease in pharmacists requiring any additional procedures prior to the sale of syringes from 51.4% in 2002 to 45.1% in 2006. Most pharmacists reported "no problems" or "very few problems" regarding their SEP experience, believed that a limit of 10 syringes per transaction was "just right".	Lack of patient perspective. Possible bias since NYS-DOH regulates SEP and also administered the survey.

Discussion

It is clear from the literature that pharmacists have a long-standing role in OUD management and harm reduction strategies, although the extent and aspects of the role are highly variable especially comparing the US and other countries. Since the introduction of methadone in the 1960s, pharmacists have been involved in dispensing treatment and are increasingly involved in collaborative practices with prescribers to manage therapy. However, this does not mean that pharmacists perceive that they are valued in that role or have sufficient training.[26,27]

A major theme that arose from the literature was concern for stigma related to OUD behaviors.[24,26,28,55] Patients are concerned about stigma and privacy, and pharmacists may be concerned with safety. However, Raisch et al reported from a survey of pharmacists, that "the majority of respondents (85%) indicated that patients with OUD did not cause problems at their pharmacies. Compared with their experiences in dispensing other narcotic medications, most respondents did not express increased concern regarding prescription forgery (75%) or diversion (80%) of buprenorphine/naloxone."[56] Pharmacists are increasingly trained in interpersonal skills including patient communication, building relationships, and empathy with specific tools including motivational interviewing. While the literature suggests that patients may not receive additional benefit from motivational interviewing in terms of retention of OUD treatment, pharmacists may be uniquely trained to navigate patients who exhibit difficult behaviors.

From this review, adoption of pharmacist led buprenorphine management is less prevalent in the literature than methadone. The use of MAT in the treatment of OUD has shown several benefits, including: a decrease in overdose deaths; an increase in social functioning and retention in treatment; and a reduction in symptoms of neonatal abstinence syndrome in opioid-dependent pregnant

women.[57–59] Higher methadone prevalence may be due to the long-standing use and understanding of methadone, resulting in more common acceptance of pharmacist involvement. However, as this review shows, retention improves when pharmacists are involved in collaboration of OUD management.[19,21,60] Additionally, pharmacist collaboration with physicians reduced office-based opioid treatment burden among physicians, therefore, further supporting the idea that pharmacists could have more expansive roles in contributing to OUD.[61] Thus, this review of the literature suggests that there is a need to improve the implementation and evaluation of innovative pharmacist-led OUD programs.

The study by Bailey et al.[35] suggests that most pharmacists are actively seeking out patients at high risk of overdose and on high-dose opioids to provide harm-reduction services. Pharmacists are one of the most accessible health professionals, thus, their role in OUD should be expected to increase over the next few years.

Evidence has shown that about 50% of individuals, who received naloxone and were trained on administration, common causes of OD, techniques for prevention, proper and improper responses,[37] successfully helped prevent an overdose. Although pharmacists agree on the importance of naloxone distribution without a prescription, not many are undertaking this approach due to lack of training.[40,53] There is more information on pharmacists providing training to patients and other third parties, but limited information on pharmacists receiving adequate training.

Pharmacist-furnished naloxone has been shown to be a feasible way to increase naloxone distribution in the community.[62] With only 23.5% of pharmacies in California providing this service and only half of them stocking naloxone, more pharmacist training is required to increase awareness on current laws enacted to curb the opioid epidemic.[36] Additionally, wide-spread third-party training

of naloxone administration by pharmacists is highly recommended, as patients are unlikely to be able to administer naloxone to themselves in the event of an emergency. In naloxone distribution programs, such as PONI, and even with financial incentives, it is difficult to discern if training resulted in prevention of an overdose due to low follow-up information from trained individuals on administration of naloxone in the community.[37] Thus, an adequate follow-up period with participants is recommended to monitor the overall success rate of the dispensed naloxone or the program, itself, training, and in reversing opioid overdoses.

From this review, there were more articles about pharmacist participation in prescription monitoring programs than identification of patients at risk of OUD through controlled substance stewardship. However, there is a lack of standardization in implementation and utilization of PMP programs across states.[49,63–65] Given that pharmacists can utilize the PMP, compulsory controlled stewardship programs allow for pharmacists to engage with other providers to address OUD.[44,66] Standardization of PMP across states would also allow for increased pharmacist identification of patients at risk of OUD. Lastly, there is limited research reported about the success of syringe exchange programs in the US. Policies and procedures, such as a strict "one-for-one" and a limited distribution of syringes to each patient per time period, could be applied and measured in the US.[51] Thus, there is a large opportunity for growth in pharmacist participation in harm reduction programs such as syringe exchange programs.

Limitations

As many of the articles in OUD were published in years before online access, there were at least five articles that were relevant to this review that could not be accessed online (2 for opioid substitution and 3 for pharmacist let methadone programs). Additionally,

the majority of direct pharmacist led studies were published outside of the US, with some studies not available in English. All pharmacist-led OST reported programs were outside of the US, whereas collaborative programs were more common in the US. Additionally, the authors suspect that there are many more programs to manage OUD patients in collaborative settings that have not been published. This may be due to the lack of novelty in traditional OUD management.

Conclusion

There is a clear need for pharmacists to be involved in OUD management to improve outcomes and to help reduce physician burden in a complex, difficult to manage disease state that requires regular patient follow-up. Interest in creating innovative collaborative practice agreements and implementing those programs to help manage OUD could significantly improve patient outcomes, notably adherence to treatment. While pharmacists can have relevant impact in OUD via direct patient management and ancillary services, barriers such as lack of training, education, time constraints, and lack of reimbursement, need to be addressed. Pharmacists have shown their willingness to implement several harm-reduction strategies within their practice sites, so their roles in OUD should be tailored towards direct-patient management given they are the most accessible and frequently visited health care professional.

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CHAPTER 3: SPECIFIC AIM #1

Community pharmacists in Virginia dispensing naloxone under a standing order: A qualitative study

First Author:

Stephen C. Ijioma, PharmD, BA

Health Economics and Outcomes Research (HEOR) postdoctoral Fellow,

Department of Pharmacotherapy and Outcomes Science, VCU School of Pharmacy, Richmond, VA, USA

Global Health Economics & Outcomes Research, Indivior Inc., Richmond, VA, USA

ORCID: 0000-0001-5270-0832

Second Author:

Elena V. Fernández, PharmD, PhD

PhD Student, Department of Pharmacotherapy and Outcomes Science, VCU School of Pharmacy, Richmond, VA, USA

ORCID: 0000-0003-4707-0383

Third Author:

Sharon B. Gatewood, PharmD, BS

Associate Professor, Department of Pharmacotherapy and Outcomes Science, VCU School of Pharmacy, Richmond, VA, USA

ORCID: 0000-0002-6099-0611

Fourth Author:

Norman V. Carroll, PhD, MS, BSPharm

Professor, Department of Pharmacotherapy and Outcomes Science, VCU School of Pharmacy, Richmond, VA, USA

Fifth and Corresponding Author:

Teresa M. Salgado, PhD, MPharm

Assistant Professor, Department of Pharmacotherapy and Outcomes Science, and Assistant Director, Center for Pharmacy Practice Innovation, VCU School of Pharmacy, Richmond, VA, USA

ORCID: 0000-0003-2708-7145

Postal Mailing Address: 410 N. 12th Street | Box 980533 | Richmond, VA 23298
Email: tmsalgado@vcu.edu
Author contribution statement: Stephen Ijioma: Investigation, Formal Analysis, Writing – Original draft preparation, Writing – Reviewing and Editing. **Elena Fernández**: Investigation, Formal Analysis, Writing – Reviewing and Editing. **Sharon Gatewood**: Resources, Writing – Reviewing and Editing. **Norman Carroll**: Conceptualization, Writing – Reviewing and Editing. **Teresa Salgado**: Methodology, Analysis Supervision, Writing – Reviewing and Editing.

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Abstract

Background: In 2016, the Virginia Health Commissioner signed a standing order into law allowing licensed pharmacists to dispense opioid receptor antagonists (ORAs) for overdose reversal.

Objectives: Using the theory of planned behavior as an initial guide to study development, the aim of this qualitative study was to explore community pharmacists' attitudes, subjective norm, perceived behavioral control, and behavioral intention toward dispensing ORAs under a standing order in Virginia.

Methods: Semi-structured interviews were conducted with community pharmacists across the Commonwealth between June 2018 and October 2019. Interviews were recorded, transcribed *verbatim*, and thematically analyzed.

Results: Twenty-one community pharmacists were interviewed. Pharmacists were confused about the specifics and the processes involved with dispensing naloxone under the standing order. Furthermore, many recognized the underuse of the standing order. Positive attitudes focused on the life-saving action of ORAs. Negative attitudes included encouraging risky behaviors by patients, negatively affecting the patient-pharmacist relationship, offending or contributing to stigmatizing patrons, and having liability issues to the pharmacy. Subjective norms regarding dispensing of ORAs under the standing order were perceived to be favorable among peer pharmacists and primary care and emergency department physicians but may be seen as profit-seeking by patients. Barriers to service provision included lack of guidance from corporate offices (in chain pharmacies), inadequate training, patient out-of-pocket costs, reimbursement issues, inadequate staffing and time, and stigma. Facilitators comprised the existence of practice site-specific protocols, the REVIVE! training, technician support, increased community awareness, physician collaboration, pharmacist training,

and employer guidance. Whereas some pharmacists intended to become more familiarized with the standing order, others did not intend to actively identify patients who were at risk of an opioid overdose.

Conclusion: Pharmacists expressed mixed behavioral intention toward dispensing ORAs under the standing order. Future research should focus on quantifying the uptake of the standing order at the state level.

Keywords: pharmacists, community pharmacy services, naloxone, Virginia, qualitative research

Key Points

Background:

- In the United States, all 50 states and the District of Columbia allow pharmacists to dispense or prescribe opioid receptor antagonists (ORAs) without a medical prescription through mechanisms such as standing orders or statewide protocols.
- In 2018, an average of 3 Virginians died of an opioid overdose daily from both prescription and illicit opioids.
- In November 2016, the Virginia Health Commissioner signed a standing order into law allowing licensed pharmacists to dispense ORAs for opioid overdose reversal.

Findings:

- Community pharmacists' attitudes, subjective norm, perceived behavioral control, and behavioral intention toward dispensing ORAs under a standing order in Virginia were identified.
- Community pharmacists recognized the current underutilization of the Virginia standing order and were confused about the specifics and the processes involved with dispensing naloxone under the standing order.
- Solutions to the unique barriers expressed by community pharmacists in Virginia are proposed.

Background

In the United States, an estimated 128 people die of an opioid overdose daily, amounting to as many as 450,000 deaths from both prescription and illicit opioids between 1999 and 2018.[1,2] The total economic burden of prescription opioid misuse alone is estimated to be as high as $78.5 billion per year.[1,3] In the Commonwealth of Virginia, on average, 3 Virginians died of an opioid overdose daily in 2018 from both prescription and illicit opioids.[4]

Opioid receptor antagonists (ORAs), such as naloxone, are used to reverse the effects of an opioid overdose.[5] If administered in a timely fashion, ORAs are effective in reversing opioid-related respiratory depression with minimal adverse effects.[6,7] Thus, ensuring the availability of ORAs to patients, family members, caregivers, or friends of patients at risk of an opioid overdose is critical.

As of January 2019, all 50 states and the District of Columbia allowed pharmacists to dispense or prescribe naloxone without a medical prescription through mechanisms such as standing orders or statewide protocols.[8-10] In November 2016, the Virginia Health Commissioner signed a standing order into law allowing licensed pharmacists to voluntarily dispense ORAs for opioid overdose reversal in accordance with the Virginia Drug Control Act x54.1-3408.[11] The standing order explicitly requires that naloxone recipients be counseled on opioid overdose prevention, overdose symptoms recognition, effectiveness and response after ORAs administration, proper administration and dosing, adverse effects, safety aspects, storage conditions, and expiration date, unless previous formal training has been received.[11] The REVIVE! program is a program in Virginia specifically developed to train

professionals, stakeholders, and members of the community on how to recognize and respond to an opioid overdose emergency.[11,12] No specific dispensing mandate exists in Virginia; thus, pharmacists use their clinical judgment to initiate codispensing of ORAs to individuals whom they believe may be at risk of an opioid overdose. Despite the Virginia standing order requiring pharmacists to counsel naloxone recipients, pharmacists are not mandated to complete any form of training before dispensing under the standing order, unlike other states such as Arizona, Indiana, Kentucky, or Wisconsin.[9]

Reported pharmacist-related barriers to the widespread dispensing of ORAs under a standing order in community pharmacies include reimbursement concerns, lack of support from management, inadequate pharmacist trainings, and ethical and moral concerns.[13-15] Pharmacists in Ohio expressed concerns about adequate staffing, space, and time.[16] In a survey of West Virginia pharmacists, approximately 38% agreed with the statement that allowing patients to acquire ORAs without a prescription would increase opioid overdosing.[17] In that study, only 20% of the pharmacists were comfortable dispensing naloxone without a prescription.[17] In regard to patient-related barriers, high out-of-pocket costs, fear of future consequences, stigma, and discomfort were some of the reasons hindering patients from accessing naloxone in community pharmacies.[18]

Objective

To the best of our knowledge, no public data regarding the uptake of the standing order across the Commonwealth of Virginia is available. It is also unknown what challenges pharmacists in Virginia face when dispensing naloxone under a standing order. Using

the theory of planned behavior (TPB) as an initial guide to study development,[19-21] this study aimed to explore community pharmacists' attitudes, subjective norm, perceived behavioral control, including barriers and facilitators, and behavioral intention toward dispensing naloxone under the standing order.

Method

Study Design

This was an exploratory descriptive qualitative study using semi-structured interviews to explore community pharmacists' experiences dispensing ORAs under a standing order in Virginia. The study was approved as exempt by the institutional review board at the Virginia Commonwealth University (HM20012772). Reporting followed the Consolidated Criteria for Reporting Qualitative Research checklist.[22]

Participants and Recruitment

Community pharmacists across Virginia with and without experience dispensing ORAs under the standing order and with various roles within the pharmacy (staff pharmacist, manager or pharmacist-in-charge, owner) were included. Three sampling strategies were employed to ensure that the opinions of pharmacists in rural, suburban, and urban areas within Virginia were captured. First, a convenience sample of community pharmacists recommended by Virginia Commonwealth University faculty members was contacted. Faculty established contact with individuals and a member of the research team followed up through e-mail to schedule a

telephone interview. This sampling technique was initially used for pilot-testing the interview guide and for subsequent interviews to obtain a broad understanding of the attitudes and beliefs of pharmacists, irrespective of geography. This sampling method was also used because of challenges in recruiting pharmacists as many pharmacists declined to participate. Second, a snowball sampling technique was employed wherein interviewees identified other individuals suitable to participate in the study. Because the initial convenience sample focused primarily on pharmacists practicing in an urban setting (Richmond, VA), we encouraged participants to identify additional pharmacists working in suburban or rural areas. Because convenience and snowball sampling are likely to reduce variation in responses, we employed an additional sampling method, random sampling, to ensure representation of perspectives from different areas of the Commonwealth, thus increasing the variability in responses. We identified counties with high, medium, and low prevalence of opioid-related deaths.[23] A list of community pharmacies in urban, suburban, and rural areas within each of these counties was created. A random sample of 2-6 pharmacies per county (66 pharmacies total), including independent, chain and mass merchandiser, was obtained by a random number generator. A member of the research team called each pharmacy to invite one of the pharmacists to participate. Verbal or written informed consent was obtained before conducting the interviews. Pharmacists were not compensated for participating in the study.

Research Instrument and Interview Method

The interview guide was developed based initially on TPB constructs[19] and adapted to reflect barriers and facilitators experienced by community pharmacists. Furthermore, the guide was thoroughly discussed by 3 of the researchers: a PhD-trained

pharmacist with extensive qualitative research experience, a PharmD-trained PhD candidate, and a PharmD-trained health economics and outcomes research postdoctoral fellow (Appendix 1). In our study, we used perceived behavioral control as a proxy for actual control because the latter can be difficult to measure.[19,24] Face validity was established by pretesting the instrument with 2 community pharmacists obtained from the convenience sampling process. Modifications to the interview guide resulting from the pilot-testing included removing or consolidating questions to avoid redundancy and clarifying confusing questions. Ultimately, the pretest interviews were not included in the analyses. The interview guide was iteratively modified following the first interviews to better guide the discussion and obtain insightful responses. When solicited by participants, the interview guide was sent through e-mail ahead of the interview. Demographic information collected included: age, sex, pharmacy degree, employment position, number of years of community pharmacy experience, employment status, and type and location of community pharmacy. No relationship between the individuals who conducted the interviews and the participants existed before the study, and no other individuals besides the participant and one of the researchers were present at the interview.

The interviews were conducted over the telephone by 1 male and 1 female PharmD researcher between 2 time frames: June 2018-September 2018 and May 2019-October 2019. Both researchers held positive views toward ORAs dispensing under the standing order, and they were cautious not to contradict or bias interviewees toward their perspectives. Participants were informed of our research objective, and they were continually recruited into the study until data saturation was achieved. Data saturation was reached when the information provided by the respondents became redundant and no new content to identified themes or additional themes arose.[25] To operationalize saturation in our study, we linked concepts and themes from multiple interviews until no new unique

findings could be derived. All interviews were digitally audio-recorded and transcribed *verbatim* by an external transcriber. The researchers read the interview transcripts to ensure accuracy. No repeat interviews were conducted, and the participants did not receive a transcript of the interviews for comments or corrections since they were recorded.

Data Analysis

A preliminary version of the codebook was developed using a deductive approach based on the TPB's constructs.[19,26] Two PharmD researchers initially coded a sample of 5 transcripts independently using Atlas.ti version 8.4.24 (Atlas.ti Scientific Software Development, GmbH Berlin, Germany). Researchers discussed any coding discrepancies with a senior investigator with expertise in qualitative research. From the preliminary analysis and discussion among the 3 researchers, new themes emerged inductively from the data and a revised version of the codebook was created.[26] The remaining transcripts were independently coded and previously coded interviews were recoded to ensure accuracy. Researchers reconvened after coding every 5 interviews to address any discrepancies or disagreements. The coded passages were grouped into themes and subthemes. For example, perceived behavioral control was subgrouped into barriers and facilitators. Once all interviews were coded, a summary table compiling the main findings was created to identify relationships among themes. The importance of a theme identified in qualitative analysis is not necessarily related to the frequency of coding. As a result, we used expressions such as "most pharmacists," "a majority of pharmacists," "many pharmacists," or "most frequently cited" to show a high commonness of a discussed idea or theme among participants. Quotations were presented to illustrate themes.

To ensure methodologic rigor, the analysis upheld the following principles: (1) triangulation, by having 2 independent researchers analyze the data and discuss theme interpretation; (2) reflexivity, by having individuals from diverse backgrounds (2 PharmD-trained and a senior PhD-trained researcher) analyze the data, thus reducing bias stemming from investigators' previous assumptions and experiences; and (3) attention to negative or deviant cases by focusing our attention on participant perspectives that were different from the majority.[27-29]

Results

Of the 74 pharmacies contacted, 21 pharmacists, each from different pharmacies located in the Southwest, Valley, Central, Eastern, Hampton Roads, and Richmond regions, agreed to participate. Eight participants were recruited by convenience and snowball sampling, whereas random sampling yielded 13 pharmacists. Pharmacists were on average 46 years-old, and 52% were females (Table 1). The interviews lasted on average 34 minutes (range 19-60) owing to time constraints while interviewing pharmacists during their regular working hours at the pharmacy. Figure 1 summarizes the study findings.

Table 1: Demographic and employment characteristics of interview participants (n=21).

Characteristics	**Mean (SD)**
Years of community pharmacy experience	19 (12)

	N (%)
Age	
20 – 30	5 (24)
> 40 – 50	8 (38)
>50 – 60	3 (14)
>60 – 70	4 (19)
Missing	1 (5)
Sex	
Female	11 (52)
Pharmacy Degree	
PharmD	15 (71)
BPharm	5 (24)
Missing	1 (5)
Employment Position	
Manager/Pharmacist-in-charge	7 (33)

Staff	5 (24)
Owner/Part-Owner	1 (5)
Missing	8 (38)
Type of community pharmacy	
Independent	9 (43)
Traditional Chain	9 (43)
Supermarket	3 (14)
Employment status	
Full-time (>35hrs/week)	9 (43)
Part-time (≤ 35hrs/week)	4 (19)
Missing	8 (38)
Urbanicity	
Rural	12 (57)
Suburban	6 (29)
Urban	3 (14)

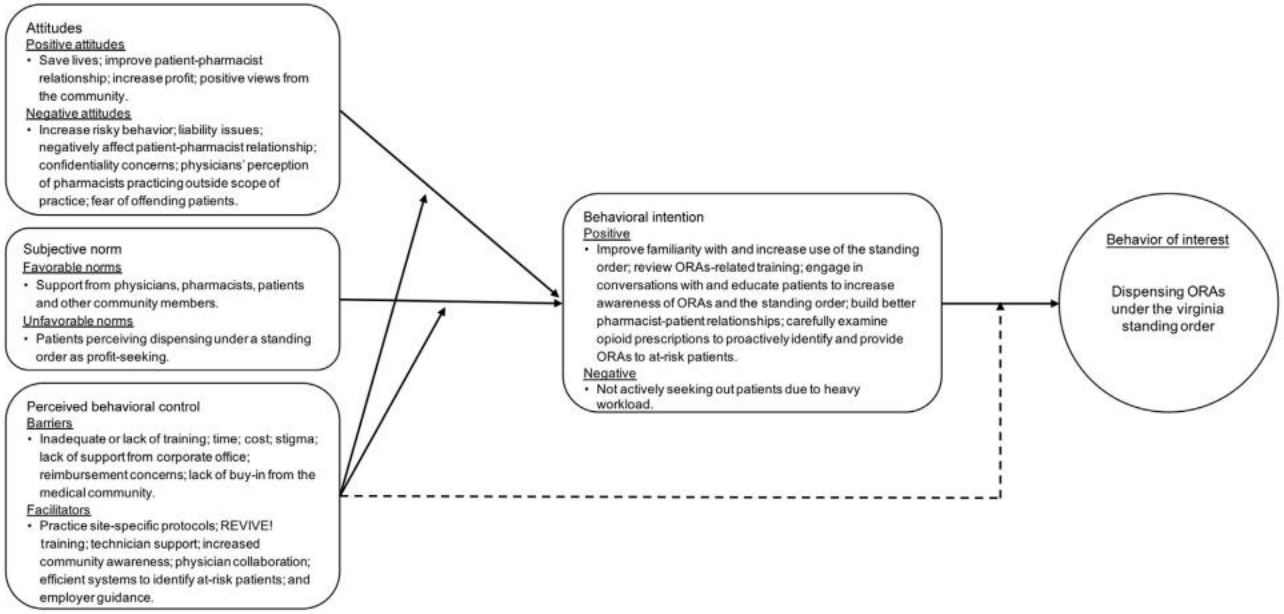

Figure 1: Conceptual map of the study findings. On the basis of the theory of planned behavior, Virginia community pharmacists' intention to dispense ORAs under the standing order is predicted by their positive or negative attitudes, favorable or unfavorable subjective norm, and perceived behavioral control (barriers and facilitators). Abbreviation used: ORA, opioid receptor antagonist.

Current role dispensing under the standing order

More than half (12 of 21) of the pharmacists indicated that they had previously dispensed ORAs under the standing order. However, there were concerns that the service was not being provided at full capacity, suggesting that the standing order is currently underused in Virginia. A quarter of the interviewees declared not having previous experience with the standing order.

An important issue that arose during the interviews was that the pharmacists were confused about the specifics and the processes involved with dispensing naloxone under the standing order. For example, when asked whether their pharmacy dispensed ORAs under the standing order up to full capacity, some pharmacists provided a response related to filling a regular medical prescription for ORAs.

Attitudes toward dispensing ORAs under the standing order

Positive attitudes

Positive beliefs held by the pharmacists focused mainly on the life-saving action of ORAs, thus resulting in positive attitudes toward dispensing under the standing order. In regard to the pharmacy as a business, benefits included profits from naloxone sales and positive views from the community for saving lives and being involved in combating the opioid epidemic. One pharmacist believed that keeping patients alive would ultimately result in retaining them as customers. Pharmacists also voiced that pharmacist-initiated ORAs codispensing contributed to improving the patient-pharmacist relationship by promoting pharmacist engagement in patient care, thus increasing trust between both parties.

Negative attitudes

Negative beliefs voiced included the perception that dispensing ORAs under the standing order would encourage risky behaviors by patients. "…people who have been taking opioids for a really long time […] might feel more like they could take more [opioids] or... take them [opioids and ORAs] at the same time because they have that extra layer of [protection]" (community pharmacist [CP6]). However, others believed that increasing ORAs availability was not associated with increased risk of overdose. "People engage in plenty of risky behavior regardless… I don't think there's going to be an increase in opioid usage now just because we have more availability of naloxone. I think having something that could save somebody's life is always a positive" (CP16).

Pharmacists feared offending patients if they initiated codispensing of ORAs under the standing order for patients whom they believed to be at risk of an opioid overdose. As a result, they felt justified not providing the service up to full capacity. "I would say not up to full capacity just because, you know, just the barriers of you not wanting to potentially offend someone […] I would say we could do a better job at [dispensing ORAs under the standing order], but we do have [ORAs] available" (CP1).

Although the Virginia standing order allows pharmacists to dispense ORAs to third parties, the participants had mixed feelings toward patient-initiated ORA's dispensing to individuals other than the end-users. In addition, pharmacists seemed to be unaware of the legislation and voiced hesitancy dispensing ORAs to someone other than the end user. "I would not offer [to someone other than the end user]... I would have to really take it on an individual basis. Really ask questions... [to] make sure that […] it was for a legitimate reason and not for continued risky behavior" (CP20).

Pharmacists initiating dispensing under a standing order was seen as a liability by some pharmacists: “Anytime you’re filling a prescription, especially per a standing order protocol, you have, you know, Board of Pharmacy risks that you did something wrong or something like that” (CP17). However, these concerns contrasted with the idea that “As long as you’re using the standing order […] I don’t think there’s too much to worry about as a liability issue” (CP16). There was also 1 remark about the unwillingness to have the involvement of law enforcement officials in their practice of pharmacy reviewing prescriptions of opioids from providers. This was seen as a concern regarding opioid dispensing in general.

Other potential risks of dispensing ORAs under a standing order were related to confidentiality, a negative impact on the patient-pharmacist and pharmacist-prescriber relationships, or the perception among physicians that pharmacists were practicing outside of their scope of practice. “Risks are... [that] they [physicians] think we’re not doing our job. That all we [do is] just fill the prescription the way the doctor wrote it. But my job is more than me just filling a prescription. It’s making sure you’re alive” (CP7).

Despite being supportive of stocking ORAs in the pharmacy, pharmacists expressed concerns about overstocking ORAs owing to the lack of patient interest and financial viability. “I’m not going to have an overstock of [ORAs]. I consistently lose money when I fill a naloxone prescription” (CP17).

Subjective Norm

Favorable norms

Pharmacists perceived that peer pharmacists and primary care and emergency department physicians would be supportive of community pharmacists dispensing ORAs under the standing order. One pharmacist noted that the type of pharmacy could determine peer pharmacists' perception. Given the workload at traditional chain pharmacies compared with independent pharmacies, pharmacists at independent pharmacies were perceived to be more likely to embrace dispensing under the standing order. "The pharmacist at the busier chains you don't think they have enough help. They're going to be the ones who fight harder against [providing the service], because it's one more thing they have to do during the day…" (CP16). Regarding patients, family members, and caregivers, pharmacists expected them to be receptive to the service.

Unfavorable norms

Despite the general perception that peer pharmacists, physicians, patients and respective family, caregivers, and friends would be receptive toward pharmacists dispensing ORAs under the standing order, there were remarks that the service could be viewed as a profit tactic by patients. "Since [the standing order] is a relatively new thing, a lot of [patients] are going to be dubious about why we are doing this, thinking that in this day of time we're trying just to improve our profit margin…" (CP11).

Another pharmacist noted that older physicians might not be welcoming of the service as this would represent a loss of physicians' prescribing authority. "[Older physicians] feel like they've lost power … [to prescribe] but … the younger and the newer ones welcome it" (CP7).

Perceived Behavioral Control

Most (18 of 21) of the pharmacists generally felt confident dispensing ORAs under the standing order at the patients' request and identifying situations that would justify dispensing an ORA. Two examples of such situations that were described by pharmacists were (1) patients who use opioids concomitantly with a benzodiazepine or other muscle relaxants and (2) using the prescription drug monitoring program to identify patients exceeding the recommended morphine milligram equivalents. Pharmacists' control beliefs were grouped into factors that hinder or facilitate their ability to dispense ORAs under the standing order.

Barriers

Pharmacist-related barriers included lack of training regarding the procedures for dispensing under the standing order and lack of technician training on how to identify and refer patients who would benefit from receiving an ORA to the pharmacist. Low confidence dispensing under the standing order and lack of participation from the medical community were also cited as hindrances.

Organizational barriers comprised lack of time to provide the service and inadequate staff. Participants also acknowledged lack of support and communication from their employer regarding the implementation of the service. Because dispensing under the standing order is voluntary, some pharmacists were unsure of any company-specific policies or standard procedures. As a result, they were concerned that there would be repercussions for doing something that was not in line with the organization's goals.

"[Corporations] have to recognize the value of this [dispensing under the standing order] and allot us the appropriate help and time to do this stuff, because right now you know they don't. […] We got no communication from our company about [dispensing under the standing order] and no company I've worked for really has communicated about the standing order…" (CP16).

Patient-related barriers noted were high patient out-of-pocket costs when ORAs were not covered by insurance companies, potential stigma of being regarded as addicts resulting in patients declining receiving ORAs under the standing order, and inadequate patient awareness of the importance of ORAs and how these should be used.

Facilitators

Current resources available to pharmacists comprised: the Virginia Department of Health, Virginia Pharmacists Association and Community Services Board, REVIVE! literature or website, patient drug information handouts, and the prescriber listed on the standing order. Pharmacists with experience dispensing under the standing order noted that they had a company protocol to guide them and suggested the need for increased community awareness on the availability of ORAs under the standing order. "[The company has] their procedures set up for everything and you want to make sure you're not going against anything that they want" (CP16).

The most commonly cited sources of training were state-provided (e.g., REVIVE! program), employer-provided, continuing pharmacy education programs, Pharmacist's Letter, community programs, and webinars. Only 1 pharmacy manager or pharmacist-in-charge at an independent pharmacy noted that they had not received any training pertaining to ORAs. Future resources needed to increase dispensing ORAs under the standing order comprised more technician training and education as well as more involvement to release pharmacists' time to provide the service; increased community awareness of the availability of ORAs from the pharmacy without the need to consult a physician; increased physician collaboration; creation of efficient systems to identify at risk patients who will benefit from ORAs; and employer guidance and communication about dispensing under the standing order.

Behavioral Intention

Whereas several pharmacists manifested an intention to make more frequent use of the standing order in their daily practice, those who had previously dispensed ORAs under the standing order did not intend to make any changes to their behavior. In addition, pharmacists planned to become more familiar with the standing order protocol, review ORAs-related training, engage in conversations with and educate patients to increase awareness of ORAs and the standing order, build better relationships with patients, carefully examine opioid prescriptions, proactively identify and provide ORAs to at risk patients, and offer ORAs on consultation, following the standing order protocol. “My next goal is first familiarizing myself as much as I can so I’m completely confident in dispensing on the standing order and knowing what my rights and abilities are as a pharmacist” (CP16).

However, a pharmacist at a rural independent pharmacy did not intend to proactively identify patients at risk for an opioid overdose given their already heavy workload. “I honestly don’t really have any intention of… actively trying to increase the number of prescriptions. I’m very open to dispensing it... but as far as… seeking out patients... most days we’re so busy I don’t have time to target another population” (CP10).

Discussion

Community pharmacists in Virginia expressed mixed intentions toward dispensing ORAs under the standing order. In addition, a quarter of the pharmacists interviewed had no experience dispensing ORAs under the standing order. Important findings from our

study include pharmacists being confused about the specifics and the processes involved with dispensing ORAs under the standing order and standing order underuse. Lack of familiarity with the standing order was also identified among Pennsylvania pharmacists,[14] as well as an underuse of naloxone prescriptive authority in New Mexico, particularly in rural areas.[30] Similar barriers to those reported in other states were described, including inadequate training, high out-of-pocket costs to patients, stigma, reimbursement issues, and inadequate staffing and time.[13-18,31]

In the recent 2019 National Pharmacist Workforce study, only a little more than half (57%) of community pharmacists were confident recommending ORAs.[32] Despite most pharmacists in our study having reported feeling confident dispensing under the standing order, a quarter had no experience with the service. Pharmacists also expressed a desire to pursue further education owing to discomfort associated with engaging in discussions about ORAs. This held true even among pharmacists with experience dispensing under the standing order and who had received previous training. Knowledge deficits regarding the standing order laws, opioid overdose, and how to use ORAs were also shared by pharmacists in Kentucky, North Carolina, and West Virginia.[13,17,33] To address knowledge deficits among Virginia pharmacists, skills-based and knowledge-based teaching methods, as suggested by Rudolph et al., could be implemented.[13] For example, to increase knowledge, pharmacists should be trained on the specifics of the standing order, namely the procedures for dispensing, the situations that would justify dispensing an ORA in cases in which patients do not ask for an ORA directly, and adequate patient counseling on opioid overdose and ORAs. Furthermore, knowledge application in the form of case studies would increase confidence in dispensing ORAs in clinical situations likely to be encountered in clinical practice. Pharmacists should also be encouraged to incorporate the service in their daily practice despite reporting limited time and staff support. Another

approach to increasing workforce preparedness relies on ensuring that pharmacy students receive adequate training and develop the required competencies to provide the service.

Similarly to pharmacists in Indiana and Michigan, Virginia pharmacists were generally supportive of stocking naloxone.[31,34] Pharmacists working in a pharmacy that stocked naloxone or that participated in a standing order were more likely to have dispensed an ORA.[35] In our study, the pharmacists who stocked ORAs seemed to display positive attitudes toward dispensing ORAs under the standing order.

Pharmacy corporations in Indiana established training programs as well as policies and procedures after the adoption of the naloxone statewide standing order.[36] Similar programs could be implemented in both supermarket and independent pharmacies. Virginia pharmacists, however, voiced a lack of support and communication from the corporate office as a barrier to the implementation of the service in practice. Adequate communication between pharmacy corporate offices and its pharmacists is essential to facilitate service implementation. For example, in New Mexico, the implementation strategy adopted consisted of both a top-down approach, involving the legislative passage of provisions for a statewide standing order, and a bottom-up approach by launching a public awareness campaign on ORAs and opioid overdose mortality, as well as pharmacist and technician trainings. The public awareness campaign was promoted through media such as radio advertising, billboards, and prescription bags printed with overdose statistics. Pharmacists were equipped with resources such as preprinted prescription pads with all necessary prescribing information under the pharmacist statewide standing order and prescription bags printed with naloxone and opioid safety messages.[37]

As implications for practice, our findings, along with evidence from other states, highlight a strong need for the profession to match advocacy efforts to passing legislation with workforce preparedness. Despite infrastructure (i.e., legislation) being in place, pharmacists report lack of preparedness to provide clinical pharmacy services, which results in the slow spread of innovations in community pharmacy.[38] In addition, there seems to be a need for more involvement from pharmacy corporate offices to communicate and provide pharmacists with practice site-specific protocols and training. Time constraints and inadequate staffing barriers could be addressed by adding technicians or reengineering the role of technicians within the pharmacy to release pharmacists for clinical services. Local health departments play a key role in increasing awareness about the availability of ORAs under the standing order. For example, Maryland launched a strong communication campaign advertising the availability of naloxone without a prescription in community pharmacies.[39,40] In addition, national and state pharmacy organizations should continue to focus their efforts on building capacity and adequately educating pharmacists. One potential strategy to increase the pharmacy workforce preparedness to dispense ORAs is to conduct mystery shopper or simulated patient exercises.[41] For example, in Australia and Jordan, mystery shopping and coaching have been used as a form of audit and feedback to improve community pharmacy practice.[42,43] This could be an opportunity for schools and colleges of pharmacy and professional organizations to collaborate. To address barriers related to stigma, educational and outreach materials for both pharmacists and patients should be developed to address misconceptions regarding ORAs.

Limitations

Our study has some limitations. Data saturation is a theoretical concept, and the chance of misinterpretation of the saturation point should be acknowledged.[25] Although 3 sampling strategies were employed in this study, we may have been unable to adequately

capture the perspectives of pharmacists with negative attitudes toward dispensing under the standing order or pharmacists in areas where the opioid epidemic is more prevalent.[4,44] The interview process may have prompted pharmacists who were unfamiliar with the standing order to think about the topic for the first time and their perceptions could have evolved as the interview unfolded.

Conclusions

In Virginia, community pharmacists showed mixed behavioral intention toward dispensing ORAs under the standing order. In addition to barriers such as out-of-pocket costs to patients, stigma from patients and pharmacists, inadequate time and support staff, important findings from our study include the underuse of the standing order to dispense ORAs, pharmacists being confused about the specifics and the processes involved with dispensing ORAs under the standing order, and lack of guidance and communication from chain pharmacy corporate offices regarding implementation of the service. Future research should focus on quantifying the uptake of the naloxone standing order at the state level, taking into consideration the findings from this qualitative study.

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Appendix 1: Interview guide used to explore community pharmacists' attitudes, subjective norm, perceived behavioral control and behavioral intention toward dispensing opioid reversal agents under a standing order.

Theme/Component	Questions
Current role & role of pharmacist	1. How much do you think the opioid epidemic applies to the patient population that you serve? 2. What role do pharmacists play in this opioid epidemic 3. Could you tell me about your current role in the opioid epidemic? 4. What training have you received regarding naloxone? 5. What information do you think patients need before having access to opioid reversal agents? 6. What could your potential role in the opioid epidemic be?
Attitude toward behavior	1. What are your thoughts about stocking opioid reversal agents? 2. What are your thoughts about: a. Opioid reversal agents as a tool to prevent opioid overdoses? b. Stocking opioid reversal agents? c. Pharmacists providing opioid reversal agents under a standing order? d. Dispensing opioid reversal agents with every eligible opioid prescription? e. The risk/ benefit of dispensing opioid reversal agents (for patients, pharmacy as a business, and patient-pharmacist relationship?
Subjective norm	1. If not dispensing under a standing order or currently dispensing but not to full capacity: How would pharmacist peers in Virginia think about you providing access to opioid reversal agents under a standing order? 1. If not dispensing under a standing order or currently dispensing but not to full capacity: How would other healthcare professionals (patients, caregivers, primary care doctors, emergency room doctors, other healthcare professionals, and other prominent members of society) in **Virginia** think about you providing access to opioid reversal agents under a standing order?

Perceived behavioral control	1. How confident do/would you feel dispensing opioid reversal agents? 2. How prepared do/would you feel in identifying situations that would justify dispensing an opioid reversal agent? 3. In thinking about your main practice site, what resources are available to support you in dispensing opioid reversal agents? 4. What would your pharmacy need to increase access to opioid reversal agents? 5. What training do you think patients should have? 6. What barriers do you encounter (or expect to encounter) when dispensing opioid reversal agents (stigma from patients or pharmacists, and time/support staff? 7. How would co-dispensing an opioid reversal agent with an opioid prescription affect your confidence to fill the opioid prescription?
Behavioral intention	1. How would you see yourself dispensing an opioid reversal agent? 2. How do you intend to increase access to opioid reversal agents in your practice?

CHAPTER 4: SPECIFIC AIM #2

Cost-effectiveness of syringe service programs, medications for opioid use disorder, and combination programs in hepatitis C harm reduction among opioid injection drug users: a public payer perspective using a decision tree

Authors:

1. Stephen C. Ijioma, PharmD, BA
   VCU-Indivior Health Economics and Outcomes Research Postdoctoral Fellow, Department of Pharmacotherapy & Outcomes Science, VCU School of Pharmacy, Richmond, VA, USA
   Phone / Email: (919)-599-5046 / ijiomas@vcu.edu
2. Vasco M. Pontinha, MPharm, MA
   PhD Student, Department of Pharmacotherapy & Outcomes Science, VCU School of Pharmacy, Richmond, VA, USA
   Phone / Email: (804)-828-8367 / vieiradasilvv@vcu.edu
3. David A. Holdford, PhD, M.S., BSPharm.
   Professor, Department of Pharmacotherapy & Outcomes Science, VCU School of Pharmacy, Richmond, VA, USA
   Phone / Email: (804)-828-6103 / daholdfo@vcu.edu
4. Norman V. Carroll, PhD, MS, BSPharm.
   Professor, Department of Pharmacotherapy & Outcomes Science, VCU School of Pharmacy, Richmond, VA, USA
   Phone / Email: (804)-514-1396 / nvcarroll@vcu.edu

Identification of the corresponding author:

Name: Stephen Ijioma, PharmD
Address: Department of Pharmacotherapy & Outcomes Science, 1112 East Clay Street, Richmond, VA 23298-0533
E-mail: ijiomas@vcu.edu
Telephone: (919)-599-5046

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Abstract

Background: : The hepatitis C virus (HCV) prevalence rate among injection drug users (IDUs) in North America is 55.2%, with 1.41 million individuals estimated to be HCV-antibody positive. Studies have shown the effectiveness of syringe service programs (SSPs) alone, medications for opioid use disorder (MOUD) alone, or SSP+MOUD combination in reducing HCV transmission among opioid IDUs.

Objective: To evaluate the cost-effectiveness of SSP alone, MOUD alone, and SSP+MOUD combination in preventing HCV cases among opioid IDUs in the United States.

Methods: We used a decision tree analysis model based on published literature and publicly available data. Effectiveness was presented as the number of HCV cases avoided per 100 opioid IDUs. A micro-costing approach was undertaken and included both direct medical and nonmedical costs. Costeffectiveness was assessed from a public payer perspective over a 1-year time horizon. It was expressed as an incremental costeffectiveness ratio (ICER) and an incremental cost savings per HCV case avoided per 100 opioid IDUs compared with cost savings with “no intervention.” Costs were standardized to 2019 U.S. dollars.

Results: The incremental cost savings per HCV case avoided per 100 opioid IDUs compared with no intervention were as follows: SSP+MOUD combination=$347,573; SSP alone=$363,821; MOUD alone=$317,428. The ICER for the combined strategy was $4,699 compared with the ICER for the SSP group. Sensitivity analysis showed that the results of the base-case cost-effectiveness analysis were sensitive to variations in the probabilities of injection-risk behavior for the SSP and SSP+MOUD combination groups, probability of no HCV with no intervention, and costs of MOUD and HCV antiviral medications.

Conclusion: The SSP+MOUD combination and SSP alone strategies dominate MOUD alone and no intervention strategies. SSP had the largest incremental cost savings per HCV case avoided per 100 opioid IDUs compared with the no intervention strategy. Public payers adopting the SSP+MOUD combination harm-reduction strategy instead of SSP alone would have to pay an additional $4,699 to avoid an additional HCV case among opioid IDUs. Although these harm-reduction programs will provide benefits in a 1-year time frame, the largest benefit may become evident in the years ahead.

Summary Bullets

- **What is already known about this subject**
    - Harm-reduction strategies such as syringe service programs (SSPs) or medications for opioid use disorder (MOUD) are effective in reducing the risk of hepatitis C virus (HCV) acquisition.
    - Using these harm-reduction strategies in combination is more effective than using them separately.
- **What this study adds**
    - The SSP+MOUD combination intervention dominated both MOUD and "no intervention" strategies when a public payer perspective was undertaken.
    - All harm-reduction strategies yielded significant cost savings when compared with a no intervention strategy over a 1-year period.
    - Among opioid injection drug users in the United States, the SSP+MOUD combination intervention is costeffective if payers are willing to pay $4,699 or more per HCV case avoided.

Introduction

Hepatitis C virus (HCV) is the leading cause of chronic liver disease, liver transplantation, and liver-related mortality and morbidity in the United States.[1-4] According to the Centers for Disease Control and Prevention (CDC), the estimated number of new HCV cases was 44,700 in 2017. The rate of acute HCV reported had increased from 0.7 per 100,000 people in 2013 to 1.0 per 100,000 people in 2017.[5] The HCV prevalence rate among injection drug users (IDUs) in North America is 55.2%, and about 1.41 million are estimated to be HCV-antibody positive.[6] Approximately 2.4 million people in the United States are living with HCV infection.[7] In 2017, there were 17,253 HCV-related deaths in the United States, which is about 4.13 deaths per 100,000 people.

IDUs are at greater risk of developing HCV infection, and the growing number of HCV cases in the United States is attributed largely to opioid misuse.[8,9] In 2018, the total economic cost of the opioid crisis was estimated at $696 billion (3.4% of the gross domestic product) and more than $2.5 trillion from 2015 to 2018.[10]

HCV infections can be reduced through syringe service programs (SSPs) and medications for opioid use disorder (MOUD). SSPs involve the distribution of sterile syringes and other injecting equipment to patients, increasing the number of clean syringes in circulation and reducing the number of contaminated syringes, consequently reducing the risk of acquisition of HCV and other diseases acquired by needle sharing.[11] SSP programs can be implemented in a fixed or nonfixed setting on a local community level. While there is very low-quality and insufficient evidence on the effect of SSP on HCV acquisition risk in North America, there is evidence of reduced HCV acquisition risk with SSPs by 56% in Europe, after stratification by region.[12,13] MOUD such as methadone or buprenorphine are used in an effort to decrease illicit opioid use or misuse as well as injection-risk behaviors.[14] MOUD programs

have been shown to reduce HCV acquisition risk by 50%.[12] Recent studies have suggested that a combination of SSP and MOUD programs has an additive effect in reducing HCV and HIV transmission. The combination of harm-reduction strategies resulted in a 6- to 7-fold decrease in the risk of HCV seroconversion and a 2- to 3-fold decrease in the risk of HIV seroconversion.[14-17] A study by Turner et al. (2011) in the United Kingdom suggested that the combination of SSP and MOUD reduced the odds of new HCV infections by almost 80%.[18] Despite these results, no study in the United States has examined the cost-effectiveness in terms of the incremental cost savings per HCV case avoided compared with cost savings with "no intervention."

The purpose of this project was to develop an economic model comparing the costs and effectiveness of SSP and MOUD as standalone interventions and SSP+MOUD in combination as harm-reduction strategies for the prevention of HCV infection in opioid IDUs. The study was conducted from a public payer perspective and considered both direct medical and nonmedical costs associated with injection-risk behaviors. The analysis was done to assist local community and public payers in decision making regarding adoption of harm-reduction strategies to prevent HCV infections and reduce the burden associated with HCV.

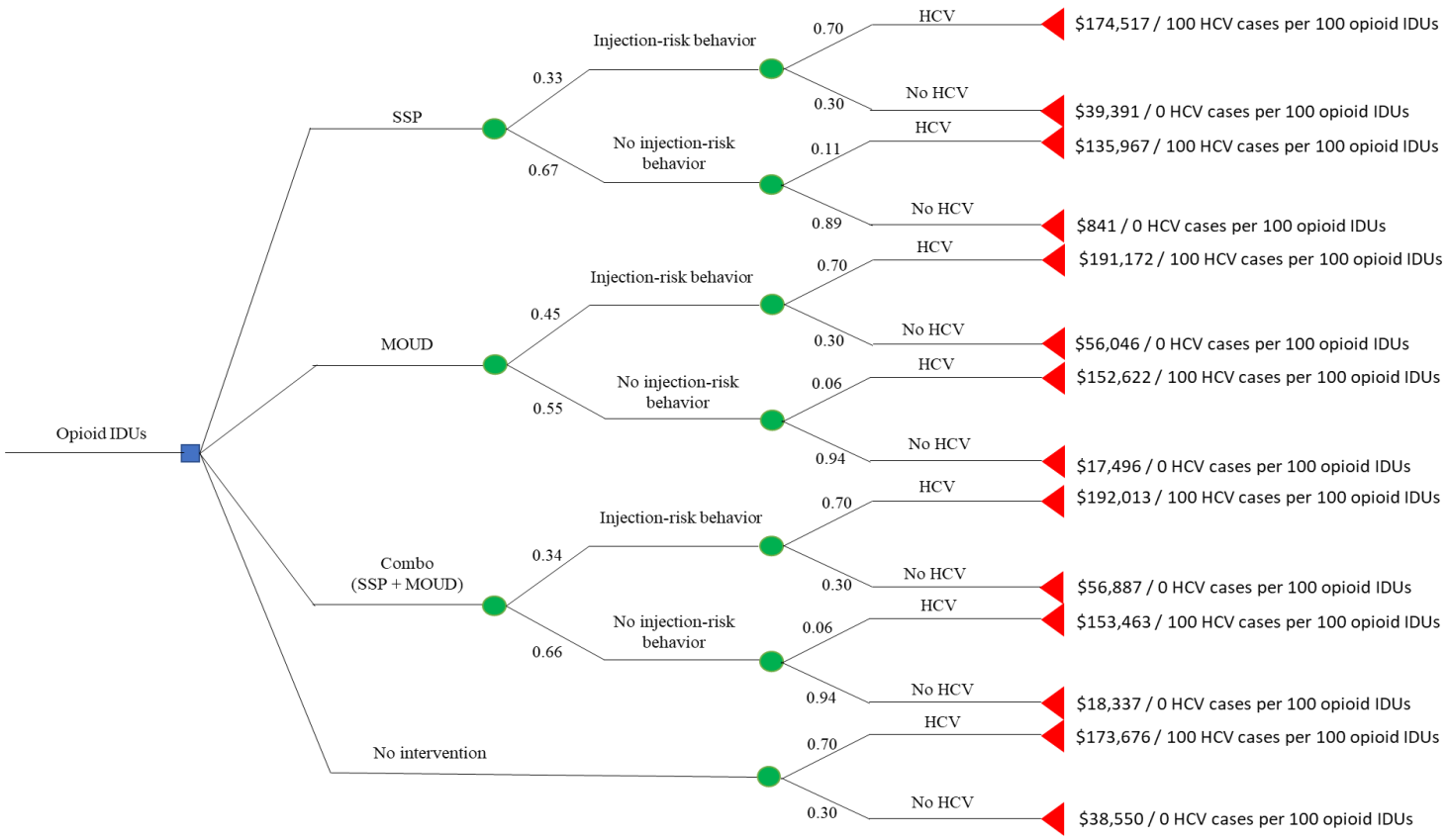
Methods

The target population studied in this analysis consisted of opioid IDUs in the United States not currently engaged in any harm-reduction strategy. The model considered a hypothetical population of patients and was designed using prevalence-based model inputs. A 1-year time period was chosen to capture the time patients engaged in the intervention, antiviral treatment, and antiviral retreatment in cases of treatment failures.

The primary outcome measure used in this cost-effectiveness study was the number of HCV cases avoided per 100 patients in the SSP, MOUD, and SSP+MOUD combination groups compared with the no intervention group. Several cost-effectiveness studies on infectious diseases similarly assessed their outcomes in terms of "cases of infection avoided or averted."[19-21]

A decision tree analytic model was built in Microsoft Excel 2016 (Microsoft, Redmond, WA), as pictured in Figure 1. The model explores the question, "Which is most cost-effective: the combination of SSP and MOUD, SSP alone, MOUD alone, compared with no intervention?" Effectiveness was assessed as a dichotomous measure: no HCV versus HCV. According to the model, opioid IDUs could be enrolled in only 1 of the interventions. There is then a probability, based on the effectiveness of the intervention, that they would continue or discontinue engagement in injection-risk behaviors, except for the no intervention group. If patients continued to engage in injection-risk behaviors, there was a probability, which was different across intervention strategies, that they either developed or did not develop HCV. Opioid IDUs discontinuing their engagement in injection-risk behaviors also either developed or did not develop HCV.

Figure 1: Decision Tree of the Cost-Effectiveness of SSP versus MOUD versus SSP+MOUD Combination versus "No Intervention"



Note: Opioid IDUs going through each decision path would incur the corresponding costs and number of HCV cases shown at the terminal node. HCV=hepatitis C virus; IDUs=injection drug users; MOUD=medications for opioid use disorder; SSP=syringe service program.

The outcomes data for this analysis were obtained from a PubMed literature search using the following search terms: “needle exchange programs,” “syringe exchange programs,” “needle and syringe programs,” “opioid substitution treatment,” “injection drug users,” “opioid or opioids,” “people who inject drugs,” and “hepatitis C,” in various combinations. Additional articles were included after reviewing the literature search. Clinical data from randomized controlled trials, cost-effectiveness studies, systematic reviews and meta-analyses, and review articles were included in the analysis. Data retrieved from the literature search pertaining to the effectiveness of harm-reduction strategies were summarized in Table 1. Effectiveness data for the base-case analysis were obtained from prior systematic reviews and meta-analyses.[12,22] The probability of injection-risk behaviors for each intervention was obtained from systematic literature reviews and meta-analyses and secondary sources.[18,23-26]

Table 1: Key Base-Case Assumptions for Model Parameters, Sources Used, and Variation Introduced in Sensitivity Analysis

Model Inputs, Clinical		**Base Case**	**Range**	**Source**
Risk Reduction of HCV with SSP	56%	0.56	Varied ± 50%	Platt et al.,[43] Cotter et al.[22]
Risk reduction of HCV with MOUD	50%	0.50	Varied ± 50%	Platt et al.[43]

Risk reduction of HCV with combination (SSP+MOUD)		0.60[a]	0.3 – 0.66	Platt et al.,[43] Assumption
Probability of NO HCV with "no intervention" (HCV naturally cleared)		0.30	Varied ± 50%	WHO,[26] Assumption
Probability of injection-risk behavior with SSP	OR= 0.5	0.33	Varied ± 50%	Sawangjit et al.,[24] Aspinall et al.[23]
Probability of injection-risk behavior with MOUD		0.45	Varied ± 50%	Gowing et al.,[25]
Probability of injection-risk behavior with Combination (SSP + MOUD)	AOR= 0.52	0.34	Varied ± 50%	Turner et al.[18]
Probability of HCV for SSP users engaging in NO injection-risk behavior		0.11[b]		Calculated
Probability of HCV for MOUD users engaging in NO injection-risk behavior		0.06[b]		Calculated

Probability of HCV for SSP+MOUD combination users engaging in NO injection-risk behavior	0.09[b]	Calculated

[a]*The base case is a more conservative estimate than the 74% risk reduction originally reported by Platt et al.12 It varied up to 0.66, the maximum upper limit that allows other probabilities in the model to fall within a reasonable range (i.e., 0-1). This seems reasonable given that the 95% CI for the 74% estimate was 11%-93%.*

[b]*See supplementary material (available in online article) for sample calculation.*

AOR=adjusted odds ratio; HCV=hepatitis C virus; MOUD=medications for opioid use disorder; OR=odds ratio; SSP=syringe service program; WHO=World Health Organization.

Both costs and effectiveness measures were estimated from a public payer perspective to capture the public payer's interest in the growing issue of opioid misuse, given that interventions were likely to be sponsored by a public entity.

Opioid IDUs who developed HCV incurred the following costs: HCV screening, biopsy, computerized tomography (CT), magnetic resonance imaging (MRI), antiviral treatment, antiviral treatment complication, HCV treatment monitoring, hepatitis A-B vaccine (3 doses). On the other hand, opioid IDUs who did not develop HCV did not incur these costs. We assumed that those

engaging in injection-risk behaviors and those in the no intervention group also incurred the direct nonmedical costs due to injection drug use-related crime.

Cost data were collected from public data sources, primary literature sources, and recently published cost-effectiveness studies (Table 2).[27- 34] The per-person-per annum cost of SSP and MOUD were obtained from literature sources.[27-29] Direct costs of CT and MRI were obtained from the 2019 National Physician Fee Schedule, while the cost of hepatitis A-B vaccine for 3 doses was obtained from the CDC.[29,30] Other direct medical costs such as costs of HCV screening, biopsy, HCV antiviral, and HCV treatment monitoring were obtained from literature sources, including recently published cost-effectiveness studies.[31,32] Similar to the approach of previous studies and due to the perspective chosen for this study, the base-case analysis considered direct nonmedical costs such as criminal justice expenditures related to substance use.[31] The public payer perspective analyses included the costs associated with the criminalization of substance use, comprising the costs of policing, court, corrections, and criminal victimization. These cost inputs were obtained from a retrospective, administrative data-based cohort study with comprehensive information on drug treatment and criminal justice system interactions.[31,33] All costs were standardized to 2019 U.S. dollars, using the medical Consumer Price Index.[35]

Table 2: Direct Medical and Nonmedical Costs Associated with HCV (in 2019 USD)

Model Inputs, Costs	**2016 ($)**	**Base Case ($), 2019 adjusted**	**Source**
Cost of SSP, annual per person	$774.30	$840.99	Teshale et al.[27]
Cost of MOUD, annual per person (2013)[a]	$14,468	$17,496.00	Mohlham et al.[28] NIDA[29]
Cost of combination (SSP+MOUD), per annum	$15,242.30	$18,336.99[b]	Calculated
Cost of Injection drug use-related crime (direct non-medical costs), annual per person	$35,494	$38,550	Stevens et al.[31] Krebs et al.[33]
Cost of HCV screening	$111.58	$121.00	Stevens et al.[31]
Cost of Biopsy	$762.00	$828.00	Stevens et al.[31]

Cost of Computerized tomography	N/A	$463.00	2019 National Fee Schedule[34]
Cost of MRI	N/A	$525.00	2019 National Fee Schedule[34]
Cost of HCV Antiviral	$61,020.00	$66,275.00	Stevens et al.[31] Barbosa et al.[32]
Cost of HCV Antiviral, complication	$61,020.00	$66,275.00	Stevens et al.[31] Barbosa et al.[32]
Cost of HCV Treatment Monitoring (12-weeks), per person	$358.50	$390.00	Barbosa et al.[32]
Cost of Hepatitis A - Hepatitis B vaccine (3 doses)	N/A	$249.00	CDC[30]

[a]Cost standardized from 2013 to 2019 using the medical Consumer Price Index.

[b]Calculation: Cost of combination (SSP+MOUD)=cost of SSP+cost of MOUD.

CDC=Centers for Disease Control and Prevention; HCV=hepatitis C virus; MOUD=medications for opioid use disorder; MRI=magnetic resonance imaging; N/A=not applicable; NIDA=National Institute on Drug Abuse; SSP=syringe service program; USD=United States dollar.

In developing the model, several assumptions were made. Considering the natural prevalence of HCV in patients with opioid IDU (70%), we postulated the following:

1. The probability of no HCV with no intervention is 0.30, the proportion of patients who do not seem to be infected by HCV virus or naturally clear the virus from the body. We also assumed that all participants (100%) receiving no intervention were engaging in injection-risk behaviors and were exposed to HCV.
2. Opioid IDUs enrolled in one of the harm-reduction strategies and still engaging in injection-risk behaviors had the same probability of developing HCV as those receiving no intervention since injection-risk behaviors are the primary means by which HCV is transmitted. If the injection-risk behavior is not decreased, then the risk of HCV is not decreased.
3. Opioid IDUs enrolled in one of the harm-reduction strategies no longer engaging in injection-risk behaviors had a lower probability of developing HCV when compared with those in the no intervention group.
4. Similar to the study by Stevens et al. (2019), we assumed that patients were retreated with antivirals for treatment failures.[31]
5. Those engaging in injection-risk behaviors incurred the cost of injection drug use-related crimes.

6. Although the risk reduction of HCV for the SSP+MOUD combination group was estimated at 74%, the confidence interval was broad from 11% to 93%.12 As a result, we assumed a conservative estimate of 60% to avoid other key probabilities in the model from falling outside a reasonable range (i.e., 0-1).

The cost-effectiveness findings were expressed in terms of cost per IDU and per 100 IDUs, number of HCV cases per 100 IDUs, number of HCV cases avoided per 100 IDUs, cost per HCV case avoided per 100 IDUs, incremental cost savings per HCV case avoided (per 100 IDUs) compared with no intervention, and incremental cost-effectiveness ratio (ICER).

A 1-way sensitivity analysis was conducted on all cost inputs considered in the model to test the robustness of the base-case cost-effectiveness analysis. The risk reduction of HCV for SSP, MOUD, and SSP + MOUD combination; the probabilities of injection-risk behavior for SSP, MOUD, and SSP+MOUD combination; the probability of no HCV infection with no intervention; and all cost inputs were varied by ±50%, according to accepted modeling research practices.[36]

Results

Figure 1 shows the costs and effectiveness associated with each arm of the decision tree. The costs for the SSP and MOUD groups were summed to derive the costs for the combination program. As a result, those enrolled in the combination program who engaged in injection-risk behaviors and who developed HCV incurred the largest cost, $192,013.

Results of the base-case cost-effectiveness analysis are shown in Table 3. The SSP+MOUD combination was the most effective intervention as it avoided 72 HCV cases among 100 opioid IDUs, while SSP alone was the least expensive as it cost $5,518,130 for 100 opioid IDUs. The ICER for the combined strategy was $4,699 per additional case of HCV avoided compared with

the SSP group. In other words, the combined intervention would cost public payers an additional $4,699 to avoid an additional case of HCV when compared with SSP. In addition, SSP alone had the highest incremental cost savings per HCV case avoided at $363,821, compared with no intervention. Both MOUD alone and no intervention were dominated by SSP alone and SSP+MOUD combination interventions. For the SSP + MOUD combination strategy to become the most cost-effective intervention, the probability of injection-risk behavior for SSP alone would have to increase to 0.52 or the risk reduction of HCV for SSP alone would have to decrease to 0.41.

Table 3: Expected Costs (in 2019 USD), Effectiveness, and Cost-Effectiveness Ratios of SSP, MOUD, SSP+MOUD Combination, and No Intervention in Base-Case Analysis

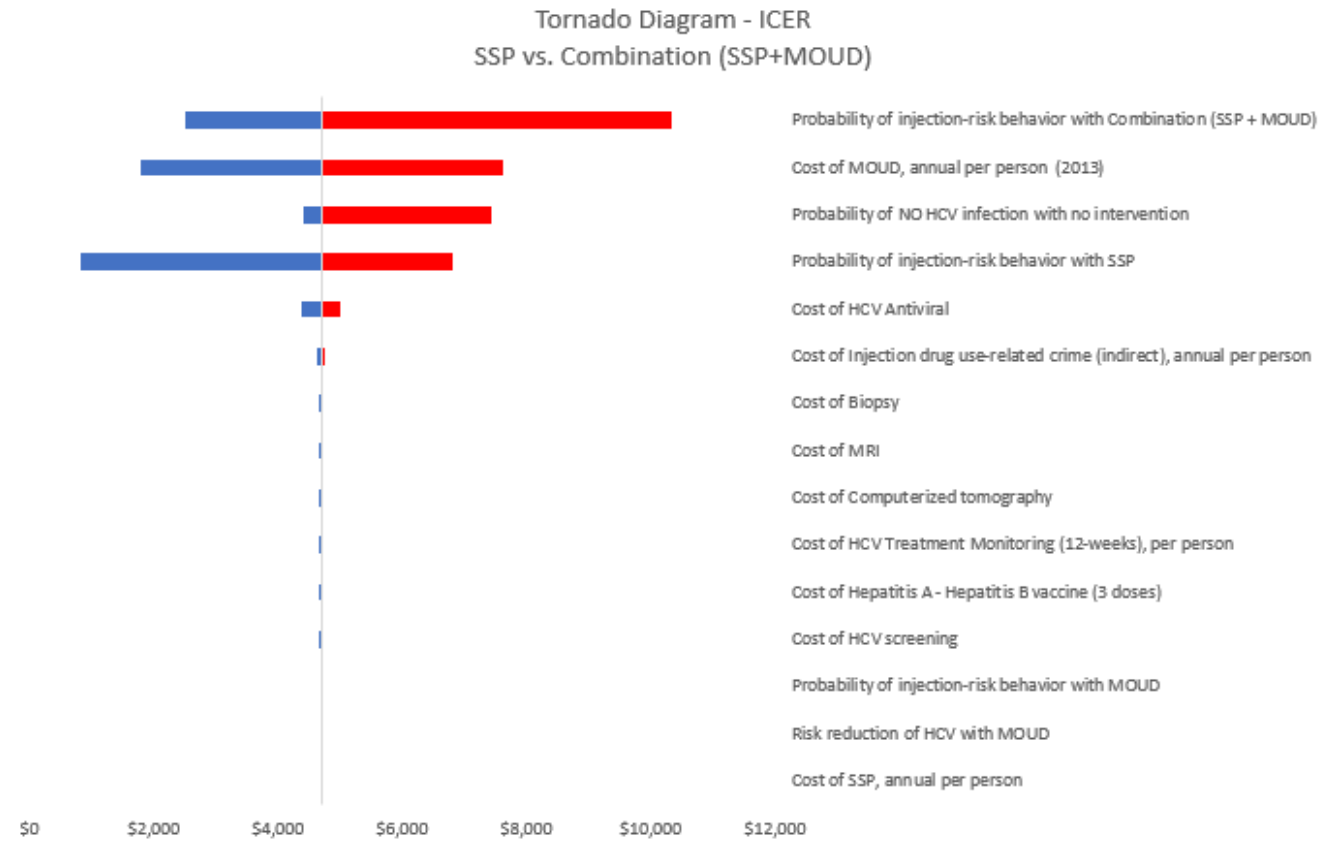
Intervention	**Cost per opioid IDU, $[a]**	**Cost per 100 opioid IDUs, $**	**# of HCV cases[b]**	**# of HCV cases avoided[b]**	**Cost per HCV case avoided ratio, $[b]**	**Incremental cost savings per HCV case avoided[b] (compared with "No Intervention"), $**	ICER, $[a]	**Dominate**s
Combination (SSP + MOUD**)**	$69,279.27	$6,927,927	28	72	$96,221	$347,573	$4,699 (compared to SSP)	MOUD alone No Intervention
SSP	$55,181.30	$5,518,130	31	69	$79,973	$363,821	--	MOUD alone No Intervention

MOUD	$82,137.60	$8,213,760	35	65	$126,366	$317,428	--	No Intervention
No Intervention	$133,138.20	$13,313,820	70	30	$443,794	--	--	--

[a]*Per opioid IDU.*
[b]*Per 100 opioid IDUs.*
HCV=hepatitis C virus; ICER=incremental cost-effectiveness ratio; IDU=injection drug user; MOUD=medications for opioid use disorder; SSP=syringe service program; USD=United States dollar.

The sensitivity analysis varied all cost and clinical variables using the ranges presented in Tables 1 and 2. The results of the sensitivity analyses are presented in Figure 2 and in the Supplementary Material (available in online article). When varying the risk reduction of HCV infection to +50%, an upper limit of 1 (probability [risk reduction] = 100%) was considered. When the risk reduction of HCV infection with SSP was increased to 0.84, SSP was the dominant intervention. At the lower range of the risk reduction of SSP (0.28), the SSP+MOUD combination was the dominant intervention. When all the cost variables were varied within their ranges, there were only 2 meaningful changes in the outcomes. These were the cost of MOUD and the cost of HCV antiviral. As the tornado diagram in Figure 2 shows, the ICER between SSP and the SSP+MOUD combination strategies was most sensitive to the probabilities of injection-risk behavior for the SSP and SSP+MOUD combination groups, probability of no HCV with no intervention, and costs of MOUD and HCV antiviral. The shift in the base-case cost-effectiveness was minimal for all other parameters tested. Discounting was not performed because both costs and outcomes occurred within a 1-year time horizon.

Figure 2: Tornado Diagram on the Incremental Cost-Effectiveness Ratio Between SSP and Combination (SSP+MOUD)



Note: Costs are in 2019 U.S. dollars.

HCV=hepatitis C virus; ICER=incremental cost-effectiveness ratio; MOUD=medications for opioid use disorder; MRI=magnetic resonance imaging, SSP=syringe service program.

Discussion

This study indicates that the SSP+MOUD combination program is an effective harm-reduction strategy to prevent HCV cases among opioid IDUs and is cost-effective if payers are willing to pay $4,699 or more per avoided case of HCV. There is evidence to support the effectiveness of these harm-reduction strategies in reducing injection-risk behaviors as well as reducing HCV and HIV transmission.[17,18] The base-case analysis suggested that (a) the combination strategy, compared with SSP alone, would cost $4,699 to avoid an additional HCV case; (b) the combination and the SSP-alone groups dominated both the MOUD-alone and no intervention groups; and (c) the MOUD-alone group dominated the no intervention group.

Most of the recent studies on the cost-effectiveness of SSP and MOUD alone and in combination were conducted outside the United States, were conducted from a societal or health care system perspective, did not directly compare the interventions used in the base case, had moderate evidence of the cost-effectiveness in some sites, estimated the outcome in terms of quality-adjusted life years, and did not examine the number of cases avoided in a 1-year time horizon.[19,31,32,37-39] To date, studies have not examined the cost-effectiveness of these harm-reduction strategies in terms of incremental cost savings per HCV case avoided, and none has undertaken a public payer perspective in the United States.

Based on the analysis, the combination of MOUD and SSP appears to be the most effective policy, from a public health perspective. By including both the direct medical and nonmedical costs due to injection drug use-related crime in the calculation, the combination program will save public payers $347,573 per HCV case avoided compared with costs for no intervention. SSP-alone and MOUD-alone interventions will also save public payers $363,821 and $317,428, respectively. Given that the total direct economic

burden of HCV-related liver disease in the United States is estimated to be $6.5 billion ($4.3 to $8.2 billion) annually and 2.4 million people in the United States live with an HCV infection, these interventions could dramatically reduce HCV-related annual costs.[7,40,41] The savings associated with these interventions would allow public institutions to redirect funds toward other health care services or public service investments. In addition, the results indicated that all the harm-reduction strategies were less costly and more effective than no intervention even though they required some up-front investments. It is also important to point out that the largest benefits could occur in the future. This is because HCV-related liver disease such as cirrhosis and hepatocellular carcinoma may take several years to occur, and SSPs are associated with reducing the risk of other diseases transmitted via needle sharing, such as HIV.[23,26]

The 1-way sensitivity analysis shows that the base-case cost effectiveness analysis was sensitive to the probabilities of injection-risk behavior for the SSP and SSP+MOUD combination groups, probability of no HCV with no intervention, and costs of MOUD and HCV antivirals. Despite varying the model parameters by ±50%, the base-case ICER was not sensitive to a majority of the key variables in the model. Considering that the cost for the combination intervention was assumed to be the sum of the costs of the SSP and MOUD individual interventions, our results can be considered as conservative estimates, given that in reality, savings and economies of scale can be achieved by a combination of efforts.

Limitations

Several limitations could affect the results of this analysis. Given the lack of evidence on the probability of HCV among opioid IDUs who are receiving no intervention, we assumed that 30% would not have HCV since they would naturally clear the HCV.[26] However, varying this variable by ±50% resulted in an ICER between SSP and combination interventions that ranged from $4,429 to $7,454 compared with the base-case ICER of $4,699. The micro-costing approach of this cost-effectiveness study could have omitted other important cost inputs. There is also weak and insufficient data on the effect of SSP on HCV transmission in North America and the effectiveness of combination programs in reducing injection risk behaviors; thus, we used outcomes data from Europe. Finally, not all populations in the studies from which our input estimates came were the same.

Future Research

This research reports the cost-effectiveness of several harm-reduction strategies: SSP alone, MOUD alone, and SSP+MOUD combination program, compared with no intervention in preventing HCV cases in the United States during a 1-year time horizon. Additional research should be performed on the cost-effectiveness of other harm-reduction strategies to examine their role in preventing HCV cases among opioid IDUs. These include antiretroviral therapy, condom programs for IDUs and their sexual partners, and targeted information, education, and communication.[42] The cost-effectiveness of harm-reduction strategies could also be examined in nonopioid IDUs. Finally, future studies should also examine the cost-effectiveness of these harm-reduction strategies from a societal perspective by including indirect costs such as costs due to lost productivity.

Conclusion

This study provides evidence that compared with no intervention, SSP, MOUD, and the SSP and MOUD combination are cost-effective and cost-saving harm-reduction strategies. The base-case scenario of the model found the combination program to be cost-effective if payers were willing to pay $4,699 or more per case of HCV avoided. Although these harm-reduction programs will provide benefits in a 1-year time frame, the largest benefit may become evident in the years ahead.

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Supplementary Material:

*** Stepwise calculation for probabilities of HCV for those not engaging in IRB:**

Step I: [(100 x 0.7) – (100 x 0.7 x (RR of the intervention))] = Total # HCV case per 100 patients for that intervention

Step II: [(Total # HCV case per 100 patients for that intervention) – (100 x (Pr (IRB)) x (Pr (HCV-IRB))] = # of HCV cases in non-IRB arm

Step III:

$$\frac{\text{number of people with HCV in the non-IRB group}}{\text{Total number of people in the non-IRB group}} = \text{Pr (HCV- non-IRB)}$$

where RR= risk reduction; Pr (IRB) = probability of injection-risk behavior for the intervention; Pr (non-IRB) = probability of NO injection-risk behavior for the intervention; Pr (HCV-IRB) = probability of HCV in the injection-risk behavior arm; Pr (HCV-non-IRB) = probability of HCV in the NO injection-risk behavior arm.

Example: Calculating the probability of HCV in the NON-IRB group for SSP

1. In the SSP group, 100 x 0.7 x 0.56 (this is the risk reduction of HCV infection with SSP) = ~39.2

Since we're starting from 70% (instead of 100%, given that only 30% will naturally clear the virus)

70 – 39.2 =30.8 (~31) will have HCV in the SSP group

Find the number of people from IRB that will have HCV

0.33 x 100 = 33 in the SSP will be in the IRB arm (remaining 67 patients will be in the non-IRB arm).

Of these 33 x 0.7 = 23.1 (~23) people in the IRB group will have HCV

2. Find the number of people from NON-IRB that will have HCV

30.8 – 23.1 = 7.7 (~8) people from the non-IRB group will have HCV

3. Find the probability of HCV in the NON-IRB group, given that 85% of people in the SSP group will be in the NON-IRB (and 15% will be in the IRB group)

$$= \frac{\text{number of people with HCV in the non-IRB group}}{\text{Total number of people in the non-IRB group}} = \frac{7.7}{67}$$ = 0.11 probability of HCV in the NON-IRB group for SSP

Supplementary Material: One-Way Sensitivity Analyses for Cost-Effectiveness, Expressed as Cost per 100 patients and Number of HCV Cases per 100 patients.

One-Way Sensitivity Analyses for Cost-Effectiveness, Expressed as Cost per patient and number of HCV cases per 100 patients														
Scenario	**SSP**			**OST**			**Combination**			**No Intervention**			**Comparison**	**ICER (per patient) or Dominant Intervention**
Risk reduction of HCV with SSP	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**		
0.56	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
0.28	$81,666	$8,166,599	50	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	N/A	Combination is dominant
0.84	$44,777	$4,477,660	11	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	N/A	SSP is dominant
Risk reduction of HCV with MOUD	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**		
0.5	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
0.25	$55,181	$5,518,130	31	$105,785	$10,578,465	53	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
0.75	$55,181	$5,518,130	31	$78,759	$7,875,945	18	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs OST	$1,814
Risk reduction of HCV with combination (SSP+MOUD)	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**		
0.6	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
0.3	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$97,656	$9,765,573	49	$133,138	$13,313,820	70	N/A	SSP is dominant
0.66	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$63,604	$6,360,398	24	$133,138	$13,313,820	70	SSP vs Combination	$1,203
Probability of injection-risk behavior with SSP	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**		

0.33	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
0.165	$48,821	$4,882,055	31	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$6,820
0.495	$66,744	$6,674,440	31	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$845
Probability of injection-risk behavior with MOUD	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**		
0.45	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
0.225	$55,181	$5,518,130	31	$73,464	$7,346,385	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
0.675	$55,181	$5,518,130	31	$108,716	$10,871,555	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
Probability of injection-risk behavior with Combination (SSP + MOUD)	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**		
0.34	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
0.17	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$62,726	$6,272,577	28	$133,138	$13,313,820	70	SSP vs Combination	$2,515
0.51	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$86,237	$8,623,747	28	$133,138	$13,313,820	70	SSP vs Combination	$10,352
Probability of NO HCV infection with no intervention	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**		
0.30	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
0.15	$64,100	$6,409,961	37	$92,272	$9,227,205	43	$77,387	$7,738,683	34	$153,407	$15,340,710	85	SSP vs Combination	$4,429
0.45	$46,263	$4,626,298	24	$72,003	$7,200,315	28	$61,172	$6,117,171	22	$112,869	$11,286,930	55	SSP vs Combination	$7,454
Cost of SSP, annual per person	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**		
$840.99	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
$420.50	$54,761	$5,476,080	31	$82,138	$8,213,760	35	$68,859	$6,885,878	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699

$1,261.49	$55,602	$5,560,179	31	$82,138	$8,213,760	35	$69,700	$6,969,977	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
Cost of MOUD, annual per person (2013)	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**		
$17,496.00	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
$8,748.00	$55,181	$5,518,130	31	$73,390	$7,338,960	35	$60,531	$6,053,127	28	$133,138	$13,313,820	70	SSP vs Combination	$1,783
$26,244.00	$55,181	$5,518,130	31	$90,886	$9,088,560	35	$78,027	$7,802,727	28	$133,138	$13,313,820	70	SSP vs Combination	$7,615
Cost of Injection drug use-related crime (indirect), annual per person	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**		
$38,550.00	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
$19,275.00	$48,821	$4,882,055	31	$73,464	$7,346,385	35	$62,726	$6,272,577	28	$113,863	$11,386,320	70	SSP vs Combination	$4,635
$57,825.00	$61,542	$6,154,205	31	$90,811	$9,081,135	35	$75,833	$7,583,277	28	$152,413	$15,241,320	70	SSP vs Combination	$4,764
Cost of HCV screening	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**		
$121.00	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
$60.50	$55,163	$5,516,266	31	$82,116	$8,211,643	35	$69,262	$6,926,233	28	$133,096	$13,309,585	70	SSP vs Combination	$4,700
$181.50	$55,200	$5,519,993	31	$82,159	$8,215,878	35	$69,296	$6,929,621	28	$133,181	$13,318,055	70	SSP vs Combination	$4,699
Cost of Biopsy	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**		
$828.00	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
$414.00	$55,054	$5,505,379	31	$81,993	$8,199,270	35	$69,163	$6,916,335	28	$132,848	$13,284,840	70	SSP vs Combination	$4,703
$1,242.00	$55,309	$5,530,881	31	$82,283	$8,228,250	35	$69,395	$6,939,519	28	$133,428	$13,342,800	70	SSP vs Combination	$4,695
Cost of Computerized tomography	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per**		

			100 patients			100 patients			100 patients			100 patients				
$463.00	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
$231.50	$55,110	$5,511,000	31	$82,057	$8,205,658	35	$69,214	$6,921,445	28	$132,976	$13,297,615	70	SSP vs Combination	$4,701
$694.50	$55,253	$5,525,260	31	$82,219	$8,221,863	35	$69,344	$6,934,409	28	$133,300	$13,330,025	70	SSP vs Combination	$4,697
Cost of MRI	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**		
$525.00	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
$262.50	$55,100	$5,510,045	31	$82,046	$8,204,573	35	$69,206	$6,920,577	28	$132,954	$13,295,445	70	SSP vs Combination	$4,702
$787.50	$55,262	$5,526,215	31	$82,229	$8,222,948	35	$69,353	$6,935,277	28	$133,322	$13,332,195	70	SSP vs Combination	$4,697
Cost of HCV Antiviral	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**		
$66,275.00	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
$33,137.50	$44,975	$4,497,495	31	$70,539	$7,053,948	35	$60,001	$6,000,077	28	$109,942	$10,994,195	70	SSP vs Combination	$5,009
$99,412.50	$65,388	$6,538,765	31	$93,736	$9,373,573	35	$78,558	$7,855,777	28	$156,334	$15,633,445	70	SSP vs Combination	$4,390
Cost of HCV Treatment Monitoring (12-weeks), per person	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**		
$390.00	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
$195.00	$55,121	$5,512,124	31	$82,069	$8,206,935	35	$69,225	$6,922,467	28	$133,002	$13,300,170	70	SSP vs Combination	$4,701
$585.00	$55,241	$5,524,136	31	$82,206	$8,220,585	35	$69,334	$6,933,387	28	$133,275	$13,327,470	70	SSP vs Combination	$4,698
Cost of Hepatitis A - Hepatitis B vaccine (3 doses)	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**	**Cost per patient**	**Cost per 100 patients**	**# of HCV cases per 100 patients**		

$249.00	$55,181	$5,518,130	31	$82,138	$8,213,760	35	$69,279	$6,927,927	28	$133,138	$13,313,820	70	SSP vs Combination	$4,699
$124.50	$55,143	$5,514,295	31	$82,094	$8,209,403	35	$69,244	$6,924,441	28	$133,051	$13,305,105	70	SSP vs Combination	$4,700
$373.50	$55,220	$5,521,964	31	$82,181	$8,218,118	35	$69,314	$6,931,413	28	$133,225	$13,322,535	70	SSP vs Combination	$4,698

CHAPTER 4: CONCLUSION

The opioid crisis has had a significant impact on patients. Because patients are more likely to interact with their pharmacists than any other healthcare provider, pharmacists have an essential role to play in curbing the ongoing opioid crisis. More specifically, they have an increasing role in OUD and opioid overdose prevention and treatment. Various statutes and legislatures have been implemented to expand access to various MOUD treatment options and preventive measures such as SSPs.

Among patients with OUD, pharmacists can provide direct patient management services such as naloxone distribution, pharmacist and physician collaboration, pharmacist-led opioid substitution services, pharmacist-led methadone programs, pharmacists providing training as well as ancillary services such as pharmacists receiving training, controlled substance stewardship, PMP/restriction programs, and syringe exchange programs. While pharmacists can have relevant impact via direct patient management and ancillary services, barriers such as lack of training, education, time constraints, and lack of reimbursement, need to be addressed.

Further examination on the distribution of ORAs showed that community pharmacists expressed mixed intentions toward dispensing ORAs under the standing order. Barriers identified included out-of-pocket costs to patients, stigma from patients and pharmacists, inadequate time and support staff, important findings from our study include the underutilization of ORAs, pharmacists confusing dispensing under a standing order with dispensing under a prescription, and lack of guidance and communication from chain pharmacy corporate offices regarding implementation of the service.

Exploring harm reduction strategies that could be employed by community pharmacists showed that, when compared to SSP

alone and MOUD alone, combining strategies (i.e., SSP+MOUD) is cost-effective in preventing HCV cases if public payers are willing to pay $4,699. As a result, pharmacists may incorporate a combination strategy as it is shown to be cost-effective if payers were willing to pay $4,699 or more per case of HCV avoided. SSP alone was dominant to both the MOUD alone and "no intervention" while MOUD alone only dominated the "no intervention" group. Although these harm reduction programs will provide benefits in a one-year time frame, the largest benefit may become evident in the years ahead.

Future research should examine other avenues through which pharmacists can help curb the opioid crisis. In addition, future studies should also examine the cost-effectiveness of these harm reduction strategies from a societal perspective by including indirect costs such as costs due to lost productivity.