Pharmacotherapies for Treatment of Opioid Use Disorder: A Narrative Review and Cost-Effectiveness Analysis

By

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A thesis submitted to the

School of Graduate Studies

in partial fulfillment of the requirements for the degree of

Master of Science in Pharmacy

School of Pharmacy

Memorial University of Newfoundland

January 2021

St. John’s, Newfoundland and Labrador

Abstract

Opioid use disorder (OUD) has become a global concern with the rapid increase in the use of illicit and prescription opioids. North America is in the midst of the opioid crisis, which requires effective (both clinically and economically) treatment interventions. Several evidence-based treatment options are available for the treatment of OUD. However, little is known about patients' perspectives on the pharmacotherapies used for OUD treatment. Additionally, with the advent of novel and more expensive treatment options, an economic evaluation against conventional treatment is warranted.

The aim of this thesis is two-fold: first, to conduct a narrative review of patients' perceptions and experiences with OUD pharmacotherapies and second, to compare the cost-effectiveness of the newer pharmacotherapies with conventional treatments. The thesis follows a manuscript style with the following chapters: Chapter 1 provides an introduction; Chapter 2 provides a narrative review of patients' perceptions and experiences with the pharmacotherapies for OUD treatment; Chapter 3 is the cost-effectiveness analysis of the newer pharmacotherapies compared against the usual treatment; and, Chapter 4 concludes.

In the narrative review, we conducted a systematic search of relevant literature on patients' perceptions and experiences with OUD pharmacotherapies. The data are coded to develop overarching themes. The findings are narratively described under these themes for the outcomes of perceptions and experiences. We critically appraised the included studies to assess their quality. We found evidence of both patient-reported positive and negative

aspects of the treatments. Other key findings of this review study are lack of patient knowledge on the available treatment options, many patients seeking harm reduction treatment strategy with opioid agonist treatment (OAT), while others seeking abstinence-based treatment interventions, and the role of patient inclusive treatment decisions to optimize treatment outcomes.

In the cost-effectiveness study, we compared five treatment strategies using the US healthcare perspective: 1) methadone-lofexidine for detoxification and buprenorphine-naloxone for maintenance; 2) methadone-lofexidine for detoxification and extended-release naltrexone for maintenance; 3) buprenorphine-naloxone for detoxification and extended-release buprenorphine for maintenance; 4) buprenorphine-naloxone for detoxification and maintenance (i.e., usual treatment); and, 5) no treatment. Effectiveness outcomes are presented in quality-adjusted life-years (QALYs), treatment retention and opioid-free days. Detoxification with methadone-lofexidine and subsequent buprenorphine-naloxone maintenance yield greater effectiveness than usual treatment but are not cost-effective at the willingness-to-pay threshold of US$100,000 per QALY gained due to the high cost of lofexidine. Usual treatment with buprenorphine-naloxone is found to be cost-effective at the conventional willingness-to-pay threshold.

Acknowledgements

I want to acknowledge and thank my supervisor, Dr. Hai Nguyen, for his continuous guidance and support throughout my Master's program. This thesis would not have been possible without his invaluable mentorship. The knowledge and training that I received from him will always help me in my future endeavors. I cannot thank him enough! I would also like to extend my sincerest gratitude to Dr. Lisa Bishop and Dr. Stephen Bornstein for critically reviewing this thesis and providing me with directions along the way amidst their busy schedules. Special thanks to my lab mate, Shweta Mital, who, on many occasions, helped me to gain perspective and get things going when the solution to a problem was right in front of me yet seemed inconspicuous.

Finally, I take this opportunity to thank my family and friends for their undying support and motivation during my graduate studies; thank you for shaping me to be the person I am today!

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List of Abbreviations

BMT: Buprenorphine maintenance treatment

BUP: Buprenorphine

BUP-NX: Buprenorphine-naloxone

CASP: Critical Appraisal Skills Program

CEA: Cost-effectiveness acceptability

CI: Conventional inpatient

CO: Conventional outpatient

CPI-U: Consumer Price Index for all urban consumers

DALY: Disability-adjusted life year

DSM-V: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

ED: Emergency department

FDA: Food and Drug Administration

FSS: Federal Supply Schedule

GHQ-28: General Health Questionnaire28

HIV: Human immunodeficiency virus

HCV: Hepatitis C virus

ICER: Incremental cost-effectiveness ratio

IDU: Injection drug user

LY: Life-year

MAT: Medication-assisted treatment

MET: Methadone

MDD: Major depressive disorder

MMT: Methadone maintenance treatment

MOUD: Medication for opioid use disorder

NADAC: National Average Drug Acquisition Costs

Non-IDU: Non injection drug user

NTX: Naltrexone

OAT: Opioid agonist treatment or therapy

OMT: Opioid maintenance treatment

OST: Opioid substitution treatment or therapy

OUD: Opioid use disorder

PCC: Patient-centered care

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PSA: Probabilistic sensitivity analysis

QALY: Quality-adjusted life year

ReQoL: Recovering quality of life

RODA: Rapid detoxification under anaesthesia

RODS: Rapid opioid detoxification under sedation

SASMAT-METHER: Scale to Assess Satisfaction with Medications for Addiction Treatment methadone for heroin addiction

SoF: Summary of findings

SUD: Substance use disorder

US$: United States dollar

VAS-MD: Visual analog scale of methadone dose

VSSS-MT: Verona Service Satisfaction Scale for methadone-treated opioid-dependent patients

WHO: World Health Organization

XR-BUP: Extended released buprenorphine

XR-NTX: Extended-release naltrexone

μ: Mu

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Chapter 1 Introduction

1.1 Background

North America is in the midst of a massive opioid misuse epidemic.[1, 2] Misuse of prescription opioids and illicit opioids have both contributed to the prevailing ravage.[2, 3] Uncontrolled use of opioids causes severe physical, mental, and economic distress. Opioid misuse is a major contributor to overdose mortality.[3, 4] Due to syringe sharing, opioid-dependent people who injects illicit drugs are at a great risk of contracting transmissible diseases like human immunodeficiency virus (HIV) and viral hepatitis.[5] Dependence on opioids may also lead to cognitive impairment, disrupting the dependents' societal skills.[6] Rising numbers of opioid-dependent patients pose a considerable financial burden on the economy and the healthcare system.[7]

Opioids are a class of drugs that include the illegal drugs such as heroin, synthetic opioids such as fentanyl, and prescription pain relievers such as oxycodone, hydrocodone, codeine, and morphine.[8] Opioids reduce the perceptions of pain and cause drowsiness, mental confusion, and euphoria.[9] Due to their ability to cause euphoria, they are often sourced illegally and abused. Patients who are on prescription opioids for a significant period may also develop opioid dependence.[8] This can lead to opioid use disorder (OUD). The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V), describes OUD as a problematic pattern of opioid use leading to clinically significant impairment or distress.[9] DSM-V criteria for the diagnosis of Opioid Use Disorder involve 11 conditions,[9, 3, 4] with a patient showing at least two within a 12-month period.[9] The severity of the

disorder is ranked according to the number of the symptoms (Mild: 2-3 symptoms; Moderate: 4-5 symptoms; Severe: 6 or more symptoms).[10]

1.1.1 Prevalence

Worldwide, over 16 million people have OUD.[3, 4] Annual OUD-related mortality is estimated to be over 120,000 deaths worldwide.[3] Studies report that four out of five recent heroin initiates (79.5%) have prior nonmedical use of opioids, and 75% of heroin-dependents report being introduced to opioids through prescription drugs.[11] Men are more likely than women to use opioids and to become dependent; they account for most opioid-related overdoses.[4] Younger adults are more likely to abuse heroin and synthetic opioids.[12] Older individuals are more likely to move from therapeutically appropriate use of opioids for acute or chronic pain to misuse the same opioids.[12]

The opioid crisis in North America is in a grim state, particularly in the US. There are an estimated three million people with OUD in the USA, of whom more than half a million are dependent on heroin.[3] More than 46,820 Americans died in 2018 because of an opioid overdose.[13] According to a report by the World Health Organization, the US contributed 42% of the total overdose deaths in 2014.[11]

The use of illegal and prescription opioids also drives the opioid crisis in Canada. Between January 2016 and June 2020, an estimated 17,702 Canadians died from opioid-related morbidity.[14] From January to June 2020, males accounted for 77% of opioid-related deaths, and individuals between 20 and 49 years of age accounted for majority of the deaths.[14] The availability of fentanyl and fentanyl analogues in illegal drug supply has exacerbated the

pre-existing opioid crisis in Canada.[15] The Canadian Centre on Substance Abuse and Addiction reported that in 2016, about 55% of all opioid-related deaths involved fentanyl-related opioids (e.g., fentanyl, carfentanil, furanyl-fentanyl),[16] and 75% of all accidental opioid-related deaths in 2020 (January to June) involved fentanyl.[14]

1.1.2 Harms Associated with Opioid Use Disorder

OUD is a chronic relapsing disorder that may last a lifetime with potentially severe consequences, including disability, relapses, and death.[9, 17] In addition to fatal and non-fatal overdoses, it can cause severe withdrawal symptoms like pain, sleep problems, diarrhea, and vomiting.[9] Opioid use is a dangerous precursor of infectious diseases. The use of shared syringes among injection drug users (IDU) is associated with viral hepatitis, HIV, bacteremia, endocarditis, and osteomyelitis.[18, 19, 5] OUD has detrimental social impacts, contributing to high levels of crime, unemployment, decreased productivity, and health risks to non-abusers (e.g., accidental pediatric and perinatal exposure).[20] There is a strong association between opioid use and psychiatric disorders. A longitudinal study found a causal relationship between lifetime nonmedical prescription opioid use and the incidence of mood, major depressive, bipolar, and anxiety disorders.[21] Another study demonstrated a greater risk for suicide among people with OUD, intravenous drug use, or mixed drug use than people with alcohol use disorder and heavy drinking habits.[22]

1.1.3 Economic Burden of Opioid Use Disorder

OUD imposes substantial economic burdens on individuals, their families, the healthcare system, and the society. It was estimated that the total economic burden of the opioid crisis in the US from 2015 through 2018 was at least $631 billion, including the cost of healthcare services, premature mortality, criminal justice activities, child and family assistance programs, and education programs.[23] Mortality costs, i.e., lost lifetime earnings for those who died prematurely due to opioid overdoses ($253 billion) and excess healthcare costs ($205 billion) due to the opioid crisis constituted most of the economic burden.[23] Twenty-nine percent of the total spending was borne by federal, state, and local governments, while the remainder was borne by the private sector and individuals.[23] In addition to higher costs, significant healthcare resource usage may lead to longer wait times, fewer appointment options, and increased staff workload.[24]

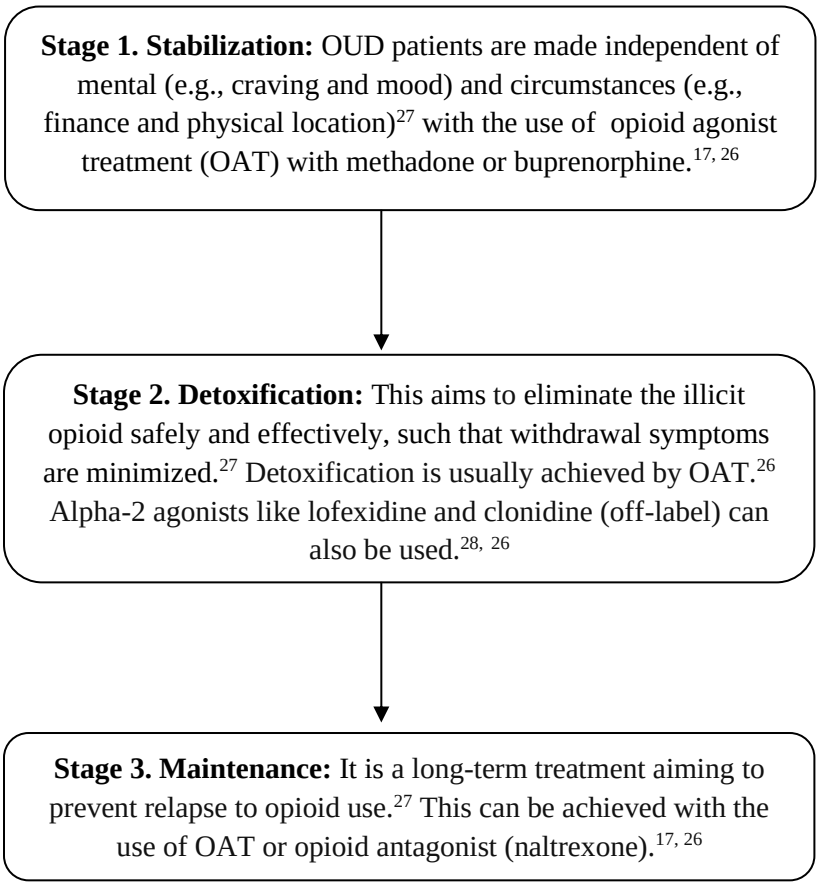
In Canada, the total incurred cost due to opioid use in 2017 was $6 billion.[25] Opioid use had the highest impact on productivity and the criminal justice system, costing $4.2 billion in lost productivity and $945 million to the criminal justice system.[25] The healthcare cost was estimated to be $439 million, including inpatient hospitalizations, day surgery treatment episodes, emergency department presentations, specialist treatment for opioid use disorders, the cost of physicians' time, and prescription drugs.[25]

1.1.4 Pharmacotherapies for Opioid Use Disorder

Treatment for OUD is multifaceted. Considering the chronic nature and behavioral impacts of the disorder, the primary aim of treatment is long-term remission of opioid-dependence related problems.[17, 26] Here, remission means return to a level of functioning that is free of active symptoms or is marked by stability in the chronic signs and symptoms that characterize opioid dependence.[26]

Although some individuals curtail opioid use and achieve abstinence on their own, evidence suggests that pharmacological treatments with support services provide optimum recovery.[12] Pharmacological treatment usually involves the use of medications coupled with psychosocial treatment. Psychosocial treatment includes psychosocial needs assessment, supportive counselling, links to existing family supports, and referrals to community services. [26] The pharmacological treatment processes are broadly categorized into three stages (Figure 1.1): stabilization, withdrawal management (referred to as "detoxification" from here on), and maintenance. [27]

Figure 1.1 Three Stages of Treatment of OUD



Opioid agonist treatment (OAT) with buprenorphine-naloxone is the recommended first-line of OUD treatment.[17] Methadone is also a recommended first-line treatment when buprenorphine-naloxone is contraindicated, or a second-line option when buprenorphine-naloxone treatment proves to have limitations or is ineffective.[17] Slow-release morphine is a potential opioid agonist in cases where both methadone and buprenorphine-naloxone are ineffective or contraindicated.[17] Buprenorphine is a partial mu (μ) opioid receptor agonist, methadone and morphine are full mu (μ) opioid receptor agonists; these medications are opioids themselves and act as OAT.[17, 26] Patients who seek opioid-free maintenance

treatment can be treated with naltrexone. Naltrexone is an opioid receptor antagonist that blocks the effects of opioids.[17, 26] Research suggest that extended-release naltrexone (XR-NTX) is superior to oral naltrexone in relapse prevention.[26] In addition to XR-NTX, there are a few more long-acting formulations like extended-release buprenorphine (XR-BUP) depot injection and subdermal buprenorphine implant.[26] Buprenorphine implant is reserved for patients who have achieved prolonged clinical stability on low-to-moderate doses of transmucosal buprenorphine.[26] It also requires invasive clinical procedures.[26] The specifications of the commonly used medications are provided in Table 1.1.

The American Society of Addiction Medicine (ASAM) National Practice Guideline for the Treatment of Opioid Use Disorder recommends methadone, sublingual buprenorphine, and buprenorphine-naloxone for detoxification and maintenance treatments.[26] It also suggests the use of selective alpha 2-adrenergic receptor agonists like lofexidine for detoxification.[26] The guideline recommends using long-acting formulations of XR-NTX, XR-BUP, and buprenorphine implant only for maintenance treatments.[26]

In Canada, CRISM National Guideline for the Clinical Management of Opioid Use Disorder recommends the use of OAT for both detoxification and maintenance.[17] Both methadone and buprenorphine-naloxone are widely used to treat OUD. Morphine is also recommended when buprenorphine-naloxone or methadone cannot be used.[17] Clonidine, a selective alpha 2-adrenergic receptor agonist, and oral naltrexone are available in Canada. However, the guideline recommends their use only if the patients wish to avoid OAT.[17] While treatment with methadone or buprenorphine-naloxone is the standard of care in most

provinces, British Columbia is also experimenting with hydromorphone (dihydromorphinone) to treat opioid dependent patients.[29] No evidence hydromorphone's use could be found elsewhere in Canada.

Cessation of opioid intake or dramatic reduction of usage leads to patients experiencing physical and mental discomforts. Effective opioid withdrawal management or detoxification helps the patients overcome the withdrawal difficulties and keeps them in treatment for a smooth transition to maintenance. No single approach to detoxification is guaranteed to work well for all patients.[26] Many opioid users are switched to opioid agonists.[17, 26, 30] Then the dose is gradually reduced.[17, 26, 30] A selective alpha 2-adrenergic receptor agonist like lofexidine, can be added to shorten the withdrawal time and relieve physical symptoms.[26, 30] Ultra-rapid detoxification can be done with the use of sedation or anesthesia.[26] Under sedation or anesthesia, patients are given opioid antagonists like naltrexone to induce withdrawal.[26] The objective of ultra-rapid detoxification is to help the patients sleep through the difficult period of withdrawal, reducing the discomfort and transitioning time to maintenance therapy. The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder, however, does not recommend ultra-rapid detoxification due to the high risk for adverse events or death.[26]

Detoxification can be the first step but not a primary treatment for OUD. It should be considered as only a part of a comprehensive and longitudinal plan of care, that is, maintenance therapy.[31, 17, 26] Although long-term maintenance treatment yields better outcomes in dealing with the recurring nature of opioid use disorder,[31, 32, 17, 26]

detoxification remains a required first step for many forms of long-term treatment such as residential rehabilitation and naltrexone maintenance.[33]

Table 1.1 Pharmacotherapy for treatment of OUD

Generic name	Therapeutic class	Indication	Available dosage forms	Route of administration
Buprenorphine[a]	Opioid agonist	**Tablet:** Treatment of opioid withdrawal syndrome and OUD **Injection:** Treatment of OUD in patients who have initiated treatment with transmucosal buprenorphine followed by dose adjustment for a minimum of 7 days **Implant:** Treatment of OUD in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine (i.e., no more than 8 mg per day)	Sublingual tablet, extended-release injection (monthly) and subcutaneous implant	Oral, subcutaneous, subdermal
Buprenorphine-naloxone[a]	Opioid agonist	Treatment of opioid withdrawal syndrome and OUD	Sublingual and film-coated tablets	Oral
Lofexidine[a]	alpha 2-adrenergic receptor agonist	Treatment of opioid withdrawal syndrome	Tablet	Oral
Methadone[a]	Opioid agonist	Treatment of opioid withdrawal syndrome and OUD	Liquid, powder, tablets, and diskettes	Oral
Naltrexone[a]	Opioid antagonist	Treatment of OUD	Tablet and extended-release injection	Oral, intramuscular
Slow release morphine[b]	Opioid agonist	Treatment of OUD	Extended-release capsule	Oral

* Buprenorphine extended-release injection (weekly or monthly, tradename "Brixadi") is not included in the table as it is not eligible for marketing in the US until November 30, 2020.
A: Specifications sourced from The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update[26]
b: Specifications sourced from CRISM National Guideline for the Clinical Management of Opioid Use Disorder[17]

1.1.5 Existing Research on Patients' Perceptions and Experiences with OUD Pharmacotherapies

With a wide array of OUD treatment options available, patients' perceptions of the pharmacotherapies and their treatment experiences may dictate their treatment choices and decisions.[34, 35] This becomes even more important with the availability of opioid agonists- and opioid antagonist-based treatments. Patients may be comfortable with the inherent euphoric nature of the OAT and thus can choose OAT as their treatment strategy. On the contrary, some may seek opioid-free or abstinence-based treatment and can prefer opioid antagonist treatment. Patients' perceptions may develop from their firsthand treatment experiences or the information provided by their peers with OUD. Experience, as the name suggests, essentially develops from events that the patients personally undergo.

There are numerous studies on patients' treatment perceptions and experiences. Some studies reported positive patients' perception of the pharmacotherapies, but many highlighted patients' concerns of treatment dependence and painful treatment experiences.[36, 37, 38, 39, 40, 41] Many patients harboured negative treatment perceptions (especially with OAT) and preferred opioid-free treatment interventions.[42, 43, 44] Patients with positive treatment experiences narrated positive treatment perceptions,[45, 46] and patients with negative treatment experiences articulated negative perceptions.[47, 48] While positive perceptions and experiences can be potential treatment facilitators, negative perceptions and experiences can be potential treatment barriers. Patients' treatment perceptions and experiences will be explored in detail in Chapter 2 of this thesis.

1.1.6 Concepts of Cost-Effectiveness Analysis for OUD Pharmacotherapeutics

Cost-effectiveness analysis (CEA) is the comparative analysis of two or more alternative interventions in terms of costs and health effects.[49] It is a widely used economic evaluation method to inform decisions of health care coverage, access to care, and resource allocation, all of which can lead to improvements in quality of care.[50] Apart from CEA, other economic evaluation tools include cost-minimization, cost-benefit analysis (CBA), and cost-utility analysis (CUA). Cost-minimization and CBA involve monetary outcomes, while CEA and CUA involve non-monetary outcomes, such as life-years gained, and quality of life gained.

The main objectives of cost-effectiveness research are to compare the value of new or expensive interventions with the standard of care and improve efficiency in delivering health care services.[50] The data of CEA serves to inform multiple audiences, namely, payers, policy-makers, patients, pharmacy formulary committees, and managed care companies.[50] As resources for healthcare spending are limited, CEA often helps to guide resource allocation decisions.[51] Interventions are compared in systematic approaches that contribute to judgements on whether interventions are highly cost-effective, highly cost-ineffective, or somewhere in between.[51] Cost-effectiveness research questions are not limited to treatment strategies (e.g., pharmaceuticals, surgery), but can also be applied to competing diagnostic, screening, or education/behavior change strategies.[50]

Economic evaluations of the pharmacotherapies for OUD mainly involve CEA and CUA approaches. This section discusses the important considerations of CEA and CUA that are

frequently employed in this thesis, and thus the readers may find it beneficial. For brevity and simplicity, we term CEA and CUA collectively as CEA.

1. Perspective: The perspective of the CEA defines the costs that are being gained or lost.[50] Commonly used perspectives are patient, health insurance, healthcare, criminal justice, and societal.[50,51] From the patient's perspective, the cost equates to out-of-pocket expenditures. From health insurance perspectives, the cost of disease and treatments is measured in terms of insurance premiums received minus the claims paid.[50] The healthcare perspective usually refers to the government, which pays for the cost. From the criminal justice perspective, the cost reflects the expense to the judicial system as a result of conviction. The societal perspective is a broad perspective, which includes all costs, that is, costs to the patient, health insurance, healthcare system, and criminal justice system.

2. Time horizon: Time horizon refers to the CEA study period, which is typically longer than the duration of most clinical trials. It is generally recommended to set a time horizon long enough to capture potential long-term economic consequences.

3. Utility: Utility, also called health preferences, are numeric ratings of the desirability of health states and should be distinguished from health status.[50] The utility at the best imaginable health states is valued as 1, and the utility measure of death is 0.

4. Disability-adjusted life years (DALYs) and Quality-adjusted life years (QALYs): DALYs and QALYs are time-based metrics of health that include the impact of interventions on years of life lost due to premature mortality and years of life lived with a non-fatal health outcome, weighted by the severity of that outcome.[51] DALYs measure loss

of health whereas, QALYs measure equivalent healthy years lived.[52] In other words, the measures of DALYs and QALYs are inverted.[52]

5. Incremental cost-effectiveness ratio (ICER): ICER is the ratio of the difference in cost and the difference in effectiveness between a pair of interventions. ICER reflects the true measure of cost-effectiveness. If the research question involves two interventions, such new treatment and usual care, only one ICER estimate would be obtained. However, if multiple interventions are concerned, the interventions are ordered according to increasing ICER estimates. The intervention having the lowest ICER value in the order is ranked the cost-effective intervention.

6. Willingness-to-pay (WTP) threshold: This measure is a benchmark of the maximum cost an entity (patient, healthcare system, payer, government, society) is willing to pay for an additional unit of benefit. Usually, newer interventions cost more than usual care, and thus ICERs for the newer interventions tend to be much higher than usual care. In such situations, a defined WTP threshold is used to make cost-effectiveness judgements. In principle, the intervention having ICER below the WTP threshold is considered cost-effective.

7. Dominance: When a new intervention is both clinically superior and cost less than the comparative intervention, it is referred to as an economically "dominant" strategy. The opposite is a "dominated" strategy.[53] This is also referred to as "strict dominance". Extended dominance occurs when the ICER of the intervention is greater than that of a

more effective intervention. The dominated interventions (both strict and extended) are always ruled out.

1.1.7 Existing Research on Cost-Effectiveness of OUD Pharmacotherapeutics

A summary table comparing the characteristics of the existing literature on the cost-effectiveness of OUD pharmacotherapies is provided in Appendix I. The table provides specific information on the cost currencies, study perspectives, study designs, time horizons, effectiveness measures, and WTP thresholds.

1.1.7.1 Evidence on Cost-Effectiveness of OUD Maintenance Treatments

As methadone and buprenorphine have been available for OUD treatment for decades, numerous economic evaluations of the two medications exist. As for the newer treatment options, there are few economic evaluations of XR-NTX, XR-BUP, buprenorphine implants, injectable heroin, diacetylmorphine, hydromorphone, and deep brain stimulation. Some studies also investigated the choice of treatment settings. Some of the cost-effectiveness studies are empirical studies conducted alongside the clinical trials, while others are model-based simulations.

Several studies compared the cost-effectiveness of OAT versus no treatment and found OAT highly effective. OAT provided to people with a history of opioid dependence released from prison was found to be cost-effective in reducing mortality in the first six months of release relative to no treatment.[54] Similarly, a UK based study found that OAT with methadone and buprenorphine cost more but generated higher quality-adjusted life

years (QALY) than no OAT.[55] The incremental cost-effectiveness ratios (ICERs) for buprenorphine maintenance treatment and methadone maintenance treatment were £13,923, and £14,206 per QALY gained, relative to no OAT.[55] From a societal perspective, the treatment strategies were cost-saving.[55] Cost-effectiveness study of long-term outpatient buprenorphine-naloxone versus no treatment found that buprenorphine-naloxone yielded an ICER of US$35,100 per QALY gained compared to no treatment after 24 months.[56]

A model-based cost-effectiveness analysis was done by Idrisov et al. (2017), which compared methadone maintenance treatment to standard care in Russian inpatient narcology hospitals among injection drug users (IDU).[57] Standard care in Russia includes diagnostic procedures, detoxification with antidepressants, antipsychotics, anticonvulsants, non-opiate analgesics, alpha-2 adrenergic receptor agonist, and rehabilitation.[57] Methadone maintenance treatment was found to be cost-effective relative to standard care due to its higher effectiveness in averting disability-adjusted life years (DALYs).[57]

Similarly, in another cost-effectiveness study conducted in Vietnam, community-based methadone maintenance treatment was cost-effective in opioid-free days compared to center-based compulsory rehabilitation in which patients with OUD are confined in centers for two years.[58] Comparisons of costs and effectiveness between methadone and heroin found that injectable opioid treatments with heroin or methadone are cost-effective relative to oral methadone.[59] However, injectable methadone has a greater probability of being

cost-effective than injectable heroin.[59] In another study, the co-prescription of methadone with heroin was found to provide higher QALYs with a lower cost than methadone alone.[60] Diacetylmorphine and hydromorphone provided more benefits than methadone at lower costs over a lifetime (QALY: 8.4, 8.3 vs. 7.4: costs: US$1.01 million, US$1.02 million vs. US$1.15 million, respectively).[61] In another study, people who received diacetylmorphine gained 7.92 QALYs on average and generated a societal cost of US$1.10 million; people who received methadone gained 7.46 QALYs and generated a societal cost of US$1.14 million, thus confirming the superiority of diacetylmorphine over methadone treatment.[62] When compared with deep brain stimulation, methadone maintenance treatment costs less.[63] Still, deep brain stimulation would be cost-effective relative to methadone maintenance if the success rate in terms of percentage of opioid-free patients was at least 49%.[63]

Carter et al. (2017) studied the cost-effectiveness of buprenorphine, another widely used medication to treat OUD. They found that buprenorphine implant costs less (-US$4,386) and provided greater QALYs (+0.031) relative to sublingual buprenorphine.[20] On the other hand, XR-BUP injection costs more but was less effective than buprenorphine-naloxone.[12] Integrating sublingual buprenorphine-naloxone treatment into clinical care for injection drug-dependent patients with HIV/hepatitis C co-infection reduced HCV reinfections by 7%, cirrhosis by 1%, and liver-related deaths by 3%.[64] The integrated treatment generated an ICER of US$57,100 per QALY gained, relative to standard HIV care with onsite HCV treatment and referral to offsite OUD care.[64]

Comparisons of cost-effectiveness of methadone and buprenorphine provide mixed findings. A cost-effectiveness study, conducted by Kenworthy et al. (2017), found that methadone maintenance treatment costs £895 more and yielded 0.063 greater QALYs relative to buprenorphine maintenance treatment.[55] There was no significant difference between methadone maintenance and buprenorphine maintenance treatments in an empirical cost-effectiveness study, although the former treatment strategy costs more than the latter.[65] In a model-based analysis, methadone maintenance treatment provided in clinics was cost-effective relative to office-based buprenorphine-maintenance treatment, yielding an ICER of US$10,437 per additional patient retained in treatment and US$8,515 per opioid abuse-free week gained.[60] Similarly, methadone treatment dominated buprenorphine treatment in terms of heroin-free days or abstinent days in another cost-effectiveness study, done alongside a randomized controlled trial.[67]

Naltrexone is a non-opioid treatment option for patients. Once a month injection of XR-NTX is costlier than methadone and buprenorphine. In an empirical study with community-dwelling participants involved with the criminal-justice system, XR-NTX generated higher QALYs and abstinent years but was not cost-effective relative to treatment as usual in the willingness-to-pay threshold of US$100,000 per QALY.[68] Higher ICER is due to the high cost of XR-NTX.[68] Yet in another study from a healthcare perspective and with a willingness-to-pay threshold of US$100,000, buprenorphine-naloxone was found to be preferable to XR-NTX in terms of QALY gained and time abstinent from opioids.[69] In another study, XR-NTX is cost-effective relative to methadone and buprenorphine

maintenance treatment with a cost of $72 per opioid-free day gained relative to methadone.[70] Buprenorphine was inferior to XR-NTX.[70]

1.1.7.2 Evidence on Cost-Effectiveness of OUD Detoxification Treatments

Evidence on the cost-effectiveness of the detoxification process for OUD is sparse. This is logical as detoxification alone is not effective in providing sustainable treatment outcomes. The guidelines recommend that the patients are maintained on relapse prevention programs after detoxification.[17, 26] Multiple literatures exist to confirm this recommendation. Comparisons of twelve months of MMT and 180-day methadone detoxification programs revealed that MMT produced significantly greater reductions in illicit opioid use than 180-day methadone detoxification.[71] MMT generated an ICER of US$16,967 per life-year (LY) relative to 180-day detoxification.[71] Similarly, 12-week BMT was cost-effective relative to a 14-day buprenorphine taper generating an ICER of US$25,049 per QALY gained and US$5,610 per opioid-free year gained from a societal perspective.[72] A cost-effectiveness study compared methadone and buprenorphine for detoxification and found methadone favourable compared to buprenorphine at the same cost regarding patient retention in treatment.[73] However, the same research found buprenorphine to be costlier and more effective than methadone with higher abstinence.[73] Another study compared OUD treatment initiation with methadone, buprenorphine and detoxification. Buprenorphine was more effective at a lower cost than both methadone and detoxification and thus was the dominant strategy.[74]

Only one study compared the cost-effectiveness of different detoxification procedures: rapid detoxification under anaesthesia (RODA), rapid opioid detoxification under sedation (RODS), conventional inpatient (CI) detoxification with clonidine and other symptomatic medications, outpatient detoxification using buprenorphine, and conventional outpatient (CO) detoxification using clonidine and other symptomatic medications.[75] Outpatient buprenorphine-based detoxification was the most cost-effective detoxification method among all strategies, and RODS was the most cost-effective inpatient method.[75]

The summary table of the study characteristics of the existing literature (Appendix I) reveals that studies widely vary in perspectives, modelling approaches, time horizon, the currency of cost, and effectiveness measures. Also, the review of the existing research provides mixed cost-effectiveness findings. Despite providing mixed evidence, the assessment of the previous studies has provided information on conventional modelling approaches for OUD pharmacotherapies, the health states associated with the disorder and treatment, the costs, and outcomes that need to be considered. All these data guided the study design in Chapter 3.

The review of the existing literature also highlights inadequate cost-effectiveness information of the newer, more expensive pharmacotherapies, like lofexidine, novel long-acting formulations of XR-NTX, and XR-BUP injections. This warrants the cost-effectiveness study of these medications, which will be focused on in Chapter 3.

1.1.8 Gaps in the Literature

Patients' perceptions of treatments and experiences with the pharmacotherapies can be key drivers in ensuring treatment uptake, continuity, and desired outcomes. Adequate understanding of the patients' treatment perceptions and experiences can predict potential facilitators and barriers. Although numerous studies documented the patients' narratives of treatment perceptions and experiences, only two systematic reviews assessed patients' perspectives of the treatments.[76,77] One of the reviews focused on the patients' experiences with methadone only and the associated treatment barriers.[76] The other study included both patient perceptions and experiences; however, it failed to highlight several key concepts of patients' perspectives of the treatments, like their treatment dose perceptions and their perceived role in treatment decisions.[77] Also, the study does not provide information on long-acting buprenorphine injections and implants which are the latest additions to OUD pharmacotherapies.[77]

Meanwhile, cost-effectiveness studies were mostly conducted for maintenance treatment strategies. However, initial withdrawal management often requires medication-assisted interventions that incur costs. Lofexidine hydrochloride has been used in the UK over the decades to manage opioid withdrawal and was recently approved in the US, but there is no cost-effectiveness study of this medication. Furthermore, there are only four cost-effectiveness studies on XR-NTX, giving mixed evidence.[70, 68, 12, 69] In addition, only one study assesses the cost-effectiveness of XR-BUP vs. sublingual buprenorphine-naloxone.[12] This study predicts XR-BUP not to be cost-effective relative to buprenorphine-naloxone.[12]

It is however not yet known the cost-effectiveness of XR-BUP compared with XR-NTX. All these warrant further research on cost-effectiveness of different combinations of drugs for detoxification including lofexidine and drugs for maintenance treatment including XR-BUP and XR-NTX to inform decision makers.

1.2 Study Objectives

Considering the identified evidential gaps in section 1.1.8, this thesis has two objectives. First, it conducts a narrative review of the patients' perceptions and experiences with OUD pharmacotherapies. In the narrative review, relevant studies are identified, and findings of the studies are described under common themes which emerged during the review of the articles. Second, it compares the cost-effectiveness of different OUD treatment strategies that account for both detoxification and maintenance stages.

1.3 Overview of the Thesis

This manuscript-style thesis is comprised of four chapters, references, and an appendix. The four chapters are an introduction chapter, two stand-alone but related research studies, and finally, a summary chapter. Data repetition in the chapters was unavoidable due to the nature of the two stand-alone studies.

Chapter 1 provides an introduction to OUD and its pharmacotherapies. This chapter describes the prevailing opioid crisis, the available treatment options, an account of existing literature and knowledge gap, a background of the research, rationale, focused research questions, and the overall thesis objectives.

Chapter 2 provides a narrative review of patients' perceptions and experiences with the pharmacotherapies to treat OUD. This study summarizes relevant literature on patient-reported perceptions and experiences. The intended study population includes patients in treatment, patients out of treatment, and patients who never received treatment. Intervention is strictly limited to pharmacotherapies for OUD, and any data on psychotherapy interventions are excluded. PubMed, PsycInfo, and SCOPUS are systematically searched to find relevant literature. Data are coded inductively to form first- and second-order themes. The literature findings are narratively discussed under second-order themes for the two outcomes, perceptions and experiences. Our decision to undertake a narrative review with data synthesis in meta-analysis is based on the heterogeneity of treatment interventions and data analysis methods in the original studies. This study is currently being prepared for publication in *Drug and Alcohol Dependence*.

Chapter 3 is a cost-effectiveness analysis of different treatment strategies using lofexidine for detoxification. The study also assesses the cost-effectiveness of the newer long-acting formulations, namely, XR-NTX and XR-BUP for maintenance treatments. Table 1.2 outlines the five treatment strategies that are included in the cost-effectiveness analysis.

Table 1.2 OUD treatment strategies for the cost-effectiveness analysis

Strategy	Detoxification regimen	Maintenance regimen
A	Methadone-lofexidine (oral)	Buprenorphine-naloxone (sublingual)
B	Methadone-lofexidine (oral)	XR-NTX (intramuscular)
C	Buprenorphine-naloxone (sublingual)	XR-BUP (subcutaneous)
D (usual treatment)	Buprenorphine-naloxone (sublingual)	Buprenorphine-naloxone (sublingual)
No treatment	None	None

The combination of the medications for detoxification and maintenance in each strategy is based on the clinical recommendations.[26] In strategies A and B, patients are stabilized by methadone taper and detoxified by lofexidine so that they can be transitioned to maintenance treatment either with usual care, that is, buprenorphine-naloxone or novel XR-NTX injection (as recommended by the ASAM National Practice Guideline for the Treatment of Opioid Use Disorder).[26] Strategy C is also designed following the ASAM National Practice Guideline for the Treatment of Opioid Use Disorder.[26] Detoxification and maintenance with Buprenorphine-Naloxone is the usual treatment of OUD (strategy D). The four treatment strategies are also compared with no treatment as a significant proportion of opioid-dependent population do not receive any medication-assisted treatment, despite the availability of multiple treatment options. The rationales of the treatment strategy designs are discussed in detail in Chapter 3.

The cost-effectiveness study employs a hybrid Decision Tree/Markov model. A hypothetical cohort of opioid-dependent patients receive either of the four treatment strategies or no treatment for a time horizon of one year. Costs are estimated for three effectiveness measures: quality-adjusted life years, treatment retention days, and opioid-free days. This study is currently being prepared for publication in *Value in Health*.

Finally, Chapter 4 provides a summary of findings from Chapters 2 and 3. The chapter also discusses the strengths and limitations of the two standalone studies (Chapters 2 and 3), research implications, and future research directions with the pharmacotherapies for OUD treatment.

1.4 Significance of the Study

The narrative review of perception studies helps to understand the patients' preferences, concerns, misconceptions, and treatment expectations that can act as potential treatment facilitators or barriers. Additionally, a comprehensive understanding of both patients' perceptions and experiences is important as many patients' perceptions are based on their own treatment experiences, while for some, the perceptions are based on what they hear from their opioid-dependent peers.[34, 42, 35, 43] This review seeks to inform clinicians and policymakers on what patients think about the available OUD pharmacotherapies and how they respond and adhere to their treatments.

There are currently significant price gaps between the newer medications and the conventional OAT. Cost of lofexidine is approximately twelve times more than the cost of

buprenorphine-naloxone and more than 300 times the cost of methadone,[78, 79, 80] while no evidence exists on its cost-effectiveness. Each XR-BUP injection is about 1.34 times the cost of XR-NTX and more than 700 times the cost of buprenorphine-naloxone (8mg/1mg).[78, 79, 80] Inadequate or mixed findings exist on the cost-effective of XR-BUP and XR-NTX. Against this context, a cost-effectiveness analysis of these newer pharmacotherapies will provide critical evidence on the economic value of these medications to aid the choice of optimal OUD treatment strategies by clinicians and policymakers.

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Co-authorship Statement

For my Master's thesis, the research was conceptualized by me and my supervisor, Dr. Hai Nguyen. Specific research questions and study designs of the two standalone but complementary studies (chapters 2 and 3) were developed in consultation with my committee consisting of my supervisor, Dr. Nguyen, and two other committee members, Dr. Lisa Bishop and Dr. Stephen Bornstein. With discussion, my committee members and I designed the two research studies, finalized the treatment strategies (for cost-effectiveness analysis), chose the relevant methodologies for data collection, analysis, and presentation of the thesis studies' findings.

For the narrative review, I (NA) conducted the literature search and screened the relevant articles. All authors discussed the article selection criteria, performed the data extraction process, and interpreted the data. I wrote the first draft of the manuscript, and co-authors (HVN, LB, and SB) suggested revisions that contributed to the final version of the manuscript. All authors read and approved the final manuscript. The manuscript is intended to be submitted for publication to *Drug and Alcohol Dependence*. For the cost-effectiveness study, I (NA) designed the study through discussion with co-authors (HVN, LB and SB), developed health state transition diagrams to model the Decision Tree-Markov model, reviewed literature to find data (probabilities, costs, and effectiveness measures) for analysis, and conducted the data analysis. HVN and LB guided me to finalize the selected OUD treatment strategies deemed relevant to the cost-effectiveness research. I wrote the first draft of the manuscript, and co-authors (HVN, LB and SB) contributed

revisions to finalize the manuscript. All authors read and approved the final manuscript. The manuscript is intended to be submitted for publication to *Value in Health*.

Chapter 2 Patients' Perceptions and Experiences with the Pharmacotherapies for the Treatment of Opioid Use Disorder (OUD)-A Narrative Review

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This manuscript is currently being prepared for publication in *Drug and Alcohol Dependence*.

2.1 Abstract

Background/aim: Despite rapidly increasing numbers of patients with opioid use disorder (OUD), the utilization of evidence-based medication treatments remains low. Patients' perceptions of treatments and experiences are important drivers of treatment uptake and outcomes. We conducted a narrative review of patients' perceptions of the pharmacotherapies for OUD and their treatment experiences to understand what patients think of the pharmacotherapies and how they react to these available treatment options.

Methods: We conducted a narrative review of both qualitative and quantitative studies. We included experimental, quasi-experimental, observational (including case-control, cohort, and cross-sectional), systematic review, and mixed methods studies. We searched PubMed, PsycInfo, and SCOPUS to identify eligible studies with a date restriction from January 1990 to April 2020. We used the Critical Appraisal Skills Program (CASP) tools for quality assessment of the studies. We narratively described the findings under themes that inductively emerged during the review of the studies.

Results: Seventy-six studies met the inclusion criteria, of which twenty-nine were qualitative (Perceptions: 15; Experiences: 14), forty were quantitative (Perceptions: 28; Experiences: 7; both: 5) and seven were mixed method (Perception: 4; Experience: 3). The studies focused on treatment with methadone, buprenorphine (oral, injection, and implants), buprenorphine-naloxone, and naltrexone (oral and injection). The review consistently identified both optimism and cynicism about the pharmacotherapies for OUD. Lack of knowledge on medications, even more so on the newer, long-acting formulations

was identified. There are mixed findings on treatment experiences, although patients with a more significant role in the treatment decisions expressed better treatment experiences.

Conclusions: Our study highlights the need to consider each patient's characteristics and treatment preferences when deciding on the optimum treatment strategy. Increasing knowledge of treatment options and facilitating shared decision making between the patients and the physicians may improve treatment entry and retention.

‘

2.2 Introduction

Opioid use disorder (OUD) has become a major public concern with detrimental health and social effects. On a global scale, over 16 million people have OUD.[1] Each year there are reportedly over 120,000 deaths worldwide, principally caused by opioid overdose.[2] In North America, the number of cases with OUD is soaring. More than 46,802 Americans died in 2018 because of an opioid overdose, 31,335 of which is due to synthetic opioids (fentanyl and fentanyl analogs).[3, 4] An estimated 17,602 Canadians died from opioid-related morbidities between January 2016 and June 2020.[5] OUD elevates social burden in the form of increased crime rates, unemployment, and decreased productivity.[6] It was estimated that the total economic burden of the opioid crisis in the US from 2015 through 2018 was at least $631 billion, and in Canada the total incurred cost due to opioid use in 2017 was $6 billion.[7, 8]

Buprenorphine-naloxone, an opioid agonist, is the recommended first-line treatment for OUD.[9] Methadone, another opioid agonist, is also a recommended first-line treatment when buprenorphine-naloxone is contraindicated, or a second-line option when buprenorphine-naloxone treatment proves to have limitations or is ineffective.[9] Slow-release morphine is a potential opioid agonist in cases where both methadone and buprenorphine are ineffective or contraindicated.[9] While opioid agonist treatment (OAT) with methadone and buprenorphine are commonly used pharmacotherapies for both detoxification and maintenance phases, naltrexone is the only available opioid antagonist for OUD treatments in maintenance phase.[9, 10] Most recently, the US approved alpha 2-

adrenergic receptor agonist called lofexidine hydrochloride that is used to manage opioid withdrawal symptoms.[11] As "off-label" medications, opiates like heroin (including diamorphine), hydromorphone, and alpha-2 adrenergic receptor agonist, clonidine are also used.[12, 13, 14, 15, 16, 9] Despite the availability of several evidence-based medication treatments, fewer than 11% of people with opioid use disorder (OUD) receive treatments in the US.[17] Even when accessible, uptake of these medications remains very low (20–25%), suggesting that patient-level barriers exist in addition to system-level barriers.[17]

Numerous studies report patients' attitudes and beliefs about the pharmacotherapies that are key determinants for treatment entry and retention.[18, 19, 20] Also, patients reported their pharmacotherapy experiences, which decided their future treatment choices and continuity.[21, 19] A comprehensive understanding of patients' treatment expectations and preferences, fears, and concerns will enable formulating effective policies, patient decision aids, and social marketing campaigns to counter misinformation, myths, and stigma associated with these pharmacotherapies. Treatment strategies and policies that are informed by evidence of patients' attitudes are associated with patients' increased treatment entry and continuation.[17]

As the empirical studies on patients' perceptions and experiences cover a wide variety of OUD treatment interventions across different study populations, a systematic review is warranted to summarize all the available evidence from diverse sources to make information more accessible to decision-makers. To our knowledge, there are only two systematic reviews elucidating patients' perspectives of the pharmacotherapies and barriers

to recovery.[22,23] These reviews, however, have a number of limitations. First, the study by Notley et al. (2015)[22] principally focuses on patients who have received treatment and provides no information on patients who never received treatment. Second, the study reports patients' experiences with methadone while no information is provided on conventional treatment with buprenorphine and the newer medications like extended-release naltrexone (XR-NTX) and extended-release buprenorphine (XR-BUP). Third, the study provides no data on dose-related experiences. Next, the review focuses heavily on the societal and structural barriers to treatment but fall short of drawing evidence on crucial patient-level factors (e.g., their perceived role in treatment plans) which affects patients' treatment decisions. Finally, many new empirical studies have been conducted since the review's date of publication, which necessitate a new review with updated data. A recent systematic review conducted by Cioe et al. (2020) captures both perceptions and experiences of patients and clinicians.[23] The study gives a broad overview of the perspectives, however, many critical details may have been missed, for example, comparison of patients' treatment preferences, patients' perceived treatment dose adequacy and their role in making treatment decisions and its association with treatment satisfaction. Also, among the newer pharmacotherapies, the study provides evidence of XR-NTX only, while no information is provided on patients' perspectives of XR-BUP and buprenorphine implants.

To overcome these limitations, in this review we identify, critically appraise, and summarize research on the patients' (in treatment, out of treatment, and never received treatment) perceptions of the pharmacotherapies and their experiences with the treatments.

In this review, we aim to update the available evidence from the previous two review studies[22,23] to provide the latest information of patients' treatment perceptions and experiences.

2.3 Method

2.3.1 Outcome Variables

We focused on two outcomes in this review: treatment perceptions and treatment experiences with OUD pharmacotherapies. Although they are closely overlapping, these two outcomes are yet distinctly different.

Patients' perceptions of OUD pharmacotherapies refer to patients' attitudes towards the pharmacotherapy, their treatment preferences, their understanding of the treatments, and finally, their treatment expectations. Information of patients' perceptions can be obtained from patients who received treatment in the past and currently receiving treatment (treatment experienced patients), or never received any treatment (treatment naïve patients). Prior or present experiences with the conditions contribute to a frame of reference that may affect a patient's perception of how much further treatment will improve his or her health status.[24]

Meanwhile, patients' experiences with OUD pharmacotherapies refer to patients' recounts of treatments, including any clinical comfort or discomfort that the patients may have faced, side effects, overall rating of treatment satisfaction, and finally if their treatment expectations have been met. Patients who received treatment in the past or currently

receiving treatment can provide information of the events that they have encountered during therapies. Often, open-text comments from patient experience surveys offer insight into the gap between perception or expectation and reality.[25] In this review, we focused on patients' experiences with the pharmacotherapies; their interactions with other healthcare components (doctors, nurses, hospital staffs) are not included.

2.3.2 Search Strategy

We conducted a comprehensive search of published literature using PubMed, PsycInfo, and SCOPUS around two central themes: 1) patients' reported perceptions of pharmacotherapies for OUD, and 2) patients' experiences with the pharmacotherapies. Keywords were formatted for the search: "patient" OR "patients" OR "people" AND "perception" OR "preference" OR "opinion" OR "belief" OR "concern" OR "knowledge" OR "barrier" OR "experience" OR "attitude" AND "medication assisted treatment" OR "medication-assisted treatment" OR "medications for opioid use disorder" OR "MOUD" OR "pharmacotherapy" OR "medication treatment" AND "opioid use disorder" OR "opioid dependence" OR "substance use disorder". All references were managed and stored using Mendeley.

We used the following patient, intervention, comparison, outcome (PICO) model[26] (Table 2.1) and detailed inclusion-exclusion criteria to select articles for this review.

Table 2.1 PICO Model

Criteria	**Included**	**Excluded**
Participants	Patients with OUD	Physician, nurse, pharmacist, policy makers, treatment program directors, treatment program staffs
Intervention	Medically prescribed pharmacotherapies for OUD	Abstinence based treatment, psychotherapy, surgical procedure, self-prescribed or illegally sourced agonists, intranasal naloxone for overdose treatment, services provided by medical staff/opioid treatment services
Comparison	No defined comparative intervention	
Outcome	Patient reported perceptions of clinical aspects of the pharmacotherapies and their clinical experiences during treatment	Program-related, logistical, and financial barriers, drug use stigma

Detailed inclusion-exclusion criteria:

1. Studies having patients of age 18 or more with confirmed OUD were included. The patients could be actively receiving treatment, have had a prior history of receiving treatment, or have never received any OUD treatment.

2. Studies on patients' perceptions and experiences with pharmacotherapy for OUD were included. Any data on short term withdrawal management or detoxification or treatment induction, psychosocial treatments, non-clinical factors like social stigma and taboo, perspectives on treatment outlets, financial constraint, treatment accessibility, experiences with clinicians or treatment program staff members were excluded.

3. Included study types: experimental, quasi-experimental, observational (including case-control, cohort, and cross-sectional studies), systematic review and mixed methods studies. Quantitative and qualitative studies were included. Excluded study types: case study, commentaries, news articles, letters, and opinion pieces.

4. Included studies were written in English.

5. Studies with a publication window from January 1990 to April 2020 were included. There is little evidence of patients' reported perceptions and experiences with OUD pharmacotherapies before 1990.

Following the search, all duplicates were removed. The study titles and abstracts were reviewed to confirm eligibility based on the defined inclusion-exclusion criteria. After removing the ineligible articles, the full texts of the remaining studies were screened to finally deem eligible. The reference lists of the screened articles were reviewed to ensure that all relevant studies were captured. Although the systematic review by Cioe et al. (2020)[23] was published after April 2020, we screened its reference list to ensure that all relevant studies have been included in the current study.

2.3.3 Quality Assessment/Critical Appraisal

Following the recommendations in Cochrane Handbook for Systematic Reviews of Interventions, we used Critical Appraisal Skills Program (CASP) tools for quality assessment.[27, 28] Currently, there are eight CASP tools for quality assessment based on study type: systematic reviews, randomized-controlled trials, cohort studies, case-control

studies, economic evaluations, diagnostic studies, qualitative studies, and clinical prediction rule.[29] We used CASP tools for qualitative studies for appraising the qualitative studies and CASP tools for cohort studies for the quantitative observational studies. We used CASP tool for cohort studies for the mixed method studies. We used CASP tool for systematic reviews to assess the quality of the studies included in this review.

The tools consist of three sections to assess internal validity, results, and relevance to practice. The CASP checklist for qualitative studies has nine closed-ended questions (Yes/No/Can't tell) and one open-ended question. It is scored on a scale of 0-9; methodological strengths or weaknesses, findings, and value of the research are noted. CASP checklist for cohort studies has ten closed-ended questions (with an answer from Yes/No/Can't tell) and two open-ended questions. It is scored on a scale of 0-10; notes are kept on methodological strengths or weaknesses, findings, and applicability to the general population. CASP checklist for systematic review has eight closed-ended questions (Yes/No/Can't tell) and two open-ended questions. It is scored on a scale of 0-8; notes on overall results and the precision of results are recorded. For all three checklists, 'Yes' is assigned as 1, and 'No' and 'Can't tell' are considered as 0.

2.3.4 Data Extraction, Analysis, and Presentation of Findings

We extracted reference information, study location, sample size and age, study aim and focus, study tool, data analysis, and key findings. Key findings include data on OUD patients' perceptions and experiences with the pharmacotherapies. Many of the studies covered aspects like patients' thoughts on treatment policies, availability, societal

acceptance, relationship with prescribing physicians or treatment program staff. However, only data conforming to the scope of the review was extracted.

Due to the heterogeneity of the study populations, treatment interventions, and method of data collection and analysis in the original studies, no data was synthesized. The findings were narratively explained rather than statistically pooled together to give a quantitative effect size. The concept of review under first order and second order themes was derived from the qualitative review on patients experiences with OUD pharmacotherapies.[22] We reviewed the included studies to code the findings in the original studies. Data was coded using NVivo. The codes constituted the first-order themes. The corresponding first-order themes are then grouped to generate common second-order themes. The findings are then summarized descriptively and organized around the overarching thematic headings (second-order themes). For example, many studies reported both positive and negative perceptions of OAT, whilst some reported patient's preferred medications, underscored some patients' total aversion towards OAT and demand for opioid-free treatments. All these individual concepts formed the first-order themes which are collectively drawn to make up the second-order theme, "Attitudes Towards the Pharmacotherapies". We used an inductive approach to construct themes and not a priori. Themes on perceptions are provided in Table 2.2 and themes on experiences are provided in Table 2.3. Simultaneous to data coding, all necessary information on methodology, sampling, data collection and analysis, and findings were extracted in a customized data extraction form.

Table 2.2 Themes on patients' perceptions of pharmacotherapies for OUD

First order themes	Second order themes
Positive Attitudes towards the Pharmacotherapies	Attitudes towards the Pharmacotherapies
Perceived Benefits of the Pharmacotherapies	
Negative Attitudes towards the Pharmacotherapies	
Perceived Concerns /Side effects of Medications	
Preferred Pharmacotherapy	
Knowledge/Awareness of Available Pharmacotherapies	Awareness/Knowledge of the Pharmacotherapies
Perceptions of Long-Acting Formulations	Perceptions of Long-Acting Formulations
Perceptions of Appropriate Dose	Perceptions of Appropriate Treatment Dose and Duration
Perceived Appropriateness of Treatment Duration	

Table 2.3 Themes on patients' experiences with pharmacotherapies for OUD

First order themes	Second order theme
Positive Experiences	Treatment Experiences
Negative Experiences	
Symptom Complaints	
Dose-Related Experiences	Dose-Related Experiences
Comparison of Experiences During Treatment switch	Experiences During Treatment Switch
Organoleptic Experiences with the Pharmacotherapies	Sensory Experiences with the Pharmacotherapies
Satisfaction with the Pharmacotherapies	Treatment Satisfaction
Factors Affecting Satisfaction	

2.4 Results

The systematic literature search yielded the following papers from online databases: PubMed (9,133), PsycInfo (318), and SCOPUS (421). After removing duplicates, we

identified 8,063 references from searching electronic and alternative sources. We reviewed the titles and abstracts for eligibility and relevance; 308 references were obtained. After a review of full text, we found 68 relevant articles for this review. We later removed five studies that reported patients' treatment perceptions and experiences with heroin, diamorphine (pharmaceutical name of "heroin") and hydromorphone because these medications are still investigational drugs and require widespread research to establish clinical equivalence with conventional treatments. Finally, review of the reference lists of the 63 studies and the review article by Cioe et al. (2020)[23] yielded additional thirteen studies.

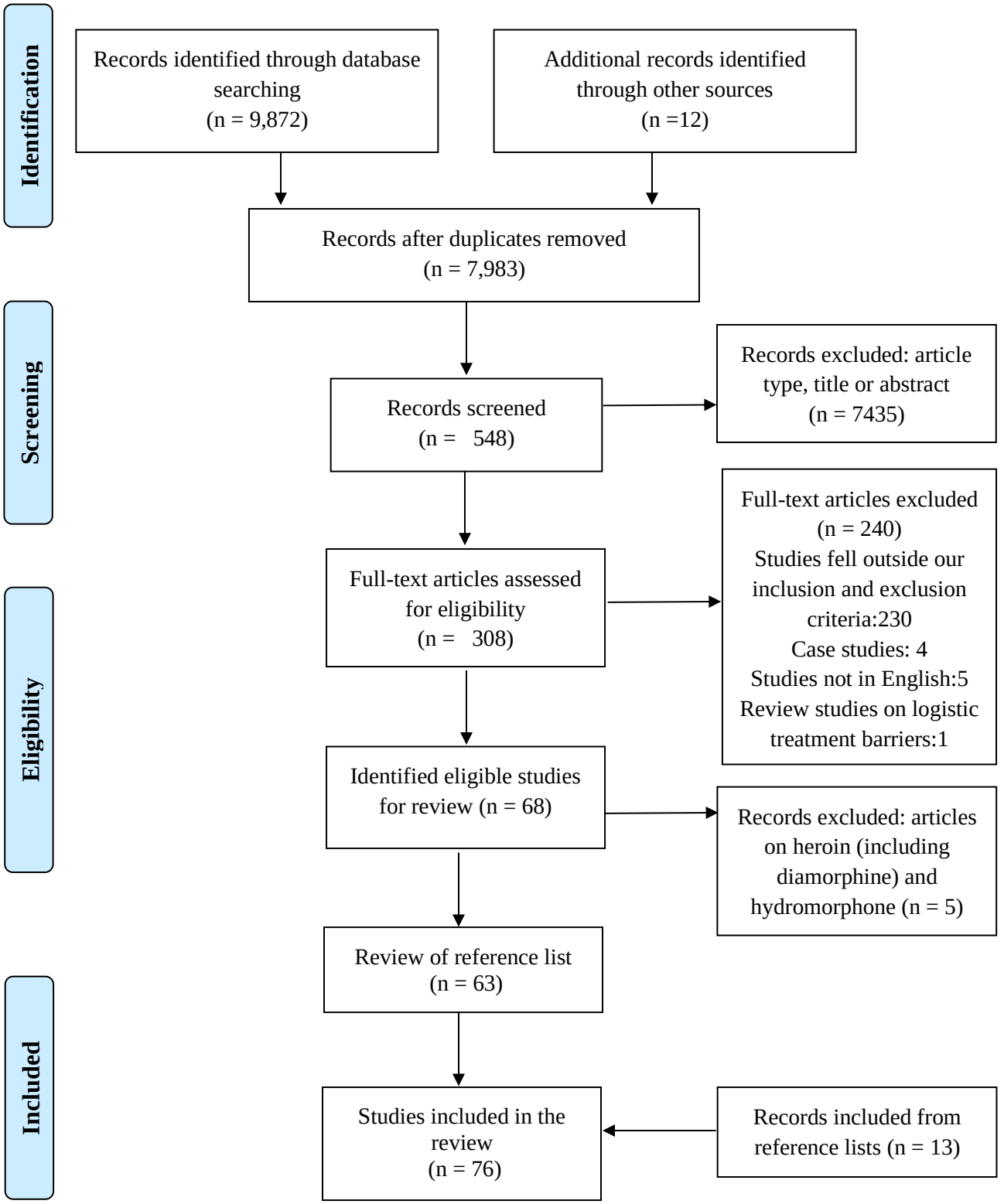
A total of seventy-six studies were included in the review. The full study selection and inclusion process is outlined in the PRISMA flowchart[30] (Figure 2.1). Forty-seven studies involved patients' perceptions of the pharmacotherapies for OUD, twenty-four studies were about patients' treatment experiences and five studies provided data on both perceptions and experiences. Twenty-nine studies were qualitative (Perceptions: 15; Experiences: 14), forty studies were quantitative (Perceptions: 28; Experiences: 7; Perception and Experiences: 5), and seven were mixed method studies (Perception: 4; Experiences: 3). The studies originated from twenty countries. The study population was individuals with OUD who were receiving treatment, out of treatment, or never received treatment. Treatment strategies were methadone, buprenorphine (sublingual, and extended-release depot injection and implant), buprenorphine-naloxone, naltrexone (oral and extended-release injection). The qualitative studies employed semi-structured in-depth

interviews, focus group discussion, and field notes as tools for data collection. The quantitative studies used interviews, survey/questionnaire, and validated self-rating scales.

CASP ratings for the qualitative studies ranged from 9 to 5 (mean: 8.0); CASP ratings for the quantitative observational studies ranged from 9 to 5 (mean: 7.5); CASP ratings for the mixed method studies ranged from 9 to 6 (mean: 7.6). CASP rating for the systematic review is 6.

Data on study and participant characteristics are provided in Tables 2.4 and 2.5, along with CASP scores. Summarized information on key findings is reported in the Summary of Findings (SoF) in Tables 2.6 and 2.7.

Figure 2.1 PRISMA Flow Diagram



2.4.1 Perceptions

A. Attitudes Towards the Pharmacotherapies

Patients in treatment reported better attitudes towards the medications than individuals who are not in treatment or never received any pharmacotherapy.[31, 32, 33, 34, 35, 36] Patients often identified the OAT's potentials to remove withdrawal discomforts, reduce cravings and improve physical and mental health.[37, 38, 39, 40, 41] Conversely, some patients reported negative attitudes towards medications and perceived OAT as same as using illicit opioids or even encouraged the use of illicit opioids.[20, 42, 35] Some considered OAT with methadone as the last treatment option when all other treatment approaches have failed.[43, 44]

The positive patient-reported aspects of methadone are its ability to relieve cravings and withdrawal symptoms, stabilize their mind and improve their quality of life.[45, 17] Patients also reported that methadone helped them to avoid getting HIV.[46, 45] Simultaneously, patients feared methadone dependence and perceived withdrawal from it as being more difficult than from heroin.[47, 48, 32, 49, 50, 45, 51, 21, 52] While some welcomed the daily dosing and supervised consumption of methadone in a clinic, for many, it acted as a treatment barrier.[53, 54, 55, 56, 21, 17]

Buprenorphine was perceived as highly effective in reducing opioid craving, suppressing the withdrawal symptoms, causing no sedation, having mild withdrawal symptoms of its own, and preventing future relapse.[57, 51, 58, 59, 17] Buprenorphine was also recognized to prevent overdose and death due to its ceiling property.[44] Like methadone, the perceived

benefits of buprenorphine were coupled with concerns about treatment harms. Patients reported concerns over buprenorphine addiction, dependence, potential side effects, and painful treatment withdrawal.[60, 59, 61]

As naltrexone, especially extended-release naltrexone (XR-NTX), is a relatively new medication, fewer studies of perceptions exist compared to methadone and buprenorphine. Patient reported benefit of naltrexone is the prevention of relapse by blocking the effects of all opioids.[62, 59, 63] The reasons which emerged for unwillingness to receive naltrexone treatment are satisfaction with OAT, unwillingness to stop opioid for pain and unwillingness to take long-acting formulation by intramuscular injection (in case of XR-NTX).[62, 63] Naltrexone was perceived to be effective only in patients with a shorter history of opioid use and in highly motivated individuals.[64, 17] Commonly reported concerns with naltrexone are precipitated withdrawal[59, 64] and inability to manage withdrawal discomforts.[17]

Although some patients preferred methadone over buprenorphine,[65, 42] a more significant number of studies reported patients' buprenorphine preference over methadone.[32, 55, 21, 40, 34] Some studies also reported patients growing preference for naltrexone (especially XR-NTX) and drug-free treatment over OAT.[59, 66] These data suggest that while OAT with methadone and buprenorphine are popular treatment choices, some patients prefer abstinence-based treatment either with naltrexone or no medication at all.

B. Awareness/Knowledge of the Pharmacotherapies

A lack of understanding of the medications and of the disorder was seen among the patients.[48, 52, 17] Lack of knowledge on the newer treatment options like XR-NTX, buprenorphine implants and extended-release buprenorphine (XR-BUP) injection was more apparent.[17] Sometimes, patients were not aware of all the treatment options and were not provided with information about the choices they may have had.[21] In his study, Brown et al. (2017) reported that only 11.8% of the study participants had ever heard of XR-NTX, and none had it prescribed.[67] Most of the patients in the study conducted by Randall-Kosich et al. (2019) reported that they learned about buprenorphine and methadone from peers and friends.[44] In contrast, they learned about XR-NTX from their doctors.[44] This is logical as methadone and buprenorphine have been used for OUD treatment much longer than XR-NTX.

C. Perceptions of Long-Acting Formulations

Long-acting formulations like XR-NTX, XR-BUP, and buprenorphine implants are the latest additions to OUD pharmacotherapies. Some patients expressed interest in long-acting formulations, while many were not willing to use long-acting injectables or implants and preferred traditional short-acting oral medications.[62, 63, 35] There was a higher preference for long-acting injectables than implants among the patients who preferred long-acting formulations (40% vs. 30%, respectively).[35] Treatment features like less frequent dosing and visits to treatment facilities, convenience, lower risk of missing dose, and longer periods of craving and withdrawal coverage made the long-acting formulations lucrative

to the patients.[68, 69, 35] Buprenorphine depots were perceived as less addictive but more effective than methadone in blocking the effects of opioids.[69]

Commonly cited fears with the long-acting formulations include medication delivery by injection, failing to suppress withdrawal symptoms for the period between doses, dependence, side effects, overdose and precipitated withdrawal when transferred from conventional OAT to long-acting formulations.[64, 68, 69] Some were anxious about losing the structured and emotional support they receive from the frequent visits to the treatment services.[69]

D. Perceptions of Appropriate Treatment Dose and Duration

Understanding patient's perceptions of dose appropriateness is important to identify optimum dose. In the study conducted by Hayashi et al. (2017) with injection drug users, the median methadone dose of 30 mg/day which the patients received was deemed as inadequate for successful treatment outcomes.[70] A median methadone dose of 30mg/day is a low treatment dose as outlined in treatment guidelines[9, 10] and hence patients' perception of dose inadequacy seems reasonable. Patients perceived their average daily methadone dose, ranging from 64.6 mg to 76 mg, to be adequate.[71, 72, 73, 74] Patients explained the factors which exerted upward pressure (i.e., the stimulus to increase methadone dose) or downward pressure (i.e., the stimulus to decrease methadone dose).[75] Fears of experiencing withdrawal discomfort acted as upward pressure on perceived ideal dose.[75] Factors like patients' limited role on dose adjustment decisions, fear of methadone

intoxication and side effects, methadone dependence, notions of doses being "too high" acted as downward pressure on perceived ideal dose.[75]

Several studies found association between patients' dose perceptions (using the visual analog scale of methadone dose (VAS-MD)) and dose decision participation. Patients who perceived the dose to be adequate had a more favourable opinion of methadone treatment and reported a significant role in dosage decisions. [71, 72, 73, 74]

There is mixed evidence on the patients' perception of the ideal treatment dose, frequency and duration. Some patients perceived methadone as a long-term treatment or indefinite treatment, whereas buprenorphine is viewed as short term treatment.[51] Alternatively, some patients believed that methadone is a short-term treatment and patients should strive to get rid of methadone due to its detrimental health effects.[77,78] In another study, the perceived duration of treatment (median) with buprenorphine preparations and oral naltrexone was one month.[59] In the same study, 83.6% of the patients reported once daily dose of buprenorphine was inadequate and 89.4% of patients reported once daily dose of oral naltrexone as ideal.[59]

2.4.2 Experiences

A. Treatment Experiences

Patients reported both positive and negative experiences with OAT. Patients reported that the treatment helped them get rid of heroin craving and dependence.[79, 80, 81] They also reported "treatment dependence" "withdrawal" and "lack of freedom" as the worst aspects

of their treatment experiences.[79, 81, 82, 83, 84, 85, 86] In a more recent study conducted by Velasquez et al. (2019) with previously incarcerated opioid users, some reported that had little intention to enroll in community-based methadone maintenance program due to difficult methadone experiences in jail.[86]

Patients on buprenorphine maintenance reported having better mental and social well-being.[87] Numerous reports suggest that treatment experiences with buprenorphine were better than with methadone.[80, 88, 89, 90, 91, 86] Opioid dependent youths described buprenorphine-naloxone experiences to be effective by eliminating all withdrawal symptoms and cravings.[89] Opioid-dependent HIV patients reported that the medication effectively reduced or eliminated cravings, blocked the euphoric effects of illicit opioids, and involved them more into HIV care.[92]

Despite the positive notions and experiences with buprenorphine (also buprenorphine-naloxone), there are accounts of difficult treatment experiences. Patients experienced severe treatment withdrawal symptoms and were wary of treatment dependence.[79, 82, 87] Like methadone patients, many buprenorphine patients were using heroin concomitantly with treatment medication.[88, 93, 85] With both buprenorphine and methadone, there is an additional concern of diversion. Some patients reported to sell their medicines to unregistered opioid-dependent patients and remained on suboptimal treatment dose.[22, 94] This may have led to the use of illicit heroin to counter the withdrawal discomforts.[85, 87]

Common symptom complaints with methadone include sedation, respiratory depression, QTc prolongation, depression, fatigue, confusion, constipation, and dependence.[80, 91]

Reported side effects of buprenorphine include headaches, nervousness, anxiety, depression, gastrointestinal issues, and withdrawal symptoms (e.g., cold sweats, nausea, cramps, sleeplessness).[92, 95, 91] Patients reported having fewer lesser side effects with buprenorphine than with methadone.[80, 90, 86]

Patients' experiences with naltrexone treatment were narrated in just one study. In one survey, patients indicated that XR-NTX blocked the euphoric effects of illicit opioids, diminished opioid craving, and prevented relapse.[86] A few participants reported side effects of XR-NTX, including headaches, upset stomach, and nausea.[86]

B. Dose-Related Experiences

In clinical practice, the optimum treatment dose is often tailored to the patient's needs and treatment goals.[9] It is already narrated under the theme "Medication Dose and Duration" of the perception outcome that many patients attributed much of the side effects to poor dose adjustments. In one study, it is seen that formerly incarcerated opioid-dependent individuals developed an aversion towards methadone treatment due to abrupt dose reduction in state prisons.[96] Rapid dose reductions caused severe withdrawal symptoms and physical and mental discomforts for these patients.[96]

C. Experiences During Treatment Switch

Several studies documented patients' experiences with buprenorphine-naloxone when transferred from methadone or plain buprenorphine treatment. Patients shared their experiences of increased mental clarity and cognitive abilities with buprenorphine-

naloxone which was unlike with methadone. [88, 91] They had a better control on opioid craving than with methadone or plain buprenorphine.[95, 97, 91] However, not all patients appreciated this improved mental clarity with buprenorphine-naloxone and preferred the euphoria with methadone.[88, 91] Few patients described poor withdrawal management with buprenorphine-naloxone when switched from plain buprenorphine and reported shivering, perspiration, yawning, and general psychophysical disturbances.[95] A small proportion of the patients attempted to abuse buprenorphine-naloxone but failed to experience any euphoria.[95] Some patients experienced treatment side effects like constipation gastrointestinal disturbances, nausea, anxiety, insomnia, sweating, and headache when switched from plain buprenorphine to buprenorphine-naloxone.[95, 97]

D. Sensory Experiences with the Pharmacotherapies

Studies have been found to report patients' sensory experiences with buprenorphine-naloxone tablets. Multiple literature indicate that patients did not like the medication taste.[69, 81, 83] Many patients reported to have experienced an unpleasant, bitter taste of the medication.[80, 95, 97] On the contrary, a significant number of patients in the study conducted by Daulouede et al. (2010) preferred the taste and tablet size of buprenorphine-naloxone than plain buprenorphine.[98]

E. Treatment Satisfaction

Despite the negative notions, patients receiving OAT reported general satisfaction with their treatment. In some studies, the patients communicated satisfaction in terms of

treatment outcomes, while in others, satisfaction was measured by scales. Madden et al. (2008) found that only 10% of the patients reported dissatisfaction with their OAT with methadone or buprenorphine.[79] In another study, the mean satisfaction score with buprenorphine-naloxone treatment was 4.4 out of 5 on a 5-point Likert-type scale.[99] It is noteworthy that these two studies measured overall satisfaction for the treatment programs, which included medications and logistic aspects of treatment such as facility staff and services.

Treatment satisfaction is also measured by the Verona Service Satisfaction Scale for Methadone-Treated opioid-dependent patients (VSSS-MT) and Scale to Assess Satisfaction with Medications for Addiction Treatment Methadone for heroin addiction (SASMAT-METHER). On average, the patients expressed satisfaction with methadone treatment.[71, 72, 73, 74] Patients with the current OUD was found to be less satisfied than patients with the remitted disorder.[73] Daulouede et al. (2010) used a visual analog scale (VAS) to measure global satisfaction. Patients rated high and similar global satisfaction with buprenorphine and buprenorphine-naloxone (6.83-7.04 vs. 6.89-7.38 respectively on a scale of 10).[98]

Several studies found an association between treatment satisfaction and treatment dose. Patients' desire to adjust methadone dose downward is associated with greater satisfaction.[71, 100, 73] Higher satisfaction was also found to be associated with perceived influences on dose decisions, general health, mental health, social functioning, and participants' ratings of their treatment progress.[72, 100, 73, 74] Lower satisfaction was found to

be associated with a higher frequency of recent heroin and benzodiazepine use, and, for women, longer treatment duration.[100, 73]

When compared by medication type, Muller et al. (2018) found that a greater proportion of patients on methadone reported satisfaction, followed by buprenorphine and buprenorphine-naloxone.[90] However, in numerous studies, patients communicated better experiences with buprenorphine (and its preparations) than with methadone.[80, 88, 89, 91, 86]

2.5 Discussion

This review is a compilation of patients' perceptions and experiences with the evidence-based pharmacotherapies to treat OUD. It provides information on the patient-reported positive and negative aspects of the pharmacotherapies and accounts of patients' experiences with these available therapies. The study consolidates evidence of treatment perceptions and experiences with various treatment interventions across a diversified population with OUD including both those who received treatment and those who never received the treatment. This current review both supports and augments the findings of patients' perspectives of the pharmacotherapies provided by Cioe et al (2020).[23]

Previously, Notley et al. (2015) studied patients' experiences with conventional OAT, methadone.[22] The study solely focused on treatment experienced patients. Understanding patients' experiences alongside perceptions is essential as prior treatment experiences shape much of the perceptions.[32, 12, 51, 38, 45, 39, 16, 60, 21, 59, 66, 63, 53, 86, 61, 44] For example, patients with negative treatment experiences reported negative treatment perceptions and

vice versa. It is equally important to understand patients' perceptions who never have had medication-assisted interventions, to call attention to their opinions on the pharmacotherapies and address the treatment-limiting factors. More recently, Cioe et al. (2020) included data of both patients' perceptions and experiences with the pharmacotherapies.[23] Our study sheds light on several themes which were not discussed in the previous systematic reviews, for example, patients' dose perceptions and experiences, their treatment experiences with buprenorphine-naloxone when transferred from methadone treatment, and their attitudes and experiences with the newer long-acting formulations, including XR-NTX, XR-BUP injection and buprenorphine implants.

Patient reported effectiveness support the clinical application of the OAT for OUD. However, our review indicated a consistent pattern of concerns among the OAT patients regarding treatment dependence, side effects and withdrawal discomfort. This fear is even more evident from the patients' perceptions of their methadone dose to be high and their desire to lower their treatment dose.[71, 72, 73, 74] There is a long-standing debate on the effectiveness and preference between methadone and buprenorphine. Based on the patients' higher positive assessment of buprenorphine experiences than with methadone,[80, 97, 88, 91, 86] this review indicates that patients may find buprenorphine treatment more favourable than methadone treatment. Buprenorphine being a partial opioid agonist, offers several clinically desirable pharmacological properties: lower abuse potential, lower level of physical dependence (less withdrawal discomfort), a ceiling effect at higher doses, and better safety from an overdose compared with methadone.[104, 105]

Although OAT with methadone and buprenorphine are widely used treatments, our review identified a sub-group of patients who consider OAT and illicit opioids as similar and are reluctant to enroll in OAT programs.[53, 51, 42, 43] Some patients showed a greater preference for opioid-free or abstinence-based treatment.[49, 60, 43] Thus, XR-NTX can be a viable treatment option for them. XR-NTX is a lesser studied medication than OATs, and this necessitates more research to establish the therapy's clinical equivalence with the extensively studied OATs.

Additionally, long-acting buprenorphine injection and implants are novel therapeutic options that can offer long-term management of opioid withdrawal and craving, less frequent dosing, and treatment facility visits. However, we observed that the patients harbour a misconception that the long-acting formulations are effective on highly motivated individuals with a short history of opioid use.[66, 17] Effective communication with the physicians can be integral in addressing many of the misconceptions and making the patients aware of the wide array of therapeutic options available that best suit the patients' preferences and treatment goals.

Incarcerated patients recounted their harrowing experiences with the pharmacotherapies in prison, especially with methadone, which led to harboring negative perceptions and possible disruptions of care.[60, 96, 40, 86] The period immediately after release from prison can be extremely challenging. In one study, it is found that former prison inmates during the first two weeks of prison release are at 12.7 times higher risk of death, principally due to overdose, cardiovascular disease, homicide, and suicide than other opioid-dependent

individuals.[106] Again, limited referrals and access to community-based treatment programs are significant barriers faced by formerly incarcerated individuals. In the US, only one in every twenty justice-referred individuals receives OAT.[107] Such a situation calls for focused policy and regulatory efforts to enhance the seamless transition of the former inmates to community-based treatment and harm reduction programs. Our review suggests that not all individuals prefer OAT,[38, 60, 63] and indeed, not everyone desires to be abstinent.[46] It is crucial to bear in mind that OUD treatment is not a "one size fits all" approach. Individual patient characteristics and preferences should be factored while choosing the optimum treatment strategy.[10]

A critical concept drawn out of this review is the lack of patients' knowledge of the treatments. The paucity of knowledge led to a wide disparity between patient's treatment expectations and outcomes. In many cases, patients were not aware of all the available treatment options and could not make the best treatment decisions.[21] Useful patient decision aids can bolster existing resources in diverse treatment settings by increasing knowledge of treatment options and facilitating shared decision making between the patients and the physicians.[108] Another key finding of this review is the importance of patients' perceived role in treatment decisions. Patients more involved in their treatment decisions articulated better opinions on OAT,[79, 82] and demonstrated higher satisfaction with treatment.[71, 72, 73] This stresses the need for the adoption of patient-centered care (PCC) in OUD treatment.[109] Titrating optimal treatment dose requires a therapeutic alliance between the clinicians and the patients. Open dialogue between the clinicians and patients

may help to fix treatment dose and aid both parties to land a mutually agreed treatment intervention, frequency, and follow-up.

In conclusion, understanding patients' experiences alongside perceptions with OUD treatments is essential for establishing effective treatment strategy for patients with OUD. Our review of a large body of studies provides new insights into patients' perceptions and treatments with OUD treatment across various patient populations. Formulations of clinical practice and treatment policies should take into account the findings of this review to best serve individuals with opioid dependence.

Table 2.4 Study and participant characteristics: Perceptions

Study	Sample	Average age, year (SD)	Gender male/female, %	Study design	Study focus	Sampling technique	CASP rating
Ahamad et al. (2015)[62] Canada	657 opioid dependents who reported any use of opioid or enrolled in MMT in past 6 months of the	47.4	209/106	Quantitative	XR-NTX	Snowball in addition to recruitment from social outreach program	7
Bachireddy et al. (2011)[38] Malaysia	102 HIV-infected male prisoners or recently released	33	All male	Quantitative	OST	The inmates were approached to participate in the study.	5
Bentzley et al. (2015)[58] USA	69 patients in buprenorphine maintenance treatment (BMT)	36.4 (± 11.4)	32/37	Quantitative	BMT	Patients enrolled in the treatment program were asked to complete the study survey.	8
Bobrova et al. (2007)[48] Russia	121 injection drug users	26	95/26	Qualitative	OST	Snowball	8
Bojko et al. (2015)[43] Ukraine	41 OST naïve people who inject drugs (PWIDs)	38	66/34	Qualitative	OST	Convenience: samples were recruited by local research assistants.	7
Brown et al. (2017)[67] Malaysia	34 opioid dependent fishermen with HIV infection	38.8 (± 8.7)	All male	Qualitative	MET, BUP, and XR-NTX	Purposive and snowball	8

Study	Sample	Average age, year (SD)	Gender male/female, %	Study design	Study focus	Sampling technique	CASP rating
Fox et al. (2015)[60] USA	21 former prison inmates (8 ever received BMT, 12 received MMT)	49	17/4	Qualitative	BMT and treatment MMT	Convenience	9
Gryczynski et al. (2013)[51] USA	80 patients on BUP treatment	45.2 (± 7.0)	Female: 33.8%	Mixed method	MET and BUP	Purposefully selected from parent study	8
Gu et al. (2012)[78] China	158 newly admitted first-time MMT clients	<35 to 40+	143/15	Quantitative	MMT	Purposive	9
Gutwinski et al. (2014)[39] Germany	968 patients receiving opioid maintenance treatment (OMT)	18-70	715/ 260	Quantitative	OMT: MET and BUP	Participants recruited in outpatient clinic and hospital	7
Haase et el. (2016)[63] Norway	720 (Detoxification unit: 34%; Outpatient unit: 31%; Opioid maintenance treatment-OMT: 25%; Prison:10%)	39	536/184	Quantitative	XR-NTX	Questionnaires handed out to opiate users at OMT sites, detoxification units, out-patient units, long-term treatment facilities for illegal drug abusers and a few prisons.	8
Hayashi et al. (2017)[70] Thailand	158 people who injects drugs who received MMT in the past 6 months	38 (median)	131/27	Mixed method	MMT	Participants were recruited through peer outreach efforts and word of mouth.	9
Kelly et al. (2012)[76] USA	417 opioid dependent adults (132 receiving	42.4	221/196	Quantitative	MET and BUP	Purposive	8

Study	Sample	Average age, year (SD)	Gender male/female, %	Study design	Study focus	Sampling technique	CASP rating
	BUP, 191 receiving MET, 94 out of treatment)						
Khazaee-Pool et al. (2018)[52] Iran	23 opioid users (12 in MMT, 7 dropped out of MMT, 4 never received MMT)	43.27	All male	Qualitative	MMT	Purposive	8
Larance et al. (2019)[68] Australia	402 regular opioid users (67% were receiving methadone and buprenorphine-naloxone during the time of the study)	42 (± 8.9)	Female: 37%	Quantitative	XR-BUP	Participants were recruited from needle and syringe programs, OAT services, snowballing and word-of-mouth.	7
Larney et al. (2017)[40] Australia	46 incarcerated participants (27 on Opioid substitution therapy-OST)	35	32/14	Qualitative	OST with MET or BUP-NX	Purposive	8
Lin et al. (2011)[50] China	30 opiate users	20-49	24/6	Qualitative	MMT	Convenience	8
Liu et al. (2013)[45] China	441 (329 heroin users detained in detoxification center and 112 MMT patients)	Detoxification center: 32.4 (± 7.2); MMT: 35 (± 6.3)	255/67	Quantitative	MMT	Convenience: recruited from clinics and detoxification centers	7
Majer et al. (2018)[34] USA	87 Oxford House residents	38.03 (± 5.04)	Male: 75%	Quantitative	MET and BUP-NX	Convenience	8

Study	Sample	Average age, year (SD)	Gender male/female, %	Study design	Study focus	Sampling technique	CASP rating
Majer et al. (2020)[36] USA	179 Oxford House (OH) residents	37.5 (±11.0)	Male: 51%	Quantitative	MOUD (BUP-NX, BUP, MET, NTX)	Investigators contacted Ohs with an online survey link.	9
Makarenko et al. (2016)[56] Ukraine	1,613 IDUs not in treatment	Median age: 35	328/93	Quantitative	OAT	Respondent driven, random and purposive	9
Marcus et al. (2018)[64] Ukraine	199 (currently, previously, and never on OAT)	18 or older	Male: 66%	Qualitative	XR-NTX	Participants were recruited by local research assistants from OAT treatment and harm reduction sites.	8
Mavis et al. (1991)[31] USA	174 participants (opioid users seeking admission to MET treatment, in MET treatment and previously in MET treatment but currently in drug-free treatment program)	Not provided	Not provided	Quantitative	MET	Purposive	6
Mukherjee et al. (2016)[102] Malaysia	96 HIV-positive and 104 HIV-negative incarcerated men with opioid dependence; 48.2% previously received	40.9 (±9.0)	All male	Quantitative	MMT	Convenience	7

Study	Sample	Average age, year (SD)	Gender male/female, %	Study design	Study focus	Sampling technique	CASP rating
	and 21.2% currently receiving treatment						
Muthulingam et al. (2019)[17] USA	81 (74 receiving pharmaco-therapies and 7 in needle exchange program)	42 (median)	46/26	Mixed method	MET, BUP, XR-NTX	Fliers, staff referrals, phone, and research assistants approaching individuals on site	8
Peterson et al. (2010)[54] USA	26 out of treatment opioid-dependent adults	44.5	12/14	Qualitative	MET	Targeted sampling	8
Philbin et al. (2010)[49] China	20 IDUs	35 (median)	Not provided	Qualitative	MMT	Participants recruited from needle exchange programs and methadone clinics.	9
Polonsky et al. (2016)[33] Moldova	56 patients who injects drugs that were recently released from prison (OAT group: 29, non-OAT group: 27)	36	Female: 20%	Quantitative	OAT	Participants recruited from an NGO that provides HIV prevention services to current and former prisoners.	7
Polonsky et al. (2016)[41] Ukraine	196 opioid users (Group 1: incarcerated; Group 2: recently released from prison)	Group 1: 36.1 (± 8.14); Group 2: 35.5 (± 8.14)	Currently incarcerated: all male; recently released: female-11.3%	Quantitative	MMT	Convenience	8

Study	Sample	Average age, year (SD)	Gender male/female, %	Study design	Study focus	Sampling technique	CASP rating
Prakash et al. (2016)[59] India	85 patients admitted in SUD management center	32.46 (±9.89)	All male	Quantitative	BUP, BUP-NX, and oral NTX	Purposive	9
Randall-Kosich et al. (2019)[44] USA	31 participants with a history of OUD	≥21	13/19	Qualitative	MET, BUP, and XR-NTX	Snowball	8
Ridge et al. (2009)[65] UK	192 patients receiving BUP (25%), MET (68%) and others (7%)	34.7 (±7.67)	144/48	Quantitative	MET and BUP	Purposive	7
Rosenblum et al. (1991)[47] USA	83 incarcerated people receiving MET in jail	34	66/17	Quantitative	MMT	Information not provided	7
Sanders et al. (2013)[75] USA	19 patients in MMT	29-60	10/9	Qualitative	MMT	Convenience	9
Saunders et al. (2020)[35] USA	40 (24 had previously received or were receiving MOUD)	36.5 (±10.0)	24/16	Quantitative	Long-acting versus short-acting MOUDs	Purposive	9
Schwartz et al. (2008)[32] USA	195 opioid users (out of treatment: 55, in treatment: 140)	41.6 (± 7.4)	Male: 50.8%	Mixed method	MET and BUP	Purposive	9
Shah et al. (2013)[20] USA	186 adult opioid users	48.3	Male: 69.8%	Quantitative	BUP	Convenience	9
Sohler et al. (2013)[55] USA	38 (8% in current BUP treatment, 58% in MET and 44% ever taken	44	Male: 87%	Quantitative	BMT and MMT	Program staffs recruited participants.	8

Study	Sample	Average age, year (SD)	Gender male/female, %	Study design	Study focus	Sampling technique	CASP rating
	BUP-prescribed or illicit)						
Stancliff et al. (2002)[46] USA	315 receiving MMT	42	Male: 60%	Quantitative	MMT	Convenience	8
Stöver H (2011)[37] Germany	400 (50% patients and 50% illicit opioid users)	35.3	Male: 66 % (patients); 70% (users)	Quantitative	OST	Participants recruited from physicians' offices and patient support centers	8
Tompkins et al. (2019)[69] UK	36 (12 heroin users not receiving any treatment, 12 receiving BUP, 12 receiving MET)	45	26/10	Qualitative	XR-BUP	Purposive	8
Uebelacker et al. (2016)[66] USA	372 opioid users in inpatient opioid detoxification treatment	31.8 (± 9.1)	Male: 262	Quantitative	MMT, BUP, XR-NTX, and no MOUD	Convenience: research staff approached patients in a detoxification center.	8
Vijay et al. (2015)[42] Malaysia	460 IDUs; few had experiences with OMT while many had used them outside treatment set-up.	38.8 (± 9.20)	Male: 96.3%	Quantitative	MMT and BMT	Snowball	6
Weicker et al. (2019)[61] Canada	1103 HIV positive and negative drug users	Willing participant: 42.4 unwilling	Female: 446	Quantitative	BUP-NX	Participants were recruited by street outreach and self-referrals.	9

Study	Sample	Average age, year (SD)	Gender male/female, %	Study design	Study focus	Sampling technique	CASP rating
		participant: 46.9					
Xu et al. (2012)[77] China	300 newly admitted patients receiving MMT	>35	277/23	Quantitative	MMT	Purposive	8
Yarborough et al. (2016)[21] USA	283 opioid dependent patients	40 (±12.2)	Female: 281	Qualitative	BUP and MET	Participants identified by EMR data and recruited from two integrated health systems.	9
Zaller et al. (2009)[53] USA	53 (60% with MET experiences)	40	41/11	Quantitative	MET	Purposive	8

Table 2.5 Study and participant characteristics: Experiences

Study	Sample	Average age, year (SD)	Gender male/female, %	Study design	Study focus	Sampling technique	CASP rating
Amato P. (2010)[97] Italy	78 patients who switched from methadone or buprenorphine to BUP-NX	Not provided	Male: 70	Quantitative	BUP-NX	Convenience: participants recruited from a treatment center	5
Awgu et al. (2010)[80] USA	114 heroin dependent individuals on MMT or BMT	40	All male	Mixed method	MMT or BUP-NX maintenance treatment	Convenience: participants recruited in a parent clinical trial	6
Barry et al. (2007)[99] USA	142 opioid dependent subjects	35.8 (± 9.2)	Male: 114	Quantitative	BUP-NX	Sampled from another randomized controlled trial	7
Bishop et al. (2018)[91] New Zealand	7 (5 transferred from MET to BUP-NX, 1 started directly in BUP-NX, 1 transferred from BUP-NX to MET)	25-65	5/2	Qualitative	BUP-NX vs MET	Potential participants were contacted by an intermediary person	9
Chandler et al. (2013)[81] UK	19 opioid dependent service users	29 (median)	5/19	Qualitative	OST: MET, BUP, and dihydrocodeine	Purposive	9
*__Cobos et al. (2005)__[71] Spain	166 opioid dependent patients receiving methadone maintenance treatment (MMT)	33.1 (6.7)	Male: 76.8%	Quantitative	Methadone maintenance treatment (MMT)	Random sampling	8

Study	Sample	Average age, year (SD)	Gender male/female, %	Study design	Study focus	Sampling technique	CASP rating
*Cobos et al. (2016)[73] Spain	185 (152 MMT patients with current substance use disorder and 33 MMT patients with remitted substance use disorder-SUD)	Current SUD: 40.1 (± 7.4); remitted SUD:41.3 (± 6.5)	Male: 75.7% (current SUD); 63.6% (remitted SUD)	Quantitative	Methadone maintenance treatment (MMT)	Consecutive and convenience sampling	8
Daulouede et al. (2010)[98] France	53 opioid dependent patients stabilized on BUP	38.9 (± 8.56)	Male: 38	Quantitative	BUP and BUP-NX	Not stated	6
Deering et al. (2012)[100] New Zealand	93 Maori (28) and non-Maori (65) patients with opioid dependence	36.8	Male: 51	Quantitative	OAT (MET)	Random sampling	6
Egan et al. (2011)[92] USA	33 HIV infected, opioid dependent patients	47.4 (± 7.6)	Male: 22	Qualitative	BUP-NX	Participants were recruited by local program staffs	9
Ghaddar et al. (2018)[87] Lebanon	81 (G1: 52 opioid agonists treatment-OAT registered patients; G2: 29 illicit opioid users)	≥18	All male	Qualitative	BUP	Convenience	8
Gourlay et al. (2005)[103] Australia	10 participants in community based MET program	34.2	5/5	Qualitative	MET	Purposive	5
Grønnestad et al.	25 opioid dependent patients in OMT	40	18/7	Qualitative	OMT with MET and/or BUP	The researcher approached the participants.	8

Study	Sample	Average age, year (SD)	Gender male/female, %	Study design	Study focus	Sampling technique	CASP rating
(2016)[85] Norway							
Madden et al. (2008)[79] Australia	432 opioid dependent patients receiving MAT	35.7 (±8.8)	Male: 266	Mixed-method	Medication assisted treatment (MAT) with methadone (MET)	Purposive	7
De Maeyer et al. (2011)[83] Belgium	25 opioid-dependent individuals	34.6 (±5.2)	17/8	Qualitative	MMT	Purposive	9
Maradiaga et al. (2016)[96] USA	21 formerly incarcerated individuals with OUD	49 (median)	Male: 17	Qualitative	MOUD with MET	Participants were recruited from a federally qualified health center and a community-based organization	9
Marchand et al. (2015)[84] Canada	160 opioid-dependent individuals	44.9 (±9.5)	86/74	Quantitative	OAT with MET or BUP-NX	Targeted and snowball	8
Montesano et al. (2010)[95] Italy	43 patients who received BUP-NX during 6 months of study	35	Male: 41	Quantitative	BUP-NX	Samples were recruited in a clinic-based evaluation.	6
Moore et al. (2014)[89] USA	22 opioid dependent patients randomized to two BUP-NX trials	≥18	Male: 14	Qualitative	BUP-NX	Convenience	9

Study	Sample	Average age, year (SD)	Gender male/female, %	Study design	Study focus	Sampling technique	CASP rating
Muller et al. (2018)[90] Norway	1011 receiving OMT	<30	Female: 345	Quantitative	MET, BUP-NX or BUP	Purposive	7
Notley et al. (2013)[22] UK	1,088 patients who received MET treatment	Not provided	Not provided	Qualitative systematic review	MET	Not applicable	6
*__Pinto et al. (2010)__[57] UK	361 opioid-dependent individuals receiving MET (63%) or BUP (37%)	MET: 33.1 (±7.9); BUP: 32.4 (±7.7)	Female: MMT: 28%; BUP: 19%	Quantitative	MET and BUP	Sampling technique not clearly mentioned	9
Syvertsen et al. (2010)[82] Mexico	Phase I: 20 IDUs; Phase II:222 IDUs	Phase I:32.1 (± 9.9); Phase II: 35 (± 7.9)	213/29	Mixed method	Residential treatment with MET	Qualitative: targeted; quantitative: respondent driven	6
Tanner et al. (2011)[88] UK	Interview: 9 receiving MET or BUP-NX; narrative account: 12 receiving BUP-NX	35	7/2	Qualitative	MET and BUP-NX	Convenience	5
*__Trujols et al. (2011)__[72] Spain	123 MMT patients	38.8 (± 7.5)	Male: 74.8%	Quantitative	MMT	Stratified random sampling	6
*__Trujols et al. (2016)__[74] Spain	122 MMT patients	38.8 (± 7.6)	Male: 70.59% (perceiving MMT dose as adequate;	Quantitative	MMT	Stratified random sampling	5

Study	Sample	Average age, year (SD)	Gender male/female, %	Study design	Study focus	Sampling technique	CASP rating
			77.46% (perceiving MMT dose as inadequate)				
Velasquez et al (2019)[86] USA	33 former jail inmates (XR-NTX: 11; MMT: 9; BMT: 4; no active treatment: 9)	47	28/5	Qualitative	XR-NTX maintenance, MMT and BMT	Purposeful and convenience	8
Wu et al. (2012)[93] China	25 patients in MMT	Kunming: 34; Shanghai: 41	Male: 54% (Kunming); 75% (Shanghai)	Qualitative	MMT	Prospective participants were invited by flyers in frequently visited MMT clinics.	7
Zamani et al. (2010)[94] Iran	30 incarcerated, opioid dependent people	Median: 38	All male	Qualitative	MMT	Purposive	8

[*]Cobos et al. (2005), [*]Cobos et al. (2016), [*2] et al. (2010), [*]Trujols et al. (2011) and [*]Trujols et al. (2016) provide data for both perception and experience. Data on characteristics of the studies and the patients are provided once under the outcome of 'Experience'.

Table 2.6 Summary of Findings (SoF): Patients' perceptions of the pharmacotherapies for the treatment of OUD

Study	Study tool	Study focus	Method of data analysis	Finding
Ahamad et al. (2015)[62] Canada	Interview	XR-NTX	Data from the interview response were recorded and statistically analyzed to determine factors associated with willingness.	**1.** 52.1% indicated willingness to take XR-NTX. Daily heroin injection was positively associated with willingness. **2.** The reasons for XR-NTX unwillingness were satisfaction with opioid agonists, unwillingness to stop opioid for pain, and unwillingness to take long acting medication.
Bachireddy et al. (2011)[38] Malaysia	Survey	OST	The participants' responses were collected from surveys and statistically analyzed.	**1.** 51% favoured OST. 32% believed OST would help them to stabilize, 46% believed it would prevent relapse and 23% believed it would help them to improve their health and social connections. **2.** 49% preferred abstinence-based treatment. They expressed concerns over OST dependence.
Bentzley et al. (2015)[58] USA	Survey	BMT	Data from the survey was statistically analyzed.	**1.** 82% of participants reported wanting to continue BMT for at least 12 months. Reasons: concerns about withdrawal symptoms, relapse, and pain. **2.** Age at first drug use, time in BMT, concern about pain and relapse were all positively associated with intended duration of BMT. **3.** Recent discussion with a treatment provider about BMT discontinuation, prior attempt to discontinue BMT, concern about withdrawal symptoms, experiencing pleasurable effects from taking buprenorphine, and perceived conflicts of BMT with life, work, or school obligations were all negatively associated with intended duration of BMT.
Bobrova et al. (2007)[48] Russia	Qualitative interviews	OST	Interviews were audio-taped and transcribed verbatim. Coding framework was developed based on the interview. The transcripts were reviewed, and all responses were assigned codes.	**1.** Many of the patients has treatment misconceptions and thus expectations did not match with their experiences. **2.** Many believed that OST, especially methadone, could control their drug use. **3.** Some of the participants shared negative perceptions on OST such

Study	Study tool	Study focus	Method of data analysis	Finding
				as fear of dependence, worse withdrawal symptoms, abuse, and diversion.
Bojko et al. (2015)[43] Ukraine	Semi-structured focus group discussion	OST	The discussions were audio-taped and transcribed verbatim. The transcripts were coded. A grounded theory inductive approach was utilized to develop concepts.	**1.** Many considered OST as last option after non-medical therapy. **2.** Many feared the long-term treatment nature of OST. **5.** Participants raised concerns of OST side effects, especially with methadone, which many of the participants thought to leading to deaths.
Brown et al. (2017)[67] Malaysia	Semi-structured interviews	MET, BUP, and XR-NTX	Interviews were digitally recorded and transcribed verbatim. The responses were numerically coded. The transcripts were reviewed, and the responses were arranged into themes.	**1.** More participants were aware of MET and BUP than XR-NTX. **2.** Many expressed favourable attitudes towards MET but had concerns like dependence and overdose. **3.** Majority of the participants displayed aversion towards BUP as they perceived it to be addictive. **4.** Lack of knowledge on XR-NTX led to participants providing no comment on it.
Cobos et al. (2005)[71] Spain	Survey	MMT	Desired dose adjustment was measured by Visual Analog Scale, Methadone dose (VAS-MD); satisfaction was measured by Scale to Assess Satisfaction with Medications for Addiction Treatment-Methadone for Heroin Addiction (SASMAT-METHER); opinions of methadone as treatment and perceived roles on dose-related decision were assessed from survey outcomes. Data was statistically analyzed.	**1.** Mean VAS-MD score (mid-level score: 0): -1.00 indicating the patients would have preferred a downward adjustment in methadone dose. **2.** 41.6% perceived their dose to be adequate, 35.5% perceived it high and wanted to reduce it, and 22.3% perceived it inadequate and wanted to increase it. **3.** 45.5% believed that their opinions influenced dose decisions**. 4.** Patients with high perceived participation, dose raisers, and non-modifiers scored high in VAS-MD than reducers of MMT dose.
Cobos et al. (2016)[73] Spain	Interview	MMT	Desire for MMT dose adjustment was measured by Visual Analog Scale of Methadone Dose (VAS-	**1.** 40.9% perceived their dose to be right; 45 % perceived their dose to be high and wanted downward adjustment. **2.** Patients with current SUD were less

Study	Study tool	Study focus	Method of data analysis	Finding
			MD). Satisfaction was measured by Scale to Assess Satisfaction with Medications for Addiction Treatment-Methadone for Heroin Addiction (SASMAT-METHER). The data was statistically analyzed.	satisfied with MMT than patients with remitted SUD. **3.** The desire for downward adjustment of methadone dose is found to predict dissatisfaction.
Fox et al. (2015)[60] USA	Semi-structured interviews	BMT and MMT	Interviews were audiotaped and transcribed verbatim. First 5 transcripts were reviewed to develop codes. Themes were developed during transcript review.	**1.** Many participants feared BMT or MMT dependence and painful withdrawal. **2.** Several participants preferred opioid-free treatment. **3.** Following relapse, BMT was perceived as an acceptable treatment option to prevent re-incarceration, especially among participants who had positive prior experience with buprenorphine.
Gryczynski et al. (2013)[41] USA	Survey and in-depth qualitative interviews	MET and BUP	Participants' responses were recorded into verbatim. The transcripts were reviewed for themes, while quantitative data were analyzed using descriptive and bivariate statistics.	**1.** Participants' BUP choice was driven by their past experiences. **2.** Patients perceived BUP to be highly effective in suppressing heroin withdrawal effects, produce mild withdrawal symptoms of its own and cause no sedation. **3.** MET was perceived as drug substitution with harmful effects. **3.** The perceived duration of treatment with MET is longer than BUP. 4. Patients cited their sources of BUP knowledge from peers, firsthand medical and non-medical experiences.
Gu et al. (2012)[78] China	Interview	MMT	Statistical analyses using univariate Cox & log binomial regression models	**1.** Misconceptions predict drop-out rates/poor adherence. **2.** Misconceived responses: MMT is intended primarily for detoxification, is a short term treatment, and one should reduce the dosage of methadone as it is harmful to one's health.
Gutwinski et al. (2014)[39] Germany	Survey	OMT: MET and BUP	The data was statistically analyzed.	**1.** Patients perceived OMT to be beneficial for both physical and mental health. **2.** They considered OMT withdrawal more difficult than heroin withdrawal. **3.**

Study	Study tool	Study focus	Method of data analysis	Finding
				Majority of the participants wished to end OMT in the long term.
Haase et el. (2016)[63] Norway	One-page survey questionnaire	XR-NTX	The data was statistically analyzed.	**1.** More than 50% were interested in opioid abstinence and treatment with XR-NTX; less than 25 % preferred their current OMT. **2.** Reasons for interest: 56% to stop opioid use; 50% to reduce craving; 45% to receive antagonist treatment for a year; 42% to avoid OMT uses. **3.** Reasons for disinterest: 32% for intramuscular treatment; 32% for not willing to take new medication (XR-NTX).
Hayashi et al. (2017)[70] Thailand	Survey and semi-structured interviews	MMT	Interviews were audio-taped and transcribed verbatim. Qualitative analyses were done inductively. Bivariate statistics were used to analyze quantitative survey data.	**1.** Many participants who perceived MMT to be ineffective, attributed the ineffectiveness to low doses of methadone. **2.** They feared the methadone withdrawal, which they perceived to be more severe than heroin withdrawal.
Kelly et al. (2012)[76] USA	Questionnaire and 28-items attitudes scale	MET and BUP	Data from the questionnaire and the attitudes scale was statistically analyzed.	**1.** Overall, all patients had better attitudes towards BUP than MET. **2.** Mean MET attitudes score: MET patients: 95.1; BUP patients: 85.5; out of treatment patients: 83.4. **3.** Mean buprenorphine attitudes score: BUP patients: 104; MET patients: 97.8; out of treatment patients: 97.5.
Khazaee-Pool et al. (2018)[52] Iran	Semi-structured interviews	MMT	The responses were recorded by memo writing and transcribed verbatim. Data were collected until saturation was obtained. Transcripts were reviewed to generate codes. Themes and subthemes were constructed based on the codes.	**1.** Majority of the patients lacked knowledge on MMT and had unrealistic expectations. **2.** Patients had mixed beliefs on MMT. Common fears with MMT: dependences, high relapse rate, difficult withdrawal than heroin withdrawal. **3.** Participants indicated that the perceived side effects of MET prevented them from attending MMT program.

Study	Study tool	Study focus	Method of data analysis	Finding
Larance et al. (2019)[68] Australia	Computer assisted structured interview	XR-BUP	Data was analyzed quantitatively using statistical tools.	**1.** 68% believed XR-BUP was a good treatment option. **2.** Perceived advantages of XR-BUP: prevents opioid craving, suppresses withdrawal for a longer time, and effective for a longer time. **3.** Perceived disadvantages: concerns of XR-BUP's inability to suppress withdrawal symptoms for the period between doses, dependence, side effects, and overdose.
Larney et al. (2017)[40] Australia	Semi-structured interviews	OST with MET or BUP-NX	Interviews were audio-taped and transcribed verbatim. Codes were developed inductively. The transcripts were reviewed to identify themes. The specific themes were described in texts, with information obtained from survey.	**1.** Perceived benefits of OST: effective withdrawal management, stability, pain relief and avoidance of relapse. **2.** Perceived concerns of OST: replacing one addiction with another and side effects. **3.** OST patients preferred BUP-NX over MET, perceiving it to have easier withdrawal, less frequent dosing than MET. **4.** Several OST patients reported the desire to cease treatment prior to release, especially with MET, as they feared that MET withdrawal was longer and tougher.
Lin et al. (2011)[50] China	Semi-structured interviews	MMT	All interviews were audio recorded and transcribed verbatim. A grounded theory approach was used. Data were coded to develop themes.	**1.** Most respondents had a favorable attitude toward MMT. **2.** Few participants were not satisfied with MET as they perceived it to be less euphoric than heroin. **3.** Many of the participants also expressed concerns of MET side effects.
Liu et al. (2013)[45] China	Survey	MMT	Data was collected from survey results and statistically analyzed.	**1.** Perceived benefits of MMT: effective in reducing opioid craving, illicit drug consumption, and HIV/HCV infections. **2.** Perceived concerns of MMT: addictive and dependence. **3.** More participants of detoxification centers reported their most preferred treatment to be community treatment; for MMT patients, preferred treatment was MMT. **4**. Patients cited their source of methadone knowledge from peers, physicians,
Majer et al. (2018)[34] USA	Online Survey	MET and BUP-NX	Data was statistically analyzed to compare the patients receiving	**1.** Patients not receiving medications expressed more negative attitudes than patients receiving the medications. **2.** Among patients receiving the

Study	Study tool	Study focus	Method of data analysis	Finding
			pharmacotherapy with patients not receiving pharmacotherapy.	pharmacotherapies, there were mixed attitudes towards MET and BUP-NX. **3.** This study found less favorable attitudes toward MET compared to BUP-NX among the residents.
Majer et al. (2020)[36] USA	Online Survey	MOUD (medications for opioid use disorder): BUP-NX, BUP, MET, NTX	Data was collected from survey results. A comparison was carried between the groups (MOUD vs. non-MOUD) using statistical analysis.	Non-MOUD residents had negative attitudes on BUP-NX and MET than MOUD residents; non-MOUD residents considered MOUD residents as addicts. They voted against to take in a prospective resident who takes buprenorphine-naloxone.
Makarenko et al. (2016)[56] Ukraine	Cross-sectional survey	OAT	Data from the survey was statistically analyzed	**1.** 35.7% of the participants were willing to initiating OAT. **2.** Higher willingness is associated with injection drug use (49.2% vs.43.1%), previous drug treatment experience (64.6% vs. 57.4%). **3.** Reasons for unwillingness: negative attitudes toward OAT, addiction with OAT, fears of treatment ineffectiveness and harms and daily visits to treatment sites.
Marcus et al. (2018)[64] Ukraine	Focus group discussion	XR-NTX	The discussions were audio-recorded and transcribed verbatim. Codes were identified based on a priori knowledge of treatments and emergent themes from the transcripts. The transcripts were coded.	**1.** Attitude towards XR-NTX was positive as many thought OAT kept them addicted and thus preferred abstinence-based treatment. **2.** Many expressed their concerns of prolonged withdrawal associated with XR-NTX.
Mavis et al. (1991)[31] USA	Survey	MET	Based on the survey questions, four themes were constructed. The findings were statistically analyzed. The answers to the open-ended questions were	**1.** Participants in treatment with MET or seeking MET treatment valued MET more than patients in drug-free treatment. **2.** Complete detoxification and drug-free state were the highest reported important indicators of treatment success.

Study	Study tool	Study focus	Method of data analysis	Finding
			categorized and compared across the six respondent groups.	
Mukherjee et al. (2016)[102] Malaysia	Interview	MMT	Data was statistically analyzed using descriptive statistics and multiple logistic regression analysis.	**1.** 42.5% were interested in receiving MMT. **2.** Interest in MMT was associated with greater likelihood of endorsing positive attitudes and decreased likelihood of endorsing negative attitudes toward MMT dependence. **3.** Common cited MMT barriers: inadequate knowledge of MMT availability in prison and treatment program inconvenience.
Muthulingam et al. (2019)[17] USA	Focus group discussion	MET, BUP, and XR-NTX	The responses were recorded and transcribed. The votes were tabulated. Highest ranking responses were pooled across the groups, and categorized as positive, negative, or neutral. Iterative rounds of thematic coding of both responses and transcript were conducted.	**1.** Perceived benefits of MET and BUP: effective in reducing craving, withdrawal symptoms and improving quality of life. **2.** Daily and on-site dosing of MET was thought to be burdensome by some, while beneficial for others. **3.** XR-NTX was perceived to be beneficial only for those who are committed to quit opioid use. **4.** Patients shared concerns of MET dependence and side effects, and XR-NTX's inability to treat withdrawal symptoms. **5.** Patients lacked knowledge on the three medications and were not sure what to expect from them.
Peterson et al. (2010)[54] USA	Ethnographic interviews	MET	Interviews were recorded, transcribed, reviewed for accuracy and completeness. Grounded theory approach was used to construct codes and themes.	Reasons for not enrolling in treatment: long-term treatment nature, perceived ineffectiveness of MET treatment, seeing their peers continue to use illicit drugs while on treatment, physical difficulties with MET, and daily treatment facility visits.
Philbin et al. (2010)[49] China	Semi-structured interviews	MMT	Interviews were audiotaped and transcribed verbatim. Researchers reviewed a first few transcripts to create codebook, which was applied to all transcripts to develop themes.	**1.** Majority of the participants supported MMT, a minority preferred abstinence-based treatment. **2.** The participants expressed concerns of MMT's side effects.

Study	Study tool	Study focus	Method of data analysis	Finding
Pinto et al. (2010)[57] UK	Questionnaire	MET and BUP	Statistical analyses	**1.** Reasons for BUP preference: negative view of MET, BUP's ability to block the effect of heroin, previous experiences with BUP, beliefs about ease of detoxification and desire for mental clarity with BUP. **2.** Reasons for MET preference: previous difficult experience with BUP, ineffectiveness of BUP to manage their opioid withdrawal. **3.** 81% identified their own experience as their primary source of information.
Polonsky et al. (2016)[33] Moldova	Online survey	OAT	The data was collected from survey responses and statistically analyzed to determine differences in attitudes between OAT and non-OAT groups.	Compared to non-OAT recipients, OAT recipients held higher knowledge, and greater positive attitudes towards OAT. They perceived OAT to have greater effectiveness. It was found that knowledge on OAT was positively associated with attitudes.
Polonsky et al. (2016)[41] Ukraine	Survey	MMT	Data was statistically analyzed.	**1.** Both groups viewed MMT negatively. **2.** Group 1 exhibited higher optimism about changing their drug use habit, were less likely to endorse MMT, and reported higher intention to recover from their addiction.
Prakash et al. (2016)[59] India	Semi-structured questionnaires and clinical interview	BUP, BUP-NX, and oral NTX	Perceptions that emerged during the interviews were noted down. The responses were categorized to various subgroups and statistically analyzed.	**1.** Perceived primary benefit of BUP and BUP-NX: ability to manage withdrawal. Perceived primary benefit of NTX: ability to prevent relapse. **2.** Perceived harms: dependence with BUP and BUP-NX, and precipitated withdrawal with NTX. **3.** The patients' perceived duration of BUP/BUP-NX and NTX treatment was less than a year. Median duration: 1 month (BUP/BUP-NX) and 3 months (NTX). **4.** Majority of patients reported that once daily dose was adequate for NTX but not for BUP/BUP-NX. **5.** Majority of participants preferred drug free treatment, followed by NTX, BUP-NX and BUP.

Study	Study tool	Study focus	Method of data analysis	Finding
Randall-Kosich et al. (2019)[44] USA	Semi-structured interviews	MET, BUP and XR-NTX	Data were audio-recorded and transcribed verbatim. Transcripts were reviewed to develop codes. All transcripts were coded independently by the researchers and themes were identified. Also, event-structure analyses were conducted where the researchers asked about the chronologies of treatment events, such as reasons for starting and ending treatment.	**1.** Most participants learned about BUP and MET from peers and friends and learned about XR-NTX from their doctors. **2.** Participants perceived BUP to prevent relapse, overdose, and death due to its ceiling property. Many of the participants perceived MET as the last option treatment. **3.** Majority reported their concerns of BUP dependence and stronger withdrawal symptoms. **4.** The participants perceived MET side effects were due to insufficient doses or lack of physician oversight. **5.** They reported daily MET dosing and doctor visits as inconvenience. **6.** XR-NTX patients stopped treatment as they felt that they have sufficiently recovered.
Ridge et al. (2009)[65] UK	Single-structured interview	MET and BUP	Data obtained from the interview was statistically analyzed.	**1.** Higher preference for MET than BUP. **2.** Patients rated their current treatment with MET or BUP higher than their previous treatment with MET or BUP. **3.** BUP patients believed that MET would cause more depression and MET patients believed that BUP would cause more anxiety. **4.** Overall, patients endorsed that MET would cause sedation and intoxication. **5.** More patients reported their own experience as source of information.
Rosenblum et al. (1991)[47] USA	Interview	MMT	Data obtained from the interview was statistically analyzed.	**1**. 58% patients reported concerns with MET treatment. **2.** Commonly cited concerns: anxiety, dependence and harms to health. **3**. More women and people who are share injection syringe reported concerns. **4.** 93% people reported that they intend to enrol in MET program after prison release.
Sanders et al. (2013)[75] USA	Semi-structured interviews	MMT	Interviews were audio-recorded and transcribe verbatim. Transcripts were reviewed by a flexible, iterative process. While reviewing the transcripts, themes	Factors like perception of medication abuse, dependence, desire to avoid adverse effects and lack of dose-related decisions contributed to the patients' intent to reduce dose. Patient's concerns of withdrawal contributed to patients wanting an increase dose.

Study	Study tool	Study focus	Method of data analysis	Finding
			were identified, following a coding scheme; narrative analysis was performed.	Participants reported that MET dose should be optimal to enhance proper functioning, neither too high a dose to intoxicate, experience dependence or adverse effects, nor too low a dose to suffer from withdrawal symptoms.
Saunders et al. (2020)[35] USA	Semi-structured telephone interviews	Long-acting versus short-acting MOUDs	Interviews were audio recorded, transcribed verbatim, and thematically analyzed. The initial code list was derived deductively. The code list was refined after review of 2 transcripts based on emerging themes within the transcripts. Rest of the transcripts were coded to emerge themes.	**1.** 10% of the participants were positive about MOUD; 24% were opposed to MOUD, citing reasons that MOUD is for the benefits of pharmaceutical companies, it is trading one drug for another, and preferred abstinence-based treatment. **2.** Most participants expressing negative thoughts had no experience of MOUD. **3.** 48% were not willing to use long-acting injections and 55% were not willing to use implants over short-acting formulations.
Schwartz et al. (2008)[32] USA	Semi-structured interviews	MET and BUP	The interviews were recorded, transcribed, and then coded. The codebook contained both deductive, a priori, and inductive, emergent codes. The transcripts were reviewed and classified into quantitative comments. Data collected from interviews was also quantitatively analyzed.	**1.** In-treatment group had significantly more positive attitudes towards MET and BUP than out-of-treatment group. Both groups had significantly more positive attitudes toward BUP than MET. **2.** Participants in both groups cited fears of dependence, side effects, greater withdrawal symptoms associated with MET. They also perceived it to be a gateway drug to illicit drugs use. **3.** They perceived BUP to have fewer side effects than MET and better block the effects of illicit drugs. **4.** Only a few perceived BUP to be a short-term detoxification treatment.
Shah et al. (2013)[20] USA	Computer assisted survey	BUP	Data from computer generated survey was statistically analyzed.	**1.** Most participants were aware of BUP, although personal experience was limited. **2.** Most participants had positive attitudes towards BUP. **3.** 25.5% believed that illicit and legal BUP have similar benefits.
Sohler et al. (2013)[55] USA	Focus group discussion	BMT and MMT	The discussions were audio-taped and transcribed verbatim. Initial coding scheme was developed based on the goals of the study.	**1.** The participants expressed greater positive attitudes towards BMT than MMT, but felt it was beneficial for highly motivated people who wanted to quit heroin. **2.** They reported their fears of MMT side effects and

Study	Study tool	Study focus	Method of data analysis	Finding
			The codes were refined with the review of transcripts. Themes were constructed from the coded data.	dependence. **3.** They expressed their discontent on daily visits while on MMT and acknowledged the scheduling and dosage benefits of BMT. **4.** The participants perceived BMT to cause less harm due to its 'ceiling effects'.
Stancliff et al. (2002)[46] USA	Survey	MMT	Data from the survey was statistically analyzed.	**1.** Although majority of the participants thought that MMT had improved their lives, they perceived it to be bad for their health; 80% believe that they should get off MMT. **2.** Some participants felt MMT helped them to avoid having HIV. **3.** Most of the participants perceived their MMT dose to be satisfactory.
Stöver H. (2011)[37] Germany	Self-complete questionnaire	OST	Responses were analyzed with descriptive statistics.	**1.** 53% patients and 51% opioid users identified the potential for OST to remove withdrawal discomfort and reduce cravings. **2.** 38% patients and 40% opioid users perceived OST to be effective in reducing crime and improve health and well-being.
Tompkins et al. (2019)[69] UK	Semi-structured qualitative interviews	XR-BUP	Interviews were audio-taped and transcribed verbatim. Coding frame was developed based on the interview guide and supplemented by codes emerging from the interviews. The transcripts were reviewed, and all responses were assigned codes.	**1.** Majority were willing to take XR-BUP. **2.** Some appreciated the need for less frequent travel to treatment services or pharmacies when on XR-BUP. Others showed anxiety on having reduced contact with treatment services. **3.** Many patients perceived XR-BUP to reduce opioid cravings, block the effects of opioids, and minimize misuse of treatment medication. **4.** There were concerns of precipitated withdrawal with XR-BUP when transferred from MET treatment.
Trujols et al. (2011)[72] Spain	Survey	MMT	Patient satisfaction was measured by Verona Service Satisfaction Scale for Methadone Treatment (VSSS-MT), mental health status with the General Health Questionnaire-28 (GHQ-28) and perception of dose adequacy with	**1.** 73.8% perceived high frequency of information about their MMT dose **2.** 54.5% believed to have influences on dose decisions. **3.** VAS-MD score: -2.5, indicating that most patients would have preferred a downward adjustment in methadone dose. **4.** 41.8% perceived their dose to be adequate; 54.1% perceived

Study	Study tool	Study focus	Method of data analysis	Finding
			Visual Analogue Scale of Methadone Dose (VAS-MD). Data on the measures was statistically analyzed.	their dose to be high and wanted a downward adjustment.
Trujols et al. (2016)[74] Spain	Survey	MMT	Perception of dose adequacy was measured by Visual Analogue Scale of Methadone Dose (VAS-MD). Patient satisfaction was measured by Verona Service Satisfaction Scale for Methadone Treatment (VSSS-MT) and mental health status with the General Health Questionnaire-28 (GHQ-28). Data was statistically analyzed.	**1.** 58.2% MMT patients perceived their MMT dose as inadequate or too high. **2.** Patients who perceived themselves as not participating in dosing decisions were more likely to consider their dose to be inadequate.
Uebelacker et al. (2016)[66] USA	Semi-structured interviews	MMT, BUP, XR-NTX, and no MOUD	Patient were interviewed, data collected and statistically analyzed.	**1.** Preferred treatment: 18% MMT, 28% BUP, 32 % XR-NTX, and 22% no MOUD. **2.** Factors driving patients' preferences: perceptions of treatment efficacy, safety, and consistency with being drug-free. Patients who preferred no pharmacotherapy had the most negative beliefs about MOUD. **3.** BUP and XR-NTX were perceived more efficacious, safer, and more consistent with being drug-free than MMT. 4. XR-NTX was perceived to be more effective in keeping them drug-free than BUP.
Vijay et al. (2015)[42] Malaysia	Survey	MMT and BMT	All data was extracted from survey response and statistically analyzed.	**1.** Most participants preferred MMT over BMT. **2.** 54.6% believed that BUP encouraged people to use more of other drugs **3.** Over three quarters of participants perceived MMT and BMT to be "replacing one addiction for another."

Study	Study tool	Study focus	Method of data analysis	Finding
Weicker et al. (2019)[61] Canada	Interview	BUP-NX	Data was statistically analyzed to determine factors associated with willingness to use BUP-NX	**1.** Participants' willingness was based on their previous experiences with BUP-NX and methadone, and their perceptions of BUP-NX. **2.** The reasons for unwillingness were lack of knowledge of BUP-NX, satisfaction with MET or other OAT, fear of withdrawal, not interested in any OAT, and previous negative experiences with BUP-NX.
Xu et al. (2012)[77] China	Interview	MMT	Statistical analyses using univariate & multivariate logistic regression models	**1.** Majority believed that MMT is short-term treatment, should be discontinued after 2–3 months and patients should reduce their MET dose as it is bad for health. **2.** Prior MET experience during detoxification is associated with the idea of MMT being short term treatment and dose reduction. **3.** Patients who were informed of the MMT program by community members and their peer were less likely to consider MMT as short term treatment.
Yarborough et al. (2016)[21] USA	Semi-structured interviews	BUP and MET	Interviews were audio-recorded and transcribed verbatim. Coding scheme was developed deductively. Results were narratively described under emerged themes. To analyze treatment preference data, 2-tailed paired t-tests were employed.	**1.** Some of the patients lacked treatment knowledge and had unrealistic expectations. **2.** Prior treatment experiences dictated treatment preferences. **3.** Patients favored BUP more than MET. Daily dosing and supervised consumption of MET in a clinic acted as a treatment barrier for some. **3.** Some perceived MET to be addictive and cause painful withdrawals than BUP. **4.** Patients with chronic pain were willing to accept long term maintenance treatment.
Zaller et al. (2009)[53] USA	Survey	MET	The responses were transformed into categorical variables and hypothesis testing was used to determine statistical significance between responses.	Majority of participants expressed negative attitudes towards MET. More than 70% believed MET was bad for health, people should try to discontinue the treatment, it is costly and inconvenient. 66% believed it was substituting one drug for another.

Table 2.7 Summary of Findings (SoF): Patients' experiences with the pharmacotherapies for the treatment of OUD

Study	Study tool	Study focus	Method of data analysis	Finding
Amato P. (2010)[97] Italy	Observation, self-rating scales and urine toxicology	BUP-NX	Patients who received BUP-NX were assessed throughout a 1-year follow-up period to make comparisons before and after the switch of medications. Satisfaction and anxiety were measured by self-rating scales. All the data were statistically analyzed.	**1.** Patients expressed more satisfaction with BUP-NX than with their previous treatments (MET or BUP). **2.** 78% of patients reported satisfactory coverage of withdrawal symptoms and improved psychosocial functioning. **3.** 20% of patients reported an unpleasant taste of BUP-NX.
Awgu et al. (2010)[80] USA	Data collected during randomized control trial and interview	MMT or BUP-NX maintenance treatment	Responses were categorized and summarized using thematic coding. Themes were developed both inductively and deductively. Group comparisons were made by statistical analysis.	**1.** 90% reported that the medications relieved their cravings for heroin and prevented withdrawal symptoms. **2.** MMT patients reported experiencing more side effects/symptoms, complained about difficult medication delivery process and treatment dependence. **2.** BMT patients complained about the taste of the medicine. **3.** More BMT patients than MMT patients reported that they intend to enroll in the community treatment after release.
Barry et al. (2007)[99] USA	Survey	BUP-NX	Data was obtained from patient survey which was conducted on week 12 of 24-week trial. Differences in satisfaction between baseline and during treatment were analyzed statistically.	**1.** Patients' mean overall satisfaction score was 4.4 (out of 5). **2.** Patients were most satisfied with the medication and ancillary services and indicated strong willingness to refer BUP-NX to their peers. **3.** Patients were least satisfied with their interactions with other opioid-dependent patients, referrals to Narcotics Anonymous, and the inconvenience of the treatment location.

Study	Study tool	Study focus	Method of data analysis	Finding
Bishop et al. (2018)[91] New Zealand	Interview	BUP-NX vs MET	The interviews were recorded and transcribed. An interpretive thematic analysis was used; codes and themes were developed from the data. The data was categorized under the themes.	**1.** Participants reported MET caused sedation, respiratory depression, dependence, loss of control, and abuse. **2.** Some BUP-NX patients reported anxiety when switched from MET. **3.** Many reported increased motivation, mental clarity, and cognitive abilities with BUP-NX than MET. They also felt reduced craving for illicit opioids with BUP-NX.
Chandler et al. (2013)[81] UK	Semi-structured interview	OST: MET, BUP, and dihydrocodeine	Longitudinal data were collected up to 1 year with participants interviewed 3 times. Interviews were transcribed. The transcripts were reviewed, coded, and categorized under themes and sub-themes; narrative analysis was done.	**1.** Many participants reported that OST helped them to manage their opioid dependence, and reduce the harms associated with drug use. **2.** Some expressed the desire to lower MET dose, and eventually remain abstinent before their babies were born. **2.** In the post-natal period, most participants who previously reduced MET dose, increased their dose. **3.** Some participants reported their dependence on OST. Also, some cited having side effects like withdrawal and feeling fuzzy.
Cobos et al. (2005)[71] Spain	Survey	MMT	Desired dose adjustment was measured by Visual Analog Scale of Methadone Dose (VAS-MD); satisfaction was measured by Scale to Assess Satisfaction with Medications for Addiction Treatment-Methadone for Heroin Addiction (SASMAT-METHER); opinions of MET as treatment and perceived roles on	**1.** Mean VSSS-MT score: 3.5. **2.** 82.4% felt satisfied with MMT. **3.** Patients who received <60 mg/day MET were satisfied than patients who received 60-100 mg/day. **4.** Patients with more perceived role in dose decisions were more satisfied than patients who did not. **5.** Patients with positive perception of MET demonstrated higher satisfaction.

Study	Study tool	Study focus	Method of data analysis	Finding
			dose-related decision were assessed from survey outcomes. Data was statistically analyzed.	
Cobos et al. (2016)[73] Spain	Interview	MMT	Adjustment of MMT dose desired was measured by Visual Analog Scale of Methadone Dose (VAS-MD). Satisfaction was measured by Scale to Assess Satisfaction with Medications for Addiction Treatment-Methadone for Heroin Addiction (SASMAT-METHER). The data was statistically analyzed.	**1.** MMT patients with current SUD were less satisfied than MMT patients with remitted SUD. **2.** Overall MMT satisfaction was positively associated with both patients' desired downward adjustment of MMT dose, patients' perceived influence on MMT dose decisions, and negatively associated with number of days of heroin use during last month.
Daulouede et al. (2010)[98] France	VAS and medical examination	BUP and BUP-NX	Overall preference was evaluated from patient's global satisfaction which was measured by Visual Analog Scale (VAS). The patients were questioned r for evidence of adverse effects. Statistical analysis was done.	**1.** Global satisfaction rates were high and similar for both BUP and BUP-NX (6.83-7.04 and 6.89-7.38). **2.** 54% preferred BUP-NX, 31% preferred BUP, and 15% had no preference. **3.** Patients preferred tablet size, taste, and dissolution rate of BUP-NX. **4.** Majority reported that the medications helped them to reduce illicit opioid use, improved health and social skills. **6.** 71% of the patients wanted to continue BUP-NX treatment.
Deering et al. (2012)[100] New Zealand	Interview	OST with MET	The responses were recorded in writing. Data was statistically analyzed to measure patients'	**1.** There was overall satisfaction with OST among the participants. **2.** Higher satisfaction was associated with general health, mental health, social functioning,

Study	Study tool	Study focus	Method of data analysis	Finding
			level of satisfaction and perception of treatment.	lower MET doses, and participants' ratings of their treatment progress. Lower satisfaction was associated with higher frequency of benzodiazepine use, and, for women, longer treatment duration. **3.** Maori participants rated their treatment progress as lower than that of non-Maori.
Egan et al. (2011)[92] USA	Semi-structured interview	BUP-NX	Interviews were audio-taped and transcribed. A grounded theory approach was used. A coding scheme was developed from the transcripts. All the transcripts were coded. The codes were used to find out main themes.	**1.** Patients reported satisfaction with BUP-NX including effectiveness in blocking cravings and controlling opioid use, decreased fear of withdrawal and/or missing doses, and an overall improvement in quality of life. **2.** They were more involved with their substance use treatment and HIV care.
Ghaddar et al. (2018)[87] Lebanon	Semi-structured Qualitative interviews	BUP	Interviews were recorded and transcribed verbatim. Codes were developed during review of transcripts; data was simultaneously analyzed. Grounded theory was employed. The themes were reviewed and analyzed based on the codes.	**1.** Majority of G1 patients were satisfied with treatment effectiveness in reducing illicit opioid use and craving. **2.** Some of the patients experienced treatment withdrawal symptoms and thus feared BUP dependence. **3.** Maintenance OAT reduced misuse of treatment BUP by injection. **4.** There are reports of medication diversion.
Gourlay et al. (2005)[103] Australia	In-depth interviews	MET	Interview transcripts were analyzed using both inductive and grounded theory.	Patients experienced the treatment benefits and like freedom from opioid dependence, although some reported the treatment to be not beneficial or

Study	Study tool	Study focus	Method of data analysis	Finding
				somewhat beneficial. Some patients reported the negative aspect of daily dosing with MET.
Grønnestad et al. (2016)[85] Norway	Field notes and semi-structured interview	OMT with MET and/or BUP	The interviews were audiotaped and transcribed verbatim. The data were analyzed by naive reading, thematically structured analysis, units of meaning, subthemes, and main themes.	**1.** There were reports of withdrawal symptoms, dependence and loss of hope from the treatment. The participants also reported abuse of MET and BUP sourced illegally. **2.** Many reported that OMT did not provide the effects the participants hoped for.
Madden et al. (2008)[79] Australia	Survey interview	MET and BUP	Responses for open ended questions were coded. Themes were developed prior to coding the responses and new themes were added if any emerged from the responses. Quantitative data were statistically analyzed.	**1.** Majority of the respondents were satisfied with the treatment and treatment doses. **2.** The best things reported about the treatments were the ability to keep them abstinent and stable. **3.**The patients reported medication 'dependence' and 'lack of freedom' as worst aspects of their treatments.
De Maeyer et al. (2011)[83] Belgium	In-depth interviews	MET	Thematic analysis with codes and themes construction	Many reported that MET provided psychological well being, emotional stability; some reported that they experienced emotional paralysis which lowered their quality of life. Some reported MET to be a temporary fix. There are also reports of methadone managing patients' heroin cravings but caused treatment dependence.
Maradiaga et al.	Semi-structured interview	MOUD with MET	Interviews were audio recorded, transcribed, and analyzed using a grounded theory approach. The codes were developed from the	**1.** Participants, sentenced of felonies and transferred to state prisons, were rapidly withdrawn from MET which led to withdrawal symptoms. **2**. Due to negative experiences with MET during

Study	Study tool	Study focus	Method of data analysis	Finding
(2016)[96] USA			transcripts. Contents of transcripts are categorized under relevant themes.	incarcerations, many individuals showed aversion to community-based MET. Few reported the intention to enter BUP community treatment, post release.
Marchand et al. (2015)[84] **Canada**	Client Satisfaction Questionnaire (CSQ-8)	OAT with MET or BUP-NX	Statistical Analysis of treatment satisfaction	**1.** Older participants, participants of Aboriginal ancestry, and participants currently in OAT had significantly higher OAT satisfaction scores. **2.** Patients with perceived ideal OAT dose of less than or equal to 39 mg had lower satisfaction OAT. **3.** Commonly expressed concerns of treatment harms like depression, nausea, and bone deterioration, sweating, treatment dependence. **4.** Slightly more women described feeling dissatisfied with the lack of control and input into methadone dose increases.
Montesano et al. (2010)[95] Italy	Interview	BUP-NX	Cross-sectional data collection was done. The data from the interview were statistically analyzed.	**1.** Most patients were highly satisfied with therapy and considered BUP-NX to provide good control of cravings. **2.** 50% of patients stated that they disliked the sensory properties (taste, colour, odour, and feel) of BUP-NX. **3**. Adverse effects like opioid induced constipation were reported. **4.** A small proportion of people attempted to misuse BUP-NX by injection but received no gratification.

Study	Study tool	Study focus	Method of data analysis	Finding
Moore et al. (2014)[89] USA	Semi-structured interview	BUP-NX	Interviews were audio-taped and transcribed. A grounded theory approach guided the analysis. Coding scheme and themes are developed after initial review and discussion of several transcripts. All the transcripts were reviewed following the codes. Data were categorized under themes.	**1.** Majority of the respondents reported satisfaction with BUP-NX. It helped them to stop opioid use and manage withdrawal symptoms, which they could not with MET. **2.** They perceived BUP-NX to have all the benefits of MET but with less drawbacks.
Muller et al. (2018)[90] Norway	Survey	MET, BUP-NX or BUP	Data were drawn from a national peer-to-peer survey. Relationships between each treatment groups, demographics, health, OMT satisfaction, and side effect were statistically analyzed.	**1.** MET users reported highest satisfaction, followed by BUP and BUP-NX users. Of the overall sample, two-third of the respondents were satisfied. **2.** MET users reported highest side effects than BUP-NX and BUP users. Most experienced side effects were libido, hyperhidrosis, sexual dysfunction, weight gain, fatigue, water retention or swelling, wheezing, and headaches or dizziness.
Notley et al. (2012)[22] UK	Qualitative systematic Review	MET	Qualitative interpretative analysis under themes which emerged during review of studies	**1.** Patients reported that MET helped them to reduce illicit opioid use, managed withdrawal, and improved health. 2. Some patients reported to experience treatment dependence. 3. Some patients experienced treatment side effects like increased perspiration, tiredness/drowsiness, and constipation and for many reduced libido

Study	Study tool	Study focus	Method of data analysis	Finding
Pinto et al. (2010)[57] UK	Questionnaire	MET and BUP	Data was statistically analyzed using univariate analysis and multivariate analysis.	**1.** More MET patients than BUP patients reported side effects (55% vs. 44%). **2.** MMT side effects: sweating, sedation, and constipation. BUP side effects: sedation and constipation.
Syvertsen et al. (2010)[82] Mexico	Semi-structured interview (phase I-qualitative) and survey (phase II-quantitative)	Residential treatment MET	Interviews from phase-I were recorded and transcribed. The transcripts were inductively and deductively coded for themes. The data from phase-II were statistically analyzed.	Participants who received MET described it as stronger, more addictive, and causing severe withdrawal symptoms than heroin. Some reported of getting dependent on MET treatment.
Tanner et al. (2011)[88] UK	Structured interviews and narrative accounts	MET and BUP-NX	Interviews and narrative accounts were transcribed. Themes were developed from the transcripts.	Participants reported more positive experiences with BUP-NX. **1.** They experienced better mental clarity compared to feeling drowsy with MET. They reported to feel better physically. **2.** The participants considered MET as a substitute for heroin. **3.** There were mixed findings on heroin use while on BUP-NX. Some reported that BUP-NX blocked the euphoric effects of heroin while others reported it did not block the effects of heroin.
Trujols et al. (2011)[72] Spain	Survey	MMT	Patient satisfaction was measured by Verona Service Satisfaction Scale for Methadone treatment (VSSS-MT), mental health status with the General Health	**1.** VSSS-MT score: 3.4 (out of 5) which indicates "slight satisfaction". **2.** Most patients preferred downward adjustment of MMT dose. **3.** GHQ-28 score (0 to 28): 8.3 **4.** Patients who perceived themselves as participating in treatment decisions

Study	Study tool	Study focus	Method of data analysis	Finding
			Questionnaire28 (GHQ-28) and perception of dose adequacy with Visual Analogue Scale of Methadone dose (VAS-MD). Data on the measures were statistically analyzed.	were more likely to be satisfied with MMT. **5.** Proportions of patients most satisfied with MET: 65.3%
Trujols et al. (2016)[74] Spain	Survey	MMT	Perception of dose adequacy was measured by Visual Analogue Scale of Methadone dose (VAS-MD). Patient satisfaction was measured by Verona Service Satisfaction Scale for Methadone Treatment (VSSS-MT) and mental health status with the General Health Questionnaire-28 (GHQ-28). Data were statistically analyzed.	**1.** VSSS-MT score: 3.37 (out of 5) which indicates "slight satisfaction". **2.** Most patients preferred downward adjustment of MMT dose. **3.** GHQ-28 score (0 to 28): 6.98
Velasquez et al (2019)[86] USA	Semi-structured interview	XR-NTX maintenance, MMT and BMT	Interviews were audio recorded, transcribed verbatim, independently coded by two researchers, and analyzed as per a grounded theory approach. Codes were derived from the data. Researchers reviewed transcripts and coded to develop themes.	**1. XT-NTX:** XR-NTX blocked the effects of opioids when some of the patients tried to use opioids. Few reported side effects of treatment which were tolerable. Many of the patients reported reduced opioid craving and expressed general satisfaction. **2. MMT:** Several patients who received MMT did not join community MMT program. They feared MET withdrawal and had misinformation on side effects of it. Patients who were on MMT expressed general satisfaction, although dissatisfied with daily observed

Study	Study tool	Study focus	Method of data analysis	Finding
				dosing. **3. BMT:** Patients reported lesser side effects and fear of withdrawal with BMT than with MMT. Most patients were satisfied with BMT.
Wu et al. (2012)[93] China	Focus group discussion	MMT	The discussions were audio-taped and transcribed verbatim. Codes were defined from the transcripts and themes developed.	**1.** Several patients experienced side effects of MMT and were wary about the addictive nature of the treatment. **2.** They reported concurrent use of heroin, even when on treatment.
Zamani et al. (2010)[94] Iran	In-depth interviews, focus group discussion	MMT	The interviews and group discussions were audio-taped and transcribed. Data was classified and organized under themes which were constructed both inductively and deductively.	**1.** Overall reduction in injecting drug use in prison. **2.** MMT was reported to improve physical and mental health. **3.** MET diversions were reported. **4.** Patients who were using injection drugs and yet to receive MMT reported greater concerns of MMT side effects than other patients.

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Chapter 3 Cost-effectiveness of Alpha-2 Adrenergic Agonist (Lofexidine) and Long-Acting Injectables for Treatment of Opioid Use Disorder

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This manuscript is currently being prepared for publication in *Value in Health*.

3.1 Abstract

Background: Lofexidine (the first US-approved non-opioid medication for opioid withdrawal management) and novel pharmaceutical formulations for long-term maintenance therapy (such as extended-release naltrexone and extended-release buprenorphine depot injection) are available alongside the traditional opioid agonists to treat opioid use disorder (OUD). These medications, however, are more costly than conventional pharmacotherapies. This study aims to evaluate the incremental cost-effectiveness of these newer pharmacotherapies from the US healthcare perspective.

Methods: We developed a hybrid Decision Tree/Markov model to estimate and compare the cost and effectiveness of five different strategies: A) use of methadone-lofexidine for detoxification and buprenorphine-naloxone for maintenance; B) use of methadone-lofexidine for detoxification and extended-release naltrexone (XR-NTX) for maintenance; C) use of buprenorphine-naloxone for detoxification and extended-release buprenorphine (XR-BUP) for maintenance; D) use of buprenorphine-naloxone for detoxification and maintenance (i.e., usual treatment); and, E) no treatment. Data is analyzed over a one-year time horizon. The effectiveness outcomes we analyzed are: quality-adjusted life-years (QALYs), treatment retention, and opioid-free days gained. Also, we calculated the costs of loss of productivity from OUD in each of the treatment strategies.

Results: Strategies B and C cost more but yield lower effectiveness than strategy A; thus, they are dominated by strategy A. Between strategies A and D, A costs US$2,454 more and yields 0.002 higher QALYs with an incremental cost-effectiveness ratio (ICER) of

US$1,247,528/QALY relative to strategy D. This ICER greatly exceeds the conventional willingness-to-pay threshold of $100,000/QALY, and hence, strategy A is not cost-effective. When two long-acting formulations (B and C) are compared with no treatment, strategy B provides greater QALYs but is not cost-effective relative to strategy C (ICER: US$5,860,107/QALY). In terms of treatment retention and opioid-free days, strategy A provides higher effectiveness relative to strategy D, costing US$175 per treatment retention day and US$1277 per opioid-free day gained. Among all treatment strategies, strategy A generated the maximum reduction in loss of productivity, although the magnitude of the change is insignificant.

Conclusion: While the use of methadone and lofexidine for detoxification followed by buprenorphine-naloxone for maintenance yields greater QALYs, higher treatment retention, and opioid-free days, it is not cost-effective due to the high cost of lofexidine. The use of buprenorphine-naloxone (the current usual treatment) for both detoxification and maintenance appears to be the cost-effective treatment strategy.

3.2 Introduction

Opioid use disorder (OUD) is a chronic relapsing illness characterized by a problematic pattern of opioid use that results in significant impairment or distress. This can include the use of prescribed or illegally obtained opioids, such as heroin, prescription opioid pain relievers, and illicit synthetic opioids like fentanyl analogues.[1, 2] Sixteen million people worldwide have been diagnosed with OUD.[3] It is a leading cause of overdose mortality. The situation is particularly grave in the US, where an estimated three million people have OUD, and 130 Americans, on average, die every day from an opioid overdose.[3, 4, 5] OUD increases the burden of infectious diseases like hepatitis C virus (HCV), human immunodeficiency virus (HIV), and endocarditis amongst injection drug users (IDU).[6, 7, 8] It has detrimental social impacts, contributing to high levels of crime, unemployment, decreased productivity, and health risks to non-abusers (e.g., accidental pediatric and perinatal exposure).[9] The total economic burden of the opioid crisis in the US from 2015 through 2018 was US$631 billion.[10]

Opioid agonist treatment (OAT) with either methadone or buprenorphine-naloxone is the gold standard treatment option.[1, 2] Despite their effectiveness, OUD treatments face considerable barriers to utilization. Fewer than 11% of people with OUD receive treatments in the US.[11] Numerous factors like treatment perceptions, stigma, treatment costs, regulations that govern public and private insurance coverage in the US, a limited number of prescribing physicians, fear of medication diversion, geographical location, and regulatory bottlenecks are common barriers to treatment uptake.[12, 13, 14, 15, 16, 17, 18]

Novel formulations like extended-release naltrexone (XR-NTX) can enhance treatment uptake, especially for those who harbor negative perceptions of OAT or prefer abstinence-based therapy, favour once a month dosing over frequent dosing, or who fail to access OAT programs due to regulatory or logistical reasons. Extended-release buprenorphine (XR-BUP) subcutaneous injection is particularly beneficial because of its once a month dose schedule and the elimination of diversion potential compared to take-home sublingual buprenorphine.[19] In 2018, the US Food & Drug Administration (FDA) approved lofexidine hydrochloride, an alpha2-adrenergic agonist, the first approved non-opioid treatment for opioid withdrawal symptoms in adults.[20] It helps to lessen the severity of withdrawal discomforts when opioids are discontinued. Once the patients are stabilized and detoxified, they can be transitioned to FDA-approved pharmacotherapies like methadone, buprenorphine-naloxone, or naltrexone maintenance treatment.[1] A recent clinical trial found that detoxification with methadone-lofexidine and buprenorphine-naloxone generated comparable outcomes in terms of rate of treatment completion and opioid abstinence. However, the withdrawal symptoms were greater with methadone-lofexidine than with buprenorphine-naloxone.[21]

There is a significant price gap between the newer medications and conventional OAT. Each lofexidine unit costs US$23, which is approximately twelve times the cost of buprenorphine-naloxone (US$2 for 8mg/1mg) and more than 300 times the cost of methadone (US$0.07 for 30mg). Each injection of XR-BUP (US$1,459) is approximately 1.34 times the cost of XR-NTX (US$1,085) and more than 700 times the cost of

buprenorphine-naloxone (8mg/1mg). With such large price disparities, it is critical to weigh the costs and effectiveness of each of the medications.

As XR-NTX and XR-BUP are relatively newer pharmacotherapies, conclusive evidence of the treatments' cost-effectiveness is sparse. Currently, there are mixed findings on the cost-effectiveness of XR-NTX relative to methadone, buprenorphine, and buprenorphine-naloxone maintenance.[23, 24, 25] There is just one study finding inferior cost-effectiveness of XR-BUP relative to sublingual buprenorphine-naloxone in terms of quality-adjusted life years (QALYs) gained.[14] Despite the recent regulatory approval in the US, there is no study on the cost-effectiveness of lofexidine. Due to these medications' high costs, clinicians and policymakers are increasingly interested in cost-effectiveness indications of the medications, especially with the current economic strain on the healthcare system. We, therefore, undertook this study to assess the cost-effectiveness of using new medications for OUD treatment relative to usual care and no treatment. Additionally, as an explorative research, we investigated the costs of loss of productivity due to OUD and the impacts of the treatments on the productivity loss.

3.3 Methods

3.3.1 Comparison Strategies

We compared five strategies (four different treatment strategies and no treatment) for OUD. The treatment strategies combine either methadone-lofexidine or buprenorphine-naloxone for detoxification with buprenorphine-naloxone, or XR-NTX, or XR-BUP for

maintenance, as shown in Table 3.1. Specifically, patients in strategies A and B are detoxified with methadone-lofexidine, followed by the use of buprenorphine-naloxone or XR-NTX for maintenance, respectively. In strategy C, patients use buprenorphine-naloxone for detoxification and XR-BUP for maintenance. Strategy D is the usual treatment with buprenorphine-naloxone detoxification and maintenance by the same. Finally, strategy E involves no treatment.

Additionally, we compared two treatment strategies having long-acting formulations (B and C) with no treatment. Two key treatment features explain the rationale for the comparison. First, due to the regulatory complexities of methadone and buprenorphine's prescribing and dispensing, a large population of opioid-dependent patients in the US does not receive treatment.[11] XR-NTX is an opioid antagonist, not a controlled medication, and there are no regulations of facilities or prescribers for its use in OUD treatment.[1] This can help to treat patients who otherwise may not receive any treatment. Second, both XR-NTX and XR-BUP are once a month pharmacotherapies. This offers dosing convenience to patients who cannot commit to strict daily dosing with the conventional OATs and thus receive no medical care.

We did not expand our study to include cohorts detoxified with buprenorphine-naloxone and maintained with XR-NTX, as patients need to be completely opioid-free before XR-NTX initiation. Such patients switching from buprenorphine-naloxone detoxification to XR-NTX may even have to wait from 7 to 14 days between the last dose of buprenorphine-naloxone and the start of XR-NTX.[1] If treatment with XR-NTX is planned, managing

withdrawal with alpha2-adrenergic agonists (FDA-approved lofexidine) may enable a more rapid initiation.[1] Also, we limited the use of XR-BUP maintenance only with prior buprenorphine-naloxone detoxification following the American Society of Addition Medicine (ASAM) National Practice Guideline for the Treatment of Opioid Use Disorder.[1]

Table 3.1 Detoxification and maintenance stages of the treatment strategies

Strategy	Detoxification regimen	Maintenance regimen
A	Methadone-lofexidine (oral)	Buprenorphine-naloxone (sublingual)
B	Methadone-lofexidine (oral)	XR-NTX (intramuscular)
C	Buprenorphine-naloxone (sublingual)	XR-BUP (subcutaneous)
D (usual treatment)	Buprenorphine-naloxone (sublingual)	Buprenorphine-naloxone (sublingual)
No treatment	None	None

3.3.2 Treatment Progression and Outcomes

Patients completing detoxification in strategies A, C, and D, do not need to be in complete opioid withdrawal for maintenance initiations. Patients who complete detoxification are assumed to be substantially stabilized and not experience precipitated withdrawal with buprenorphine-naloxone maintenance. Meanwhile, in strategy B, only the opioid-free patients who give opioid-negative urine samples after detoxification are initiated with XR-NTX maintenance. This is done to avoid precipitated withdrawal with XR-NTX (opioid antagonist). In all treatment strategies, A-D, patients who do not complete detoxification

are considered to drop out of treatment and have outcomes identical to those of untreated opioid-dependent individuals.

Different outcomes may occur over time. Patients may continue to use opioids while on treatment (on medication with opioid use), stop using opioids while on treatment (on medication with no opioid use), or discontinue treatment and relapse to opioid use (off medication with opioid use). Only the patients in strategy B are required to retake methadone-lofexidine detoxification upon relapse in maintenance. This is due to possible precipitated withdrawal with XR-NTX. Individuals who discontinue treatment are assumed to receive no further therapy and relapse to opioid use. Patients in no treatment group are considered to continue opioid use. Overdose deaths, HIV, or HCV-related mortalities are associated with opioid use, in and out of treatment. The incidence of HIV or HCV mortality is only attributed to injection drug use, in or out of treatment.

3.3.3 Model Structure and Study Cohort

We developed a hybrid Decision Tree/Markov model using TreeAge Pro 2020 to estimate and compare the costs, QALYs, treatment retention, and opioid-free days gained. The detoxification phase was modelled as a Decision Tree and the maintenance phase as a Markov model. Only in strategy B, detoxification was modelled inside the Markov model due to its recurring need after opioid relapse. We considered a hypothetical cohort of injection and non-injection opioid dependent patients, diagnosed with the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) criteria for opioid dependence. During detoxification, patients may complete detoxification or drop out of

treatment. Patients who complete detoxification were initiated with maintenance in the health states in which they finish detoxification, that is, either opioid-free or relapse state.

The Markov model structure (Figure 3.1) consists of four health states through which the hypothetical cohorts passed monthly for 12 months: i) on medication with opioid use, ii) on medication with no opioid use, iii) off medication with opioid use, and iv) death. The health state "death" is overdose-related, HIV-related, or HCV-related mortalities. The key differences between our model and previous models are the addition of overdose death to our model and the exclusion of opioid-free patients when not in treatment. The exclusion is based on our assumption that the proportion of patients who become opioid-free without treatment in 12 months would be insignificant to impact our analysis. Our choice of 12 months' time horizon is justified by the use of 12-month modeled-time in previous similar studies and the National Institute on Drug Abuse guidelines that recommend a minimum of 12 months of opioid use disorder substitution therapy.[26, 23, 9] A detailed clinical pathway with detoxification and maintenance phases for each strategy is provided in Appendix II.

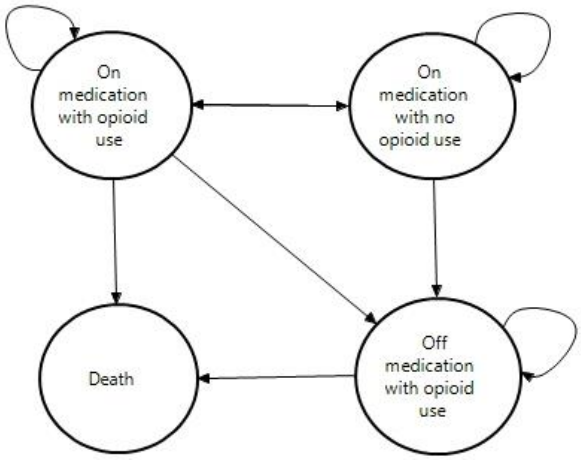


Figure 3.1 State Transition Diagram

3.3.4 Model Inputs

Model inputs are provided in Table 3.2 and described as follows.

Rates and probabilities: The health state probabilities in each treatment strategy are determined by the outcomes of both detoxification and maintenance therapies. The probabilities of being opioid-free and treatment discontinuation in the strategies formed integral data inputs in our model. For the health states' initial and transition probabilities, we used the data from Law et al. (2017), Lee et al. (2018), and Haight et al. (2019).[21, 27, 19] A comparison of the population demographics and clinical characteristics across the three clinical trials is provided in Table 3.3. In the clinical trial by Law et al. (2017), 58% and 53% of the patients completed methadone-lofexidine and buprenorphine-naloxone detoxification, respectively.[21] In the same trial, 80% of the patients on both detoxification methods were opioid-free.[21] We used these proportions to allow the cohorts to complete detoxification or drop out and begin the maintenance in the respective initial health states. Consistent with previous cost-effectiveness studies on OUD pharmacotherapies, data on

proportions of opioid-free, retention, and discontinuation were used to model health state transitions in the maintenance phase. Lee et al. (2018) reported that 35% of the patients on XR-NTX maintenance and 43% on buprenorphine-naloxone maintenance were opioid-free after 24 weeks of treatment.[27] The same study also reported that patients on XR-NTX experienced greater treatment discontinuation than patients on buprenorphine-naloxone.[27] The probability of XR-NTX discontinuation was obtained by multiplying the hazard ratio (1.36) to the probability of discontinuation in buprenorphine-naloxone maintenance (0.31).[27] Probabilities of opioid-free and treatment discontinuation in XR-BUP maintenance were taken from Haight et al. (2019).[19] The study reported that the proportion of opioid-free patients (41%) are less than the proportion of opioid-free patients on buprenorphine-naloxone maintenance.[19] The same study reported that 36% of the patients did not complete XR-BUP maintenance.[19] This proportion accounted for the probability of XR-BUP discontinuation in our model.

For any treatment strategy, we assumed that the transition probability of patients moving from "on medication with no opioid use" to "on medication with no opioid use" in the subsequent cycle is the same as the probability of patients moving from "on medication with opioid use" to "on medication with no opioid use" health state. Similarly, we assumed the same treatment discontinuation probability for a given strategy at any time during treatment. These probabilities were varied in the sensitivity analysis.

We took the overdose incidence from Morgan et al. (2019).[28] HIV and HCV seroconversion data were taken from a cost-effectiveness study of medication-assisted

treatment for OUD conducted by the Institute for Clinical and Economic Review. [14] The probabilities of overdose, HIV, and HCV-related mortalities were taken from a meta-analysis and the National Center for Health Statistics, USA.[29, 30, 31] All Markov model inputs were converted to monthly probabilities to accommodate the use of the monthly cycle. The Decision Tree inputs were used as the proportions reported in the clinical trial.[21]

Costs: We used the US healthcare system perspective in estimating costs. For each treatment strategy, medical costs included costs of treatment drugs and treatment procedures. The treatment drugs are sublingual buprenorphine-naloxone, methadone, lofexidine, XR-NTX injection, XR-BUP depot injection, and the adjunctive medications used in detoxification. We considered the cost of lofexidine, XR-NTX, and XR-BUP, as 121% of the drug costs reported in the Federal Supply Schedule (FSS) of U.S. Department of Veteran Affairs to represent the usual cost in the U.S. healthcare system, as recommended by the Health Economics Research Center (HERC), U.S. Department of Veteran Affairs.[32, 33] Costs of methadone, buprenorphine-naloxone, and adjunctive medications are National Average Drug Acquisition Costs (NADAC) from Centers for Medicare and Medicaid Services.[34] Costs relating to treatment procedures varied across the treatment strategies and the health states. Costs of treatment procedures in the assigned schedules are provided in Table 3.4.

Patients who continue using opioids incurred additional costs for health services utilization. Costs related to the use of opioids (in and out of treatment) captured costs of emergency department (ED) visits, inpatient hospitalization, and outpatient visits due to relapse-

related complications, overdose, HIV, and HCV treatments. Costs of HIV and HCV treatments were applicable for injection drug users only.

Costs of loss of productivity due to OUD includes the lost wages from medically-related and disability-related absenteeism. Costs of medically-related absenteeism are the lost wages for the days the patient seeks medical care like emergency department (ED) visits, inpatient hospitalizations, and outpatient visits (counted as a half-day absence from work).[35] Costs of disability-related absenteeism refers to wage lost due to disability resulting from illicit opioid use.

All costs were adjusted to 2020 USD using the Consumer Price Index for all urban consumers (CPI-U).[36]

Effectiveness: Effectiveness was measured by three separate outcomes: QALYs, treatment retention days, and opioid-free days in each of the treatment strategies. Quality of life was specific to health states. We also accounted for disutility from any incidence of overdose, positively diagnosed HIV, and HCV seroconversions.

Table 3.2 Model inputs

Variable	Value	Source
Proportions and transition probabilities		
Proportion of Injection Drug Users (IDU)	0.61	Computed[#]
Strategy A		
1. Detoxification (methadone-lofexidine)		
Proportion of cohorts detoxified	0.58	21
2. Maintenance (buprenorphine-naloxone)		
Initial probability: on medication with no opioid use	0.80	21
Initial probability: on medication with opioid use	0.20	21
Transition probability: on medication with no opioid use to-		
On medication with no opioid use	0.10	27
Off medication with opioid use	0.06	27
On medication with opioid use	0.84	Computed[¶]
Transition probability: on medication with opioid use to-		
On medication with no opioid use	0.10	27
Off medication with opioid use to	0.06	27
On medication with opioid use	0.84	Computed[¶]
Strategy B		
1. Detoxification (methadone-lofexidine)		
Initial probability: on medication with opioid use	1	Assumption
Transition probability: on medication with opioid use to-		
On medication with no opioid use	0.23	21
Off medication with opioid use	0.22	21
On medication with opioid use	0.55	Computed[¶]
2. Maintenance (extended-release naltrexone)		
Transition probability: on medication with no opioid use to-		
On medication with no opioid use	0.07	27
Off medication with opioid use[*]	0.08	27
On medication with opioid use	0.85	Computed[¶]
Strategy C		
1. Detoxification (buprenorphine-naloxone)		
Proportion of cohorts detoxified	0.53	21
2. Maintenance (extended-release buprenorphine depot)		
Initial probability: on medication with no opioid use	0.80	21
Initial probability: on medication with opioid use	0.20	21
Transition probability: on medication with no opioid use to-		
On medication with no opioid use	0.10	19
Off medication with opioid use	0.08	19

On medication with opioid use	0.82	Computed[¶]
Transition probability: on medication with opioid use to-		
On medication with no opioid use	0.10	19
Off medication with opioid use	0.08	19
On medication with opioid use	0.82	Computed[¶]
Strategy D		
1. Detoxification (buprenorphine-naloxone)		
Proportion of cohorts detoxified	0.53	21
2. Maintenance (buprenorphine-naloxone)		
Initial probability: on medication with no opioid use	0.80	21
Initial probability: on medication with opioid use	0.20	21
Transition probability: on medication with no opioid use to-		
On medication with no opioid use	0.10	27
Off medication with opioid use	0.06	27
On medication with opioid use	0.84	Computed[¶]
Transition probability: on medication with opioid use to-		
On medication with no opioid use	0.10	27
Off medication with opioid use to	0.06	27
On medication with opioid use	0.84	Computed[¶]
Common transition probabilities for all strategies		
Positive HIV seroconversion	0.005	14
Positive HCV seroconversion	0.026	14
Opioid overdose in treatment	0.002	28
Opioid overdose in treatment discontinuation	0.003	28
Opioid overdose in no treatment	0.004	28
HIV-related mortality	0.0000014	30
HCV-related mortality	0.0000031	31
Opioid-related mortality in treatment	0.0002	29
Opioid-related mortality out of treatment	0.0006	29
Opioid-related mortality in no treatment	0.002	29
Costs per cycle		
Medical costs		
Strategy A		
Methadone	$2[a]	34
Lofexidine	$3889[a]	32,33
Adjunctive medications	$262[b]	34
Buprenorphine-Naloxone maintenance dose (16mg/4mg)	$91[a]	34
Strategy B		
Methadone	$2[a]	34
Lofexidine	$3889[a]	32,33

Adjunctive medications	$262[b]	34
Extended release naltrexone injection	$1085/injection	32,33
Strategy C		
Buprenorphine-naloxone detoxification dose (8mg/2mg)	45[a]	34
Adjunctive medications	$202[b]	34
Extended-release buprenorphine depot injection	$1459/injection	32,33
Strategy D		
Buprenorphine-naloxone detoxification dose (8mg/2mg)	45[a]	34
Adjunctive medications	$202[b]	34
Buprenorphine-Naloxone maintenance dose (16mg/4mg)	$91[a]	34
Treatment procedure costs		
Initial patient assessment (H0001)	$153[c]	37
Outpatient physician visit in treatment (CPT 99211)	$23.46/visit	38
Extended-release naltrexone or buprenorphine administration (CPT 96372)	$14.44/dose	38
Weekly 1-hour counselling (CPT H0005)	$42/visit	37
Urine drug screen (CPT 80104)	$25.18/analysis	39
Medication dispensing fee	$12.59/prescription	40
Opioid use-related costs		
Relapse related outpatient cost	$630[d]	41
Relapse related ED visits	$352[d]	41
Relapse related inpatient hospitalization	$674[d]	41
Cost to treat each overdose	$4455[d]	42
Cost to treat HIV	$2836[e]	14
Cost to treat HCV	$12868.47[f]	14, 34
Health State Utilities		
On medication with no opioid use	0.766	14
On medication with opioid use: non-IDU	0.700	14
On medication with opioid use: IDU	0.618	14
Off medication with opioid use: non-IDU	0.694	14
Off medication with opioid use: IDU	0.574	14
Disutility associated with overdose	0.200	43
HIV Disutility Multiplier	6.9%	14
HCV Disutility Multiplier	7%	14
Data inputs for estimation of costs of loss of productivity		
Average annual workday loss due to ED visits	1.24 days/person	35
Average annual workday loss due to inpatient hospitalizations	2.38 days/person	35
Average annual workday loss due to outpatient visits	20.6 days/person[†]	35

Average annual workday loss due to disability	9.74 days/person	35
Average wage per hour	$29.35/hour	44

[#] Weighted average across interventions

¶ Transition probability of moving to "on medication with opioid use" health state in a treatment strategy is calculated as (1-(P+p)), where "P" is the transition probability of moving to "on medication with no opioid use" health state and "p" is the transition probability of moving to "off medication with opioid use" health state.

* The transition probability is calculated by multiplying the hazard ratio of treatment discontinuation in extended-release naltrexone maintenance to the probability of discontinuation in buprenorphine-naloxone maintenance.

† To be considered as half-day absence of work

Costs are in 2020 US$, converted using Consumer Price Index for all urban consumers (CPI).

a. Medical costs are obtained by multiplying the total doses in a month and unit costs.

b. Adjunctive medications include Zopiclone 3mg, Ibuprofen 400mg, Promethazine 12.5mg and Hyoscine 5mg in doses described by Law et al. 2017[21]

c. A one-time cost considered during the initial patient assessment.

d. Costs apply to both on medication and off medication with opioid use health states.

e. Costs apply to injection drug users only, on or off medication with opioid use health states. Costs include medication and diagnostic tests.

f. Costs apply to injection drug users only, on or off medication with opioid use health states. Costs include medications, diagnostic tests, and HIV-specific community care programs.

HCV is treated with Mavyret (glecaprevir/pibrentasvir), assuming all new cases of diagnosed HCV patients have no liver cirrhosis.

Table 3.3 Comparison of the population demographics and clinical characteristics across the clinical trials

Treatment	**Methadone-Lofexidine detoxification**	**Buprenorphine-naloxone detoxification**	**Extended-release naltrexone maintenance**	**Extended-release Buprenorphine maintenance**	**Buprenorphine-naloxone maintenance**
Data source	Law et al. (2017)[21]	Law et al. (2017)[21]	Lee et al. (2018)[27]	Haight et al. (2019)[19]	Lee et al. (2018)[27]
Demographics					
Mean age, years (SD)	23.0 (5.9)	23.2 (5.1)	34·0 (9·5)	39·3 (11·0)	33·7 (9·8)
Sex: Female, (%)	35.0	22.5	31.0	33.0	28.0
Ethnic origin, (%)	Not provided	Not provided	Caucasian: 73.0	Caucasian: 71.0	Caucasian: 75.0
Clinical characteristics					
Intravenous drug use (%)	66.7	71.8	63.0	41.0	64.0
Duration of opioid use, years	2.5	3	12.8	11	12.2
Types of drug use	Heroin, amphetamines, cannabis, cocaine, tranquilizers, alcohol, tobacco	Opioids, amphetamines, cannabis, cocaine, tranquilizers, alcohol, tobacco	Heroin, Methadone, Buprenorphine, Opioid analgesics	Heroin, amphetamines, cannabis, cocaine, methadone, buprenorphine, tranquilizers	Heroin, Methadone, Buprenorphine, Opioid analgesics

Table 3.4 Treatment procedures with usage schedules

Procedure	Detoxification	Maintenance
Initial patient assessment[a]	Once	-
Physician visit[a]	Five times a week	Once a week during initiation; once a week if relapse, and once a month if opioid-free
Urine drug screen[a]	Three times a week	Three times a week if relapse, and once a week if opioid-free
Patient counselling[a]	One-hour, once a week	One-hour, once a week if relapse, and half-hour once a week if opioid-free
Medication dispensing[a, b]	Daily	Strategy A and D: Once a week if relapse, and twice a month if opioid-free. Strategy B and C: Once a month
Injection administration[a]	-	Strategy B and C: Once a month

a: The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder 2020 Focused Update[1]
b: CRISM National Guideline for the Clinical Management of Opioid Use Disorder[2]
Strategy A: Detoxification by methadone-lofexidine, followed by buprenorphine-naloxone maintenance
Strategy B: Detoxification by methadone-lofexidine, followed by extended-release naltrexone maintenance
Strategy C: Buprenorphine-naloxone detoxification and extended-release buprenorphine maintenance
Strategy D: Usual treatment with buprenorphine-naloxone detoxification and maintenance

3.3.5 Cost-Effectiveness Analysis

3.3.5.1 Base Case Analyses

We used the Decision Tree and Markov model to estimate the costs, QALYs, treatment retention days, and opioid-free days of the five strategies over a 12 months' time horizon. We evaluated the incremental cost-effectiveness ratio (ICER) of the strategies as the difference between the total costs of the two strategies divided by the difference in effectiveness. A strategy that generates a lower ICER than the conventional willingness-to-pay threshold of $100,000 per QALY is cost-effective relative to the other strategy.[45]

3.3.5.2 Sensitivity Analyses

To test for parameter uncertainties, we conducted a series of sensitivity analyses. In the one-way sensitivity analysis, we varied the following parameters in a range of ±25% of base input values: i) the cost of lofexidine, buprenorphine-naloxone, adjunctive medications, and healthcare services; ii) the proportions of cohorts using injection drugs; iii) the proportion of cohorts detoxified; and iv) the transition probabilities of moving to opioid-free state (on medication with no opioid use) and treatment discontinuation (off medication with opioid use). We conducted subgroup analyses to re-run our analyses separately for injection drug users and non-injection drug users. This was done as the health-specific quality of life estimates vary across these two patient types. Also, injection drug users can experience disutility associated with HIV and HCV seroconversions and treatments, which lead to QALY decrements. This is not applicable for people who do not inject opioids.

In addition to one-way sensitivity analyses, we conducted a probabilistic sensitivity analysis (PSA). In the PSA, inputs (costs, probabilities, and utilities) were varied simultaneously according to pre-defined distributions and ranges for 1000 simulated iterations of the model. We used beta distributions for probabilities and utility weights and gamma distributions for costs.[26, 46, 9]

The proportion of people injecting drugs who are not in treatment may contract HIV or HCV, and the morbidities may not be diagnosed. Also, upon OUD treatment discontinuation, the patients' HIV and HCV treatments may get disrupted. In these cases,

the patients do not incur the additional costs of HIV and HCV care. So, we eliminated the HIV and HCV treatment costs and the associated disutility to patients who discontinued treatment and patients in the "no treatment" group to examine if the parameters have any profound effect on the strategies' cost-effectiveness. Finally, we conducted a threshold analysis to identify the cost threshold of lofexidine that could alter the cost-effectiveness across the treatment strategies in the defined willingness-to-pay threshold. We suspected that the high cost of lofexidine might impact the ICERs.

3.3.6 Costs of Loss of Productivity

Combining the lost wages from medically- and disability-related absenteeism due to illicit opioid use, we calculated the average annual costs of loss of productivity per opioid-dependent patient. Following Birnbaum et al. (2011)[47], we estimated the costs of medically related absenteeism by multiplying the number of days of healthcare utilization by the average daily wage. ED visits and inpatient hospitalization accounted for a full day of missed work; outpatient visits were counted as half-day of missed work. Similarly, we estimated the costs of disability-related absenteeism by multiplying the number of days of disability-related missed work with the average daily wage. Each workday is considered as an 8-hour work shift.

We then multiplied the costs of medically-related and disability-related absenteeism with the proportion of the cohort using illicit opioids (both in on medication with opioid use and off medication with opioid use) in each treatment strategy after one year of treatment. We compared the reduction in loss of productivity day and costs across the treatment strategies.

3.4 Results

3.4.1 Base Case Analyses

Base case cost-effectiveness results are provided in Table 3.5. As shown in panel A of Table 3.5, strategy A cost US$2,454 more and yielded 0.002 greater QALYs than strategy D. The higher total cost of strategy A stemmed from the high cost of lofexidine. Higher QALYs resulted from a greater proportion of patients completing detoxification than in strategy D. However, it is not cost-effective relative to strategy D in the willingness-to-pay threshold of US$100,000 per QALY (ICER: 1,247,528/QALY). Strategies B and C were dominated by strategy A, that is, the treatment strategies cost more and yield fewer QALYs than strategy A. The high costs of strategy B and C arose from the high cost of lofexidine, XR-BUP, and XR-NTX and the costs of frequent detoxification upon relapse with XR-NTX (strategy B). The lower effectiveness in strategy B and C resulted from a lower probability of being opioid-free and a higher probability of treatment discontinuation during XR-NTX maintenance in strategy B and a higher XR-BUP maintenance treatment discontinuation probability in strategy C than in strategy A.

When the strategies having long-acting maintenance treatment (B and C) were compared to no treatment, the treatment strategies were more costly and effective (panel B, Table 3.5). However, the resulting ICERs are not cost-effective in the defined willingness-to-pay threshold (strategy C: US$330,265/QALY relative to no treatment; strategy B: US$5,860,107/QALY relative to strategy C).

Results using treatment retention and opioid-free days outcomes are provided in Table 3.6. Strategy A retained fourteen additional days in treatment than Strategy D generating an ICER of US$175 per treatment retention day gained relative to Strategy D (panel A). Similarly, Strategy A provided two additional opioid-free days with an ICER of US$1227 per opioid-free day gained relative to Strategy D (panel B). Strategies B and C are dominated by strategy A.

Table 3.5 Incremental cost-effectiveness results with outcome as QALY gained

Strategy	Cost (US$)	Incremental cost (US$)	Effectiveness (QALY)	Incremental Effectiveness (QALY)	ICER (US$/QALY)
Panel A: All strategies					
No treatment	24,464	-	0.670	-	-
Strategy D	26,460	1,997	0.691	0.021	95,760
Strategy A	28,914	2,454	0.693	0.002	1,247,528
Strategy C	30,802	1,888	0.689	-0.004	Dominated
Strategy B	44,088	15,174	0.691	-0.001	Dominated
Panel B: strategy B and C versus no treatment					
No treatment	24,464	-	0.670	-	-
Strategy C	30,802	6,338	0.689	0.019	330,265
Strategy B	44,088	13,286	0.691	0.002	5,860,107

Strategy A: Detoxification by methadone-lofexidine, followed by buprenorphine-naloxone maintenance
Strategy B: Detoxification by methadone-lofexidine, followed by extended-release naltrexone maintenance
Strategy C: Buprenorphine-naloxone detoxification and extended-release buprenorphine maintenance
Strategy D: Usual treatment with buprenorphine-naloxone detoxification and maintenance
All costs are in 2020 US dollars (US$).
These base case analyses are based on one-year time horizon. Willingness-to-threshold: US$100,000/QALY
In panel A, strategy A costs more and provides a greater QALY than strategy D (usual treatment), but the ICER exceeds the willingness-to-pay threshold and hence not cost-effective relative to strategy D. Strategies B and C are dominated.
In panel B, strategy B costs more and provides a greater QALY than strategy C, but the ICER exceeds the willingness-to-pay threshold.
QALY, quality adjusted life years

Table 3.6 Incremental cost-effectiveness results with outcome as number of days of treatment retention and opioid-free gained

Strategy	Cost (US$)	Incremental cost (US$)	Effectiveness (Day)	Incremental Effectiveness (Day)	ICER (US$/ day)
Panel A: Cost per day of retention gained					
Strategy D	26,460	-	146	-	-
Strategy A	28,914	2,454	160	14	175
Strategy C	30,802	1,888	132	-28	Dominated
Strategy B	44,088	15,174	145	-15	Dominated
Panel B: Cost per day of opioid-free gained					
Strategy D	26,460	-	27	-	-
Strategy A	28,914	2,454	29	2	1,227
Strategy C	30,802	1,888	25	-4	Dominated
Strategy B	44,088	15,174	28	-1	Dominated

Strategy A: Detoxification by methadone-lofexidine, followed by buprenorphine-naloxone maintenance
Strategy B: Detoxification by methadone-lofexidine, followed by extended-release naltrexone maintenance
Strategy C: Buprenorphine-naloxone detoxification and extended-release buprenorphine maintenance
Strategy D: Usual treatment with buprenorphine-naloxone detoxification and maintenance
All costs are in 2020 US dollars (US$).
These base case analyses are based on one-year time horizon.
In panel A, strategy A costs more and provides a greater number of treatment retention days than strategy D (usual treatment). Strategies B and C are dominated.
In panel B, strategy A costs more and provides a greater number of opioid-free days than strategy D (usual treatment). Strategies B and C are dominated.
ICER, incremental cost-effectiveness ratio.

3.4.2 Sensitivity Analyses

Results of parameters affecting the ICER most in the one-way sensitivity analyses are presented as Tornado diagrams (Figures 3.2-3.4). The impacts of varying the model inputs are illustrated by the lengths of the horizontal bar in the Tornado diagram. Larger the length of the bar, greater the impact of varying the model input of the parameter. The Tornado analyses indicated that while the magnitudes of the ICER were sensitive to the costs of lofexidine, the cost-effectiveness rankings across the strategies were profoundly determined by the efficacy of the medications.

For the outcome of QALY, when strategies A and D were compared (Figure 3.2), the ICERs were most sensitive to the proportion of injection drug users receiving the treatments, cost of lofexidine and proportions of cohorts detoxified in the respective treatment strategies. With the higher proportion of patients with a history of injection drug use, the ICER value of the treatment strategies decreased. Varying the costs of lofexidine in the defined range lowered the ICER value of strategy A but did not yield cost-effectiveness in the conventional willingness-to-pay threshold. With a higher proportion of patients detoxified with buprenorphine-naloxone, strategy D dominated strategy A. Alternatively, with a lower proportion of patients detoxified with methadone-lofexidine, strategy D dominated strategy A. Varying these proportion inputs caused the difference in the effectiveness among the two strategies (A and D) to approach zero and thus indicated infinite ICER value in the Tornado diagram.

For the outcome of treatment retention days gained, our findings were most sensitive to the cost of lofexidine, the treatment discontinuation probabilities in buprenorphine-naloxone maintenance, and the proportions of cohort completing detoxification (Figures 3.3). Lowering the costs of lofexidine decreased the cost per additional day of treatment retention in strategy A. Varying the treatment discontinuation probability during buprenorphine-naloxone maintenance also impacted the ICER of strategy A. However, in both cases strategy A persisted to be cost-effective relative to strategy D. Like the outcome of QALY, a higher proportion of patients detoxified by buprenorphine-naloxone or a lower proportion of patients detoxified by methadone-lofexidine altered the cost-effectiveness

rankings; strategy A was dominated by strategy B. Varying these two inputs generated infinite ICER values, as indicated in the Tornado diagrams.

For the outcome of opioid-free days gained, our findings were most sensitive to the cost of lofexidine, probability of being opioid-free in buprenorphine-naloxone maintenance, and the proportions of patients completing detoxification (Figure 3.4). Decreasing cost of lofexidine and increasing probability of being opioid-free during buprenorphine-naloxone maintenance favoured strategy A. Similar to the outcomes of QALY and treatment retention days, a higher proportion of patients completing buprenorphine-naloxone detoxification or a lower proportion of patients completing methadone-lofexidine rendered strategy D cost-effective instead of strategy A. Varying these two inputs led to no difference in the effectiveness across the two strategies (indicated by the infinite ICER value in the Tornado diagram) and an eventual alteration in the strategies' cost-effectiveness rankings.

Figure 3.2 Tornado Diagram, strategy A vs. strategy D, (outcome: QALY)

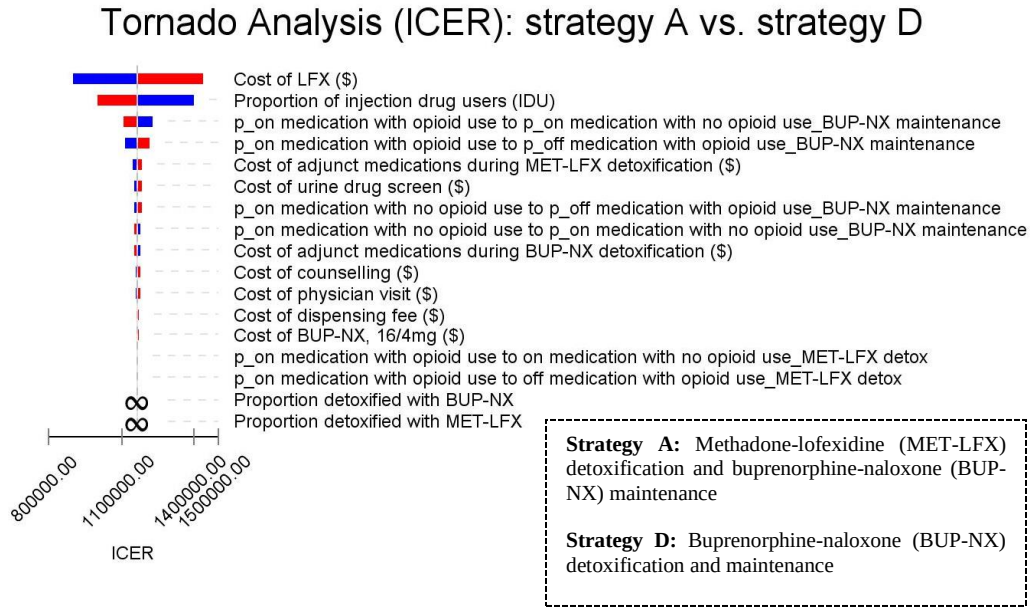


Figure 3.3 Tornado Diagram, strategy A vs. strategy D, (outcome: treatment retention days)

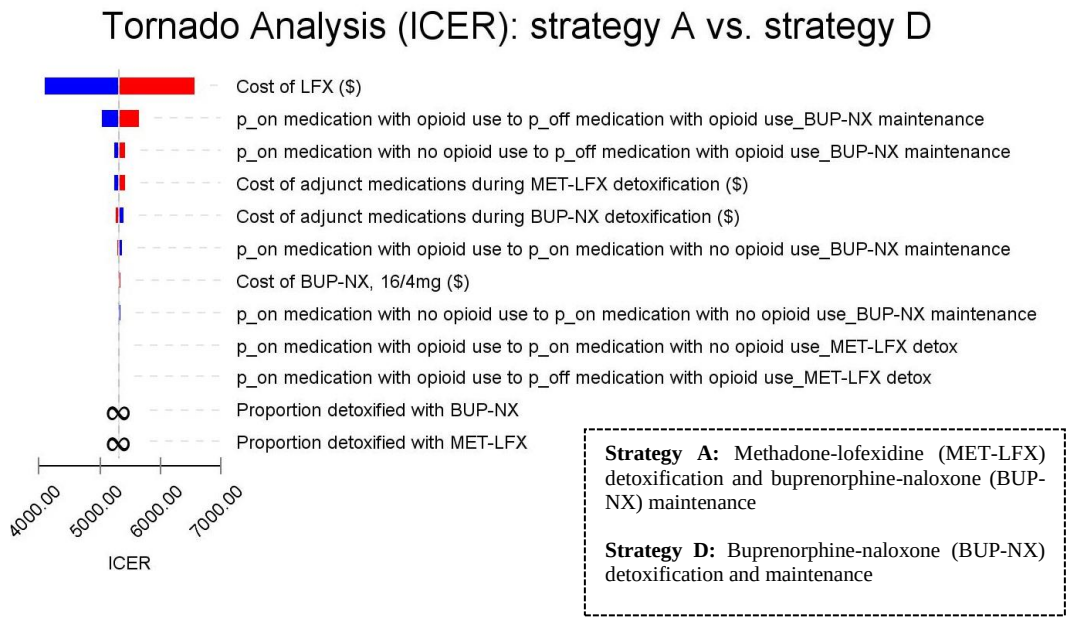
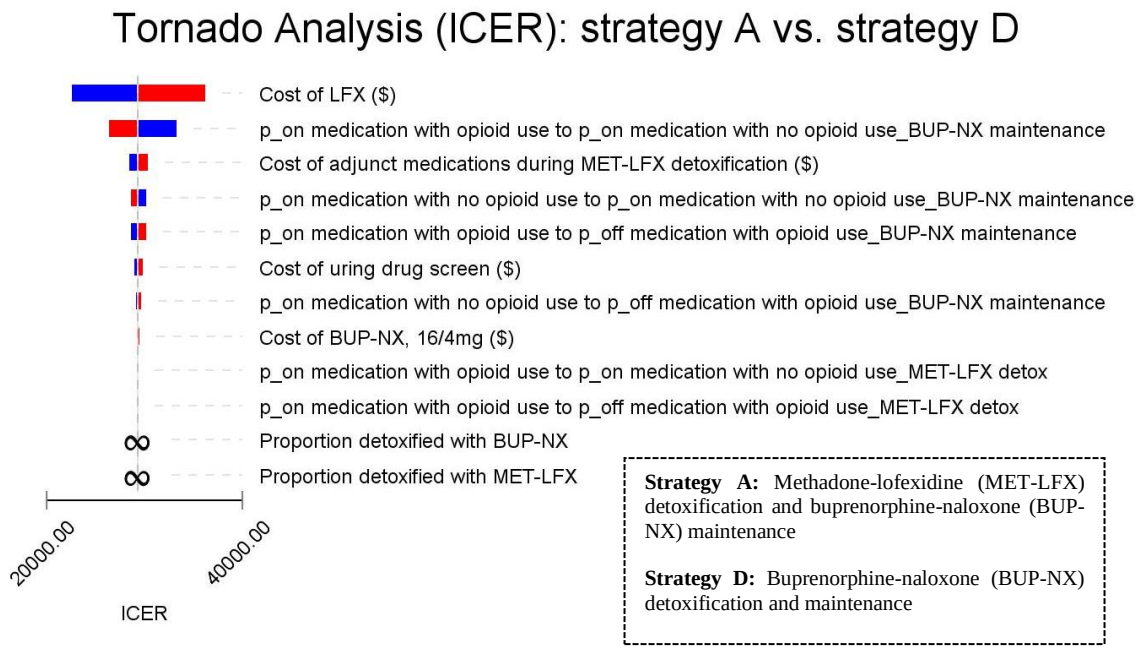


Figure 3.4 Tornado Diagram, strategy A vs. strategy D, (outcome: opioid-free days)



The results from the PSA confirm the robustness of to the base case results (Table 3.7). The cost-effectiveness acceptability (CEA) curve for the outcome defined in QALY indicated that at the willingness-to-pay threshold of US$100,000, strategy D (usual treatment) was the optimal treatment strategy in 47%, while strategy A in 9% of 1000 iterations (Figure 3.5). When strategies B, C, and no treatment were compared, strategy B was cost-effective in only 1% and strategy C in 21% of 1000 iterations (Figure 3.6).

Table 3.7 PSA with outcome as quality-adjusted life years, number of days of treatment retention, and opioid-free gained

Strategy	Cost (US$)	Incremental cost (US$)	Effectiveness	Incremental Effectiveness	ICER
Panel A: Cost per QALY gained					
No treatment	24,702	-	0.662	-	-
Strategy D	26,647	1,944	0.683	0.021	91,686
Strategy A	29,627	2,981	0.686	0.003	859,274
Strategy C	31,183	1,556	0.681	-0.005	Dominated
Strategy B	44,453	14,826	0.686	0.000	Dominated
Panel B: Cost per day of retention gained					
Strategy D	26,921	-	149	-	-
Strategy A	29,883	2,961	180	31	96
Strategy C	31,915	2,033	134	-46	Dominated
Strategy B	45,159	15,276	149	-31	Dominated
Panel C: Cost per day of opioid-free gained					
Strategy D	26,798	-	27	-	-
Strategy A	29,803	3,005	33	6	501
Strategy C	31,736	1,932	25	-8	Dominated
Strategy B	44,972	15,168	29	-4	Dominated

Strategy A: Detoxification by methadone-lofexidine, followed by buprenorphine-naloxone maintenance
Strategy B: Detoxification by methadone-lofexidine, followed by extended-release naltrexone maintenance
Strategy C: Buprenorphine-naloxone detoxification and extended-release buprenorphine maintenance
Strategy D: Usual treatment with buprenorphine-naloxone detoxification and maintenance
All costs are in 2020 US dollars (US$).
These probabilistic sensitivity analyses are based on one-year time horizon. Willingness-to-threshold: US$100,000/QALY
In panels A, B and C, strategy A costs more and provides higher QALYs, treatment retention, and opioid-free days than strategy D but not cost-effective in the willingness-to-pay threshold for the outcome of QALY.
Strategies C and D are dominated.
ICER, incremental cost-effectiveness ratio. QALY, quality adjusted life years

Figure 3.5 Cost-effectiveness acceptability curve of all strategies

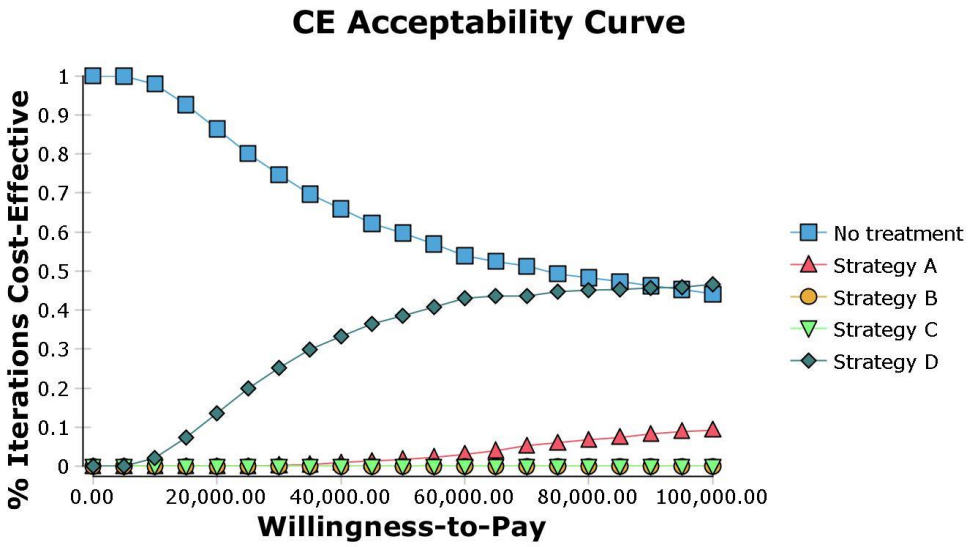
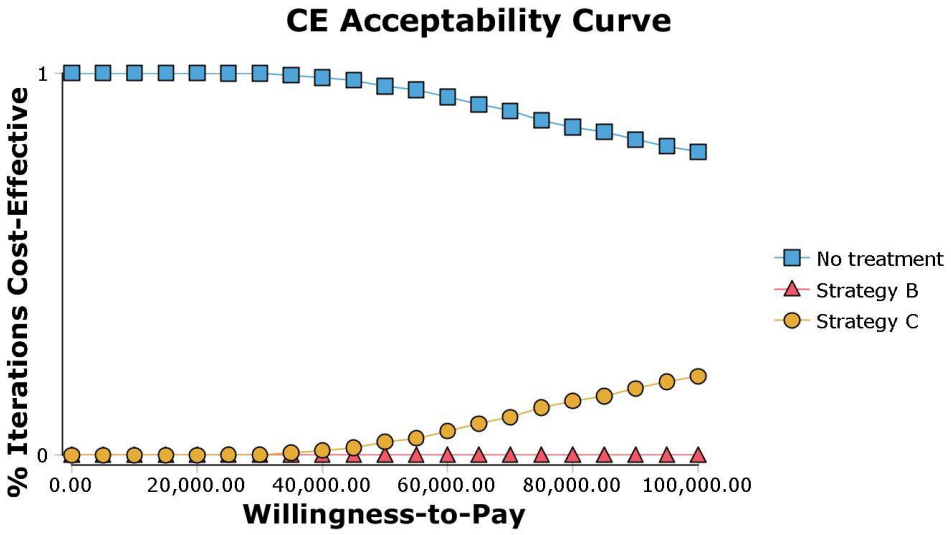


Figure 3.6 Cost-effectiveness acceptability curve of strategy B and C versus no treatment



Strategy A: Detoxification by methadone-lofexidine, followed by buprenorphine-naloxone maintenance
Strategy B: Detoxification by methadone-lofexidine, followed by extended-release naltrexone maintenance
Strategy C: Buprenorphine-naloxone detoxification and extended-release buprenorphine maintenance
Strategy D: Usual treatment with buprenorphine-naloxone detoxification and maintenance

Similar results as base case analyses were obtained with separate cohorts of injection drug users and non-injection drugs; although for injection drug users, the ICER of strategy D compared to no treatment was found to exceed the willingness-to-pay threshold. This is because the difference in the effectiveness (QALY) between strategy D and no treatment cohorts of non-injection drug users appears smaller than that in injection drug users. With non-injection drug users, there are no decrements in QALY in the form of disutility associated with HIV and HCV. This resulted in a narrower difference in the QALYs among the non-injection drug users in strategy D and no treatment. The results are provided in Table 3.8.

Table 3.8 Sub-group analyses: Incremental cost-effectiveness results with outcome as QALY gained

Strategy	Cost (US$)	Incremental cost (US$)	Effectiveness (QALY)	Incremental Effectiveness (QALY)	ICER (Cost/QALY)
Panel A: Injection drug users (IDU)					
No treatment	26,096	-	0.618	-	-
Strategy D	27,975	1,880	0.648	0.029	64,034
Strategy A	30,418	2,443	0.651	0.003	882,135
Strategy C	31,946	1,528	0.645	-0.005	Dominated
Strategy B	45,594	15,175	0.648	-0.002	Dominated
Panel B: Non-injection drug users (Non-IDU)					
No treatment	21,911	-	0.751	-	-
Strategy D	24,090	2,179	0.758	0.008	288,711
Strategy A	26,561	2,471	0.759	0.001	3,469,771
Strategy C	29,013	2,452	0.758	-0.001	Dominated
Strategy B	41,732	15,171	0.759	-0.0003	Dominated

Strategy A: Detoxification by methadone-lofexidine, followed by buprenorphine-naloxone maintenance
Strategy B: Detoxification by methadone-lofexidine, followed by extended-release naltrexone maintenance
Strategy C: Buprenorphine-naloxone detoxification and extended-release buprenorphine maintenance
Strategy D: Usual treatment with buprenorphine-naloxone detoxification and maintenance
All costs are in 2020 US dollars (US$).
These sub-group analyses are based on one-year time horizon. Willingness-to-threshold: US$100,000/QALY
In panels A and B, strategy A cost more and yield higher QALYs than strategy D but not cost-effective in the willingness-to-pay threshold. Strategies B and C are dominated.
ICER, incremental cost-effectiveness ratio.
QALY, quality adjusted life years

Sensitivity analysis using the cohorts who discontinue treatment or receive no OUD treatment, are HIV or HCV positive, and do not receive HIV or HCV care, yielded similar results as base case findings (Table 3.9). However, the ICER value of strategy D compared to no treatment for the outcome of QALY, was found to be higher than the base-case. This is because there was no QALY reduction associated with HIV or HCV disutility for patients who discontinue treatment or receive no treatment. In the sensitivity analysis, it was assumed that these patients with HIV or HCV infection, were undiagnosed or did not receive HIV or HCV care.

Table 3.9 Results of eliminating HIV- HCV costs and disutility in no treatment and treatment discontinuation

Strategy	Cost (US$)	Incremental cost (US$)	Effectiveness	Incremental Effectiveness	ICER
Panel A: Cost per QALY gained					
No treatment	21,911	-	0.671	-	-
Strategy D	24,892	2,981	0.692	0.020	146,564
Strategy A	27,439	2,547	0.694	0.002	1,327,079
Strategy C	29,140	1,701	0.690	-0.004	Dominated
Strategy B	42,548	15,109	0.692	-0.001	Dominated
Panel B: Cost per day of retention gained					
Strategy D	24,892	-	146	-	-
Strategy A	27,439	2,981	160	14	213
Strategy C	29,140	2,547	132	-28	Dominated
Strategy B	42,548	1,701	145	-15	Dominated
Panel C: Cost per day of opioid-free gained					
Strategy D	24,892	-	27	-	-
Strategy A	27,439	2,981	29	2	1018
Strategy C	29,140	2,547	25	-4	Dominated
Strategy B	42,548	1,701	28	-1	Dominated

Strategy A: Detoxification by methadone-lofexidine, followed by buprenorphine-naloxone maintenance
Strategy B: Detoxification by methadone-lofexidine, followed by extended-release naltrexone maintenance
Strategy C: Buprenorphine-naloxone detoxification and extended-release buprenorphine maintenance
Strategy D: Usual treatment with buprenorphine-naloxone detoxification and maintenance
All costs are in 2020 US dollars (US$).
These sensitivity analyses are based on one-year time horizon. Willingness-to-threshold: US$100,000/QALY
In panels A, B and C, strategy A costs more and yields higher QALYs, treatment retention and opioid-free days than Strategy D but not cost-effective in the willingness-to-pay threshold for the outcome of QALY.
Strategies C and D are dominated.
ICER, incremental cost-effectiveness ratio.
QALY, quality adjusted life years

Finally, the threshold analysis indicated that based on the conventional willingness-to-pay threshold of US$100,000/QALY, the cost of lofexidine would have to be massively reduced by 99% from the base case (US$24) for the strategy A to be cost-effective relative to strategy B. If we use an alternative threshold of 3 times the national annual GDP per capita as recommended by the WHO[22] (i.e., 3 times the US GDP per capita of

US$65,118.4)[48], strategy A would be cost-effective if lofexidine cost was reduced by 91% of its current cost (cost: US$369; ICER: US$195,341/QALY).

3.4.3 Costs of Loss of Productivity

From the model, we estimated the proportion of the cohort using illicit opioids (in treatment and out of treatment) in each treatment strategy after one year of treatment: strategy A: 0.971; strategy B: 0.98; strategy C: 0.979; and strategy D: 0.973. The costs of loss of productivity are provided in Table 3.10. Among the four treatment strategies, strategy A generated a maximum reduction in the days and costs of loss of productivity (-0.69 days, a cost reduction of 2.90%), followed by strategy D (-0.64 days, a cost reduction of 2.70%), strategy C (-0.5 days, a cost reduction of 2.10%) and strategy B (0.47 days, a cost reduction of 2%).

Table 3.10 Loss of productivity from OUD

Reason for work loss	**Days of loss of work**	**Strategy A p=0.971**	**Strategy B p=0.98**	**Strategy C p=0.979**	**Strategy D p=0.973**
Emergency department visits	1.24	1.20	1.22	1.21	1.21
Inpatient hospitalization	2.38	2.31	2.33	2.33	2.32
Outpatient visits*	10.30	10.00	10.09	10.08	10.02
Disability	9.74	9.46	9.55	9.54	9.48
Total workdays lost	**23.66**	**22.97**	**23.19**	**23.16**	**23.02**
Total costs of loss of productivity	**5,555**	**5,394**	**5,444**	**5,439**	**5,405**
Percent reduction in cost		**2.90%**	**2.00%**	**2.10%**	**2.70%**

* Days of outpatient visits are halved to represent half-day of work missed.

3.5 Discussion

The goals of OUD treatment are to treat the OUD, manage withdrawal symptoms, reduce drug-related harms, and support long-term recovery. In this study, we conducted a cost-effectiveness analysis of four treatment strategies, incorporating both detoxification and maintenance phases of the treatments and of no treatment. Our study is the first to assess the ICER of potential treatment strategies that involve the use of lofexidine for detoxification. Our study is also the first to compare the cost-effectiveness of XR-NTX intramuscular injection with XR-BUP subcutaneous injection and no treatment. We found that detoxification with methadone-lofexidine and successive buprenorphine-naloxone maintenance costs more but also provides higher QALYs, treatment retention, and opioid-free days than conventional treatment with buprenorphine-naloxone detoxification and maintenance. However, the treatment strategy is not cost-effective at a willingness-to-pay threshold of US$100,000 per QALY.

Both the strategies with long-acting formulations are dominated by detoxification with methadone-lofexidine and buprenorphine-naloxone maintenance. When we compared these long-acting treatment strategies with no treatment, they cost more and yield greater effectiveness but are not cost-effective. Detoxification with methadone-lofexidine and buprenorphine-naloxone maintenance provides increased treatment retention and opioid-free days at a higher cost than treatment with buprenorphine-naloxone (detoxification and maintenance).

The high ICER estimate of methadone-lofexidine and buprenorphine-naloxone maintenance is principally due to the high cost of lofexidine. This high cost has made lofexidine's US FDA approval controversial.[49] Lofexidine hydrochloride is only available as a branded medicine, Lucemyra™.[50] Our findings support the proponents' claims of the beneficial aspects of lofexidine while also bearing evidence of the predicted elevated costs to the healthcare system. A higher proportion of patients was found to complete detoxification with methadone-lofexidine than buprenorphine-naloxone detoxification, which enhanced the entire strategy's overall performance. But due to the higher total cost than conventional treatment, its use may remain debatable. The detoxification with methadone-lofexidine and maintenance with XR-NTX is dominated due to a higher probability of treatment discontinuation and a lower probability of being opioid-free in XR-NTX maintenance. The detoxification with buprenorphine-naloxone and maintenance with XR-BUP is dominated due to a higher probability of treatment discontinuation in XR-BUP maintenance (thus QALY reduction).

The high ICER of methadone-lofexidine detoxification and buprenorphine-naloxone maintenance relative to usual treatment with buprenorphine-naloxone in terms of QALY gained does not necessarily dismiss the need for this treatment strategy. The inference on a higher cost per QALY gained is subjected to the healthcare system's willingness-to-pay threshold. While low-income or senior patients in the US are mostly covered by Medicaid and Medicare, many others are covered by private healthcare insurances or simply pay out-of-pocket. The willingness-to-pay threshold for the different patient demographics may be different.

Apart from QALY, our study suggests that methadone-lofexidine detoxification and buprenorphine-naloxone maintenance generate more treatment retention days and opioid-free days. Although QALY is a universally accepted generic measure used in the cost-effectiveness analysis for treatment interventions, treatment retention days and opioid-free days are two critical outcomes for OUD interventions due to the disorder's recurring nature.

Compared to no treatment, XR-BUP maintenance (preceded by buprenorphine-naloxone stabilization) and XR-NTX maintenance (preceded by methadone-lofexidine detoxification) are found to be superior. But the increased effectiveness comes with high costs that overwhelmingly exceeds the willingness-to-pay threshold of $100,000 per QALY. However, we note that there are several intangible benefits of the two treatment strategies which could not be captured in our cost-effectiveness analysis. These benefits may hold significance while making treatment decisions. Methadone-lofexidine detoxification and XR-NTX maintenance can be offered to under-served populations who fail to access conventional OAT due to a shortage of agonist medication providers or logistical reasons. It can help overcome fears of physical dependence, stronger withdrawal discomfort, and offer greater patient convenience with once a month medication dosing. XR-BUP diminishes the possibility of medication diversion with sublingual buprenorphine, a benefit that we could not incorporate in our study due to the lack of reliable data. Also, it offers patient convenience due to its once a month dosing and the need for less frequent visits to the healthcare settings.

We explored the effects of the treatment strategies on the loss of productivity due to OUD. Although preliminary, the findings indicate that detoxification with methadone-lofexidine and maintenance with buprenorphine-naloxone may result in the highest reduction in work loss days (-0.69 days) and costs of loss of productivity (-$161). We suspect that the treatment strategy would not be cost-effective in our defined willingness-to-pay threshold with such a small magnitude of changes. However, the results predict the potential of the treatment strategy to have a positive impact on productivity loss. We could not assess the economic burden of OUD on work productivity loss due to unemployment, incarceration and, mortality. So, the results are likely to underestimate. A full-scale cost-effectiveness study from a societal perspective can better inform the implications of the treatment strategies on the loss of productivity.

In conclusion, detoxification with methadone-lofexidine and maintenance therapy with buprenorphine-naloxone generates higher QALYs, treatment retention, and opioid-free days. However, given the current costs of lofexidine, the strategy may not be an economically viable treatment option. When the intended outcome of the treatment is QALY, the usual treatment with buprenorphine-naloxone is the cost-effective option. Stakeholders who favour the primary treatment goals of increased treatment retention and opioid-free days may prefer methadone-lofexidine detoxification and buprenorphine-naloxone maintenance rather than usual treatment, although at a much higher total cost.

3.6 Chapter 3 References

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Chapter 4 Summary

4.1 Overview of Chapter

The final chapter re-directs readers to the background involved in developing the research studies, the study rationale, summarizes the study findings which answers the overall research aim of the thesis, highlights research strengths and weaknesses, discusses the clinical and policy implications, and finally proposes future research directions. In brief, Chapter 2 is a narrative review, which examined patients' perceptions and experiences with commonly used opioid use disorder (OUD) pharmacotherapies. Two outcomes, that is, perceptions and experiences, were assessed in the review, and findings narratively described under emergent themes. Chapter 3 is a cost-effectiveness analysis that compared the incremental cost-effectiveness ratio (ICER) of five OUD treatment strategies from the US healthcare perspective: A) use of methadone-lofexidine for detoxification and buprenorphine-naloxone for maintenance; B) use of methadone-lofexidine for detoxification and XR-NTX for maintenance; C) use of buprenorphine-naloxone for detoxification and XR-BUP for maintenance; D) use of buprenorphine-naloxone for detoxification and maintenance (i.e., usual treatment); and, E) no treatment. The effectiveness measures for the cost-effectiveness study are, quality-adjusted life years (QALYs), treatment retention days and opioid-free days gained. Also, an explorative analysis has been described in Chapter 3 which investigates the cost implications of the treatment strategies on loss of productivity from OUD.

4.2 Research Background and Development of Research Questions

OUD is a severe global concern with detrimental health and social effects. The impacts are particularly alarming in North America with the recent rise in the use of prescription opioids and availability of synthetic opioids like fentanyl and its analogs. Despite the availability of several evidence-based OUD pharmacotherapies, treatment uptake remains remarkably low.[1, 2]

There are multiple factors at play that act as potential treatment facilitators or barriers. Evidence from the literature suggests that patients' treatment perceptions and experiences and treatment cost notably influence their treatment decisions.[3, 4, 5, 6, 7] There are only two systematic reviews that investigated patients' perspectives with OUD pharmacotherapies;[8,9] however, with numerous treatment options currently available, especially the newer pharmacotherapies, namely, lofexidine, extended-release naltrexone (XR-NTX), extended-release buprenorphine (XR-BUP), and buprenorphine implants, a reexamination of patients' experiences along with perceptions becomes important. Also, the advent of the newer pharmacotherapies raises one vital question, "is it affordable?"—an area with inadequate evidence. Two complementary studies were designed to address these issues, which are presented in this thesis.

4.3 Summary of Findings

The narrative review in Chapter 2 consolidates patient-reported evidence on methadone, buprenorphine (sublingual, extended-release depot injection, and implants),

buprenorphine-naloxone, naltrexone (oral and extended-release injection), extended-release buprenorphine (XR-BUP) and no treatment. Four emergent themes on patients' perceptions are, 1) attitudes towards the pharmacotherapies, 2) awareness/knowledge of the pharmacotherapies, 3) long-acting formulations, and 4) medication dose and treatment duration. Five emergent themes pertained to patients' experiences are, 1) treatment experiences, 2) dose-related experiences, 3) experiences during treatment switch, 4) sensory experiences with the pharmacotherapies, and 5) treatment satisfaction.

The narrative review guided our choice of treatment strategies for the cost-effectiveness study (Chapter 3). The review's findings such as patient's growing interest in long-acting formulations, increasing aversion towards conventional OATs, and some patients favouring opioid-free treatments motivated the inclusion of an alpha-2 adrenergic agonist (lofexidine) and long-acting formulations (XR-NTX and XR-BUP) in the cost-effectiveness study. The cost-effectiveness study predicts that detoxification with lofexidine (in combination with methadone) followed by buprenorphine-naloxone maintenance was found to provide greater effectiveness but not cost-effective relative to usual care (buprenorphine-naloxone detoxification and maintenance) in the conventional willingness-to-pay threshold of US$100,000 per QALY gained. High ICER of methadone-lofexidine detoxification and buprenorphine-naloxone maintenance stemmed from the high cost of lofexidine. Treatment strategies having XR-NTX and XR-BUP maintenance were also found not cost-effective relative to usual care. The explorative research on the impacts of the treatments on the loss of productivity indicates a small improvement on productivity loss. Methadone-lofexidine detoxification followed by buprenorphine-naloxone

maintenance generated a better reduction in workday loss and cost of productivity loss than the other three treatment strategies. Further cost-effectiveness research considering costs to the society (including the costs to the criminal justice system) is warranted.

Based on the findings of the two complementary studies (Chapters 2 and 3) we piece together information on the potential treatment strategies in Table 4.1. Owing to the mixed-method nature of the two complementary studies, we took a descriptive approach to draw overarching inferences from the two research. From the review article in Chapter 2, we found that patients acknowledged OAT with methadone and buprenorphine (also its combination with naloxone) to provide the clinical benefits of OUD treatment like reduced illicit opioid dependence, craving, and improved quality of life. These positive clinical benefits are also reflected from the cost-effectiveness study in Chapter 3. Treatment strategies having either methadone-lofexidine detoxification (strategy A) or buprenorphine-naloxone detoxification (strategy D) followed by buprenorphine-naloxone maintenance generated higher QALYs, treatment retention and opioid-free days than the treatment strategies having the long-acting injectables for maintenance therapies. From the cost perspective, usual care with buprenorphine-naloxone (strategy D) appears to be a better treatment option than methadone-lofexidine detoxification and buprenorphine-naloxone maintenance (strategy A).

The review in Chapter 2 also highlights the negative OAT perceptions borne by some opioid-dependent patients; they prefer abstinence-based therapy or no treatment at all. Daily dosing and frequent visits to the treatment facility with OAT have been identified as

potential treatment limiting factors by some patients. These patients can benefit from initial detoxification with either methadone-lofexidine or buprenorphine-naloxone and can be maintained on once a month XR-NTX injection (strategy B) or XR-BUP injection (strategy C). However, the cost-effectiveness study does not support these treatment strategies compared to usual care (strategy D, detoxification, and maintenance with buprenorphine-naloxone). These treatment strategies are beneficial compared to no treatment but not cost-effective.

We acknowledge that it is difficult to draw concrete evidence of optimal treatment choice based on patients' perceptions and cost-effectiveness analysis. The two studies aim to address two distinct aspects of pharmacotherapies. While perceptions are mostly patients' opinions of the pharmacotherapies, cost-effectiveness takes clinical efficacy and cost into consideration. Patients may perceive OAT negatively, but clinically it is found to be efficacious. So, perception may widely vary from treatment efficacy. However, based on the overall findings of this thesis, it can be concluded that conventional OUD treatment with buprenorphine-naloxone appears to be the ideal treatment option for the general population from a perception, efficacy, and cost point of view.

Table 4.1 Overarching evidence of potential treatment strategies for OUD

Treatment strategies	Evidence from Chapter 2	Evidence from Chapter 3
Methadone	Patients acknowledged the clinical benefits of methadone in OUD treatment; however, there were concerns of treatment dependence and reports of difficult treatment experiences. Medication diversion was noted.	When methadone and lofexidine are used for detoxification followed by buprenorphine-naloxone maintenance, the treatment strategy generates higher QALYs, and a greater number of treatment retention days and opioid-free days than usual care (buprenorphine-naloxone). The strategy, however, is not cost-effective relative to usual care.
Lofexidine	No data were found on patients' perceptions and experiences.	
Buprenorphine-naloxone	Patients reported positive assessments with accounts of concerns of treatment dependence, side-effects and diversion.	In the defined willingness-to-pay threshold of US$100,000 per QALY gained, buprenorphine-naloxone (detoxification and maintenance) is predicted to be cost-effective treatment strategy.
XR-NTX	Patients seeking complete abstinence preferred this medication due to its ability to completely block the effects of illicit opioids, less frequent dosing, and control of cravings for longer periods. Lack of adequate knowledge among the patients was identified. Patients who show total aversion to OAT can be treated with XR-NTX.	Treatment strategy with methadone-lofexidine detoxification and XR-NTX maintenance cost more but provides lower effectiveness than strategy having methadone-lofexidine detoxification and buprenorphine-naloxone maintenance; thus, it is dominated. Compared with no treatment, methadone-lofexidine detoxification and XR-NTX maintenance cost more and provide greater effectiveness but not cost-effective.
XR-BUP	Few studies were found to report patients' perceptions and experiences with the medications. Medication attributes like less frequent dosing, longer coverage of opioid craving, and diminished potential to misuse contributed to patients' preference for XR-BUP. Again, a lack of knowledge among the patients was noted.	Treatment strategy with buprenorphine-naloxone detoxification and XR-BUP maintenance cost more but provides lower effectiveness than strategy having methadone-lofexidine detoxification and buprenorphine-naloxone maintenance; thus, it is dominated. Compared with no treatment, buprenorphine-naloxone detoxification and XR-BUP maintenance cost more but not cost-effective.

4.4 Study Strengths and Limitations

The narrative review studies patients' attitudes, fears and concerns, preferences and willingness, along with their experiences with the OUD pharmacotherapies. Inclusion of both perceptions and experiences offers a thorough assessment of the patients' reported facilitators and barriers to the relevant pharmacotherapies. The addition of qualitative, quantitative, and mixed-method studies in this review provides a greater chance of encompassing all aspects of patient-reported perspectives. The findings of this study were compared with the latest published review on patients' perspectives of the treatments.[9] Our study captured all the concepts of patients' perspectives reported in the previous review. Additionally, our review highlighted several critical concepts, such as patients' perceptions and experiences with treatment doses, their perspectives on novel XR-BUP injection and buprenorphine implants which were missing in the previous literature. This review has several limitations, however. Due to the heterogeneity of study types, population, and interventions, data could not be synthesized to receive quantifiable findings. Instead, the findings were integrated across a wide variety of literature and narratively described under common themes. The themes included in this review were developed inductively and not a priori. As a result, probable critical concepts pertaining to the review topic, which could not be identified during the review, may have been missed. Also, we limited our review scope to the clinical aspects of the pharmacotherapies, and patients' perceptions and experiences with the logistical and regulatory aspects of the treatments were not covered. Finally, due to a lack of quality acceptance threshold for the quality assessment tools to

critically appraise the studies, all the relevant studies were included in the review. It is possible that all evidence may not come from the highest quality literature.

The cost-effectiveness study has several strengths. A pragmatic economic model was developed to incorporate the disease's natural progression and possible health outcomes of the treatment interventions. The modelled clinical pathways for each of the strategies are congruent with the real-world evidence. The model-based analysis enabled extrapolation of costs and outcomes beyond the clinical trials' study periods. Also, it incorporated multiple comorbidities associated with the use of opioids, overdose, human immunodeficiency virus (HIV), and hepatitis C virus (HCV). These comorbidities have detrimental health and economic impacts in terms of mortality and treatment costs. The costs of medication dispensing, which were not considered in any previous cost-effectiveness studies on OUD interventions, are included in this study. Medications are dispensed more frequently in detoxification than maintenance treatment and more regularly with oral medications than with once-a-month extended-release injection. So, the medication dispensing costs varied across the phases of treatment and the strategies that profoundly impacted the total costs. Several previous model-based cost-effectiveness studies on OUD treatments focused principally on the maintenance therapies and did not account for the costs and health events during stabilization and detoxification.[10, 11, 12, 13] Detoxification is of paramount importance, especially with XR-NTX maintenance, due to the difficulty with XR-NTX initiation and the risk of precipitated withdrawal. Costs and treatment events with methadone-lofexidine detoxification leading to XR-NTX maintenance provide a more comprehensive cost estimate for XR-NTX maintenance

treatment. Our study, too, underscored the importance of an effective detoxification strategy that determines long term effects. A higher proportion of detoxified patients with methadone-lofexidine than with buprenorphine-naloxone rendered the entire strategy of methadone-lofexidine detoxification and buprenorphine-naloxone maintenance more effective than usual treatment.

This cost-effectiveness study also has several notable limitations. First, there is a lack of evidence on methadone-lofexidine effectiveness in a US population. Two clinical trials support lofexidine's clinical efficacy for US FDA approval.[14, 15, 16] However, the trials compared lofexidine with placebo and focused on changes in withdrawal severity and treatment completion rates; abstinence rates were not reported. Hence, these could not be used in our analysis. Data on maintenance therapies with buprenorphine-naloxone, XR-BUP, and XR-NTX are specific to the US population. Second, data was sourced from multiple clinical trials with varying study populations.[17, 18, 19] There is a moderate age difference between the opioid-dependent patients undertaking the detoxification treatments and those taking the maintenance treatments. Also, there is a considerable difference in the duration of illicit opioid use among the patients. Patients taking the detoxification treatments reported a lesser number of illicit opioid use days than the patients taking the maintenance treatments (Appendix I). While we could not control the variations in population demographics, we conducted several rigorous sensitivity analyses, which yielded reproducible results. The weight-adjusted mean proportion of the population using injection drugs were included in the model to account for any difference in injection drug use among the study populations. Third, the common non-serious adverse effects of the

pharmacotherapies could not be included in the cost-effectiveness analysis. However, the inclusion of the adjunctive medications during detoxification may have minimized the cost impacts of the non-serious adverse effects. These adjunctive medications were used in the clinical trial to relieve the patients from the non-serious adverse effects.[17] We considered the costs of the medications in proportions used by the patient groups in the trial.[17] Finally, this cost-effectiveness analysis did not consider the proportion of patients achieving opioid-free status without treatment due to the lack of reliable data. As OUD is a chronic, relapsing disorder, it is unlikely that a considerable number of opiate-dependent patients will be opioid-free without treatment to alter our findings in a time span of one year.

4.5 Implications of the Current Study

The study's results hold value to different treatment stakeholders, namely, patients, physicians, and policymakers. The review elucidates the patients' attitudes and responses to the OUD pharmacotherapies. Understanding their opinions and experiences with treatments may help fine-tune the existing policies or highlight the need for significant policy revisions. This study also informs clinical practice and treatment policies on the pressing need for patient inclusive decision making.

The cost-effectiveness study indicates higher effectiveness with methadone-lofexidine detoxification and buprenorphine-naloxone maintenance than usual treatment but with an extravagant cost. This high cost is a matter of great consideration for policymakers. Healthcare resource is limited and must be spent judiciously. The probable availability of

generic forms of the medications will likely lower the cost of lofexidine, making the strategy more competitive in the commonly used willingness-to-pay benchmark.

The narrative review in Chapter 2 identified a group of opioid-dependent patients who are less inclined to taking OAT with methadone or buprenorphine and favor opioid-free or abstinence-based treatment approaches. Detoxification with methadone-lofexidine and maintenance with XR-NTX appears to be more effective than detoxification with buprenorphine-naloxone and maintenance with XR-BUP. This treatment approach certainly holds value for clinicians and decision-makers as they plan efforts to tailor treatment best suited to patients' requirements. Some patients may also find daily treatment schedules with the conventional OAT arduous and seek a once-a-month treatment dosing. Our study predicts better effectiveness with methadone-lofexidine detoxification and XR-NTX maintenance than buprenorphine-naloxone detoxification and XR-BUP maintenance. However, the preceding strategy entails a high cost, which overwhelmingly exceeds the willingness-to-pay threshold.

The cost-effectiveness study has been conducted from the US healthcare perspective, using the US cost data. The choice of country perspective in this study is governed by the regulatory status of the pharmacotherapies and their availability in the market. Currently, lofexidine, XR-NTX, and XR-BUP are approved and available for treatment in the US; these pharmacotherapies are not available in Canada. Although prescription medicines are less expensive in Canada compared to the US,[20] the sensitivity analyses (including the cost threshold analysis for lofexidine) predict that it is unlikely the treatment strategies would

be cost-effective from the Canadian healthcare perspective. Buprenorphine-naloxone detoxification and maintenance, which is the usual care both in Canada and the US, appears to be the optimal treatment option for both countries.

4.6 Future Research

The current narrative review focuses on patient perceptions and experiences with OUD treatments. Stigma, treatment availability, and accessibility across rural and urban regions, as well as socio-economic indicators like income and treatment regulatory bottlenecks are salient barriers to treatment uptake and utilization. Future work needs to investigate the patients' views on these impediments to supplement the findings of the current review. With increasing efforts to improve the adoption of evidence-based treatments, understanding all stakeholders' perspectives may help formulate effective treatment strategies.

OUD is a recurring disorder that inflicts both physical and mental health damages. It will be valuable to plan cost-effectiveness studies using Recovering Quality of Life (ReQoL) measures. While QALY is an important measure to evaluate the quality and quantity of life lived, ReQOL is a patient-reported outcome that captures mental health conditions.[21] ReQOL is rapidly gaining popularity in mental health disorder interventions, but little is known about the ReQOL gained by opioid-dependent patients. Future research can be directed towards learning more about opioid-dependent patients' mental health status in terms of ReQOL gained from each treatment intervention. The number of overdoses

averted is also a crucial success indicator of OUD treatment. The number of overdoses averted and the associated cost with each treatment strategy needs to be researched.

A broader cost-effectiveness investigation from a societal perspective will expand lofexidine, XR-NTX, and XR-BUP's breadth and scope in reducing the economic burden of OUD. It is also important to undertake economic evaluations of several other latest OUD pharmacotherapies like buprenorphine and naltrexone implants to have a wider knowledge of suitable treatment options.

4.7 Conclusions

The thesis aims to shed light on patients' perceptions and experiences with pharmacotherapies for OUD treatment and on the cost-effectiveness of newer OUD pharmacotherapies versus the treatment as usual.

The narrative review reports both positive and negative aspects and experiences with the available OUD pharmacotherapies which contributed much to shaping patients' treatment decisions, lack of patient knowledge on the pharmacotherapies which leads to forming unrealistic treatment expectations, the preference of OAT by some patients, while some seeking opioid-free treatments, and highlights the significance of patient inclusive treatment plans and decisions. The cost-effectiveness analysis predicts increased effectiveness with detoxification by methadone-lofexidine and buprenorphine-naloxone maintenance relative to usual treatment with buprenorphine-naloxone detoxification and maintenance. However, the treatment does not appear to be cost-effective using generally

accepted value thresholds for QALYs due to the high cost of lofexidine. The strategy is more effective in keeping patients in treatment and opioid-free longer than usual treatment. Of the long-acting formulations, detoxification with methadone-lofexidine with subsequent XR-NTX maintenance is predicted to provide higher effectiveness relative to detoxification with buprenorphine-naloxone and XR-BUP maintenance at a cost well exceeding the defined willingness-to-pay threshold. In conclusion, comparing the five treatment strategies (including no-treatment), usual treatment with buprenorphine-naloxone (detoxification and maintenance) appears to be the most cost-effective treatment option.

Overall, the results of the thesis suggest that it is critical for interventionists to take a contextual approach that considers patients' perceptions of the treatment, prior or current experiences with the treatment, and costs of the treatment. While knowledge of patients' treatment perceptions and experiences helps to predict patients' responses to the different treatment options and thus choose the optimum treatment strategy based on patients' needs and preferences, information of cost-effectiveness may be discussed among patients and clinicians so that they are well aware of the treatment cost that best complement their treatment choices.

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Appendix I Review of Existing Research on Cost-Effectiveness of OUD Pharmacotherapeutics

Study	Cost year/ Currency/ Country	Type of evaluation	Perspective	Treatments evaluated	Time horizon	Study Design	Effectiveness Measure	WTP Threshold	Findings
OUD Maintenance Treatment									
Bansback et al. (2018)[1]	2015 (USD, $), Canada	CUA	Societal	Hydromorphone & diacetylmorphine vs MET	Lifetime	Markov Model	Cost/QALY gained	Not defined	MET was dominated by hydromorphone & diacetylmorphine; ICER, hydromorphone vs. diacetylmorphine: $6.7 million/QALY gained
Barocas et al. (2019)[2]	2017 (USD, $), USA	CEA	Healthcare system	Standard HIV care with onsite HCV and BUP-NX treatment (integrated care) vs. standard HIV care with onsite HCV treatment and referral to offsite OUD care (status quo)	Lifetime	Monte Carlo microsimulation	Cost/QALY, reinfection, cirrhosis & liver-related deaths averted	$100,000/QALY gained	Integrated care ICER: $57,100/ QALY relative to status quo
Byford et al. (2013)[3]	2007/08 (GBP £), UK	CUA	NHS/PSS, criminal justice & societal	Supervised injectable heroin and injectable methadone vs. oral MET	26 weeks	Randomized controlled trial	Cost/QALY gained	£30,000/QALY gained	Injectable heroin and injectable methadone were dominant relative to oral MET
Carter et al. (2017)[4]	2016 (USD, $), USA	CUA	Societal	BUP implant vs sublingual BUP	1 year	Markov Model	Cost/QALY gained	$50,000/QALY	BUP implant was cost-saving (-$4,386) and generated greater

Study	Cost year/ Currency/ Country	Type of evaluation	Perspective	Treatments evaluated	Time horizon	Study Design	Effectiveness Measure	WTP Threshold	Findings
									QALYs (0.031) relative to BUP
Dijkgraaf et al. (2005)[5]	2001 (Euro, €) Netherlands	CUA	Societal	Co-prescription of heroin & MET vs MET alone	1 year	Randomized controlled trial	Cost/QALY gained	€50,000/QALY gained	Co-prescription yield 0.058 more QALYs and a mean cost saving of €12,793/patient/ year relative to MET.
Doran et al. (2003)[6]	1998-1999 (USD, $) Australia	CEA	Treatment provider	BMT vs MMT	6 months	Randomized controlled trial	Cost/heroin free day gained	Not defined	MMT dominated BMT
Extended-Release Opioid Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder: Effectiveness and Value (2018)[7]	2018 (USD, $), USA	CEA	Societal	XR-BUP, BUP implant, CAM2038, XR-NTX vs. sublingual BUP-NX		Hybrid Decision-Tree/Markov Model	Cost/QALY & cost/LY gained	$50,000/QALY, $100,000/QALY & $150,000/QALY	XR-BUP & XR-NTX are dominated by BUP-NX; CAM2038 yields greater QALYS than BUP-NX but ICER not calculated; ICER of BUP implant: $265,000/QALY gained relative to BUP-NX
Gisev et al. (2015)[8]	2012 (AUD $), Australia	CUA	Healthcare provider & criminal justice system	OAT vs. to no OAT at prison release	6 months	Population-based, data linkage	Cost/life-year saved	$25,000/life year saved	OAT post-release was dominant relative to not OAT

Study	Cost year/ Currency/ Country	Type of evaluation	Perspective	Treatments evaluated	Time horizon	Study Design	Effectiveness Measure	WTP Threshold	Findings
Idrisov et al. (2017)[9]	2015 (USD, $), Russia	CEA	Healthcare system	MMT vs. current treatment policy with no MMT	10 years	Population-based data	Cost/DALY averted	< 3x the per-capita gross domestic product (GDP)	$343/ 50,0000 DALY averted with nationwide MMT program
Jackson et al. (2015)[10]	Year not mentioned (USD, $), USA	CEA	State health program	XR-NTX, MMT & BMT	6 months	Markov Model	Cost/opioid-free day gained	Not defined	BMT is dominated by MMT; ICER of XR-NTX relative to MMT: $72/opioid-free day gained
Kenworthy et al. (2016)[11]	2016 (GBP £), UK	CUA	UK National Health Service (NHS)/ Personal Social Service (PSS) & societal	BMT, MMT vs. no treatment	1 year	Decision Tree	Cost/QALY gained	£30,000/ QALY	**ICER vs. no OAT** ***NHS:*** BMT: £13,923/QALY MMT: £14,206/QALY ***Societal:*** BMT and MMT: Dominant
King et al. (2016)[12]	2014 (USD, $), USA	CEA	Third-party payer	Clinic based MMT vs. office-based BMT	1 year	Markov Model	Cost/patient retained in treatment & cost/opioid abuse–free week gained	$14,000/ patient retained in treatment	MMT is cost-effective relative to BMT; ICER: $10,437/ additional patient retained, $8,515/opioid abuse–free week gained
Murphy et al. (2017)[13]	2014 (USD, $), USA	CEA	Taxpayer	XR-NTX vs. treatment as usual (TAU)	25- & 78-weeks	Randomized controlled trial	Cost/QALY gained and cost/abstinent year	$100,000/QALY, $200,000/QALY, $300,000/QALY &	XR-NTX vs. TAU **QALY**

Study	Cost year/ Currency/ Country	Type of evaluation	Perspective	Treatments evaluated	Time horizon	Study Design	Effectiveness Measure	WTP Threshold	Findings
								$400,000/QALY gained	25 weeks: 162,150/QALY gained 78 weeks: 76 400/QALY gained **Abstinent year** 25 weeks: 46,329/abstinent year 78 weeks: 16,371/abstinent year
Murphy et al. (2019)[14]	2016 (USD, $), USA	CEA	Health care system and societal	XR-NTX vs. BUP	24- & 36-weeks	Randomized controlled trial	Cost/QALY gained and cost/abstinent year	$100,000/QALY	XR-NTX vs. BUP-NX **QALY:** XR-NTX is dominated by BUP-NX at 24 & 36 weeks **Abstinent year:** XR-NTX is dominated by BUP-NX at 24 & 36 weeks
Nosyk et al. (2012)[15]	2009 (CAD, CA$), Canada	CUA	Societal	Diacetylmorphine vs MET	1-, 5-, 10-years & lifetime	Semi-Markov Model	Cost/QALY gained	$100,000/QALY	Diacetylmorphine was the dominant strategy in all time horizons.
Schackman et al. (2011)[16]	2010 (USD $), USA	CUA	Healthcare provider & patient	Long-term office based BUP-NX vs. no treatment	2 years	Markov Model	Cost/QALY gained	$100,000/QALY	BUP-NX: $35,100/QALY
Stephen et al. (2011)[17]	2011 (USD, $),	CUA	Societal	Deep brain stimulation	6 months	Decision Tree	Cost/QALY gained	$100,000/QALY	DBS costs less than no treatment

Study	Cost year/ Currency/ Country	Type of evaluation	Perspective	Treatments evaluated	Time horizon	Study Design	Effectiveness Measure	WTP Threshold	Findings
	USA			(DBS) vs. MMT and no treatment					but costs more than MMT; it would need a success rate of at least 49% to be cost-effective relative to MMT.
Vuong et al. (2016)[18]	2013 (USD, $), Vietnam	CEA	Treatment provider & patient	MMT vs compulsory drug rehabilitation (CCT)	3 years	Retrospective and prospective, non-randomized cohort comparison	Cost/ drug-free days	Not defined	MMT is the dominant strategy
OUD Detoxification Treatment									
Maas et al. (2013)[19]	2010-2011 (GBP £), UK	CEA	Drug treatment clinic	MET vs BUP for detoxification	6 months	Empirical	Cost/patient retained in treatment for six months & cost/abstinent patient	Not defined	MET dominated BUP treatment program in terms of cost/patient retained. BUP is cost-effective relative to MET for the outcome cost/abstinent patient (ICER: £903/patient)
Masson et al. (2004)[20]	Year not mentioned (USD, $), USA	CEA	Healthcare system	MMT vs. 180 days MET detoxification	10 years	Markov Model	Cost/Life year (LY) gained & cost/ QALY gained	$50,000/LY& $50,000/QALY gained	MMT vs. detoxification ICER: $16,967/LY gained; $ $6, 271-$19 997/QALY gained
Polsky et al. (2010)[21]	2006 (USD, $), USA	CEA	Healthcare system	12 weeks buprenorphine-naloxone	1 year	Empirical	Cost/QALY gained	$100,000/QALY gained	ICER of BUP-NX relative to detox:

Study	Cost year/ Currency/ Country	Type of evaluation	Perspective	Treatments evaluated	Time horizon	Study Design	Effectiveness Measure	WTP Threshold	Findings
				treatment versus 14 day BUP-NX detoxification					$25,049/QALY gained
Premkumar et al. (2019)[22]	2017 (USD, $) USA	CUA	Health care payor	MET, BUP vs detoxification	16 weeks	Hybrid Decision Tree/Markov Model	Cost/QALY gained	$100,000/QALY gained	MET & detoxification were dominated by BUP
Shanahan et al. (2006)[23]	1999 (AUD, $), Australia	CEA	Treatment provider	Rapid detoxification under anaesthesia (RODA), rapid opioid detoxification under sedation (RODS), conventional inpatient (CI) detoxification with clonidine and other symptomatic medications, and outpatient detoxification using buprenorphine vs. conventional outpatient (CO) detoxification using clonidine and other symptomatic medications		Quasi-experiment cohort study	Cost/abstinent patient & cost/patient entering post-detoxification pharmacotherapy	Not stated	Buprenorphine-based outpatient detoxification method was the cost-effective treatment among all strategies

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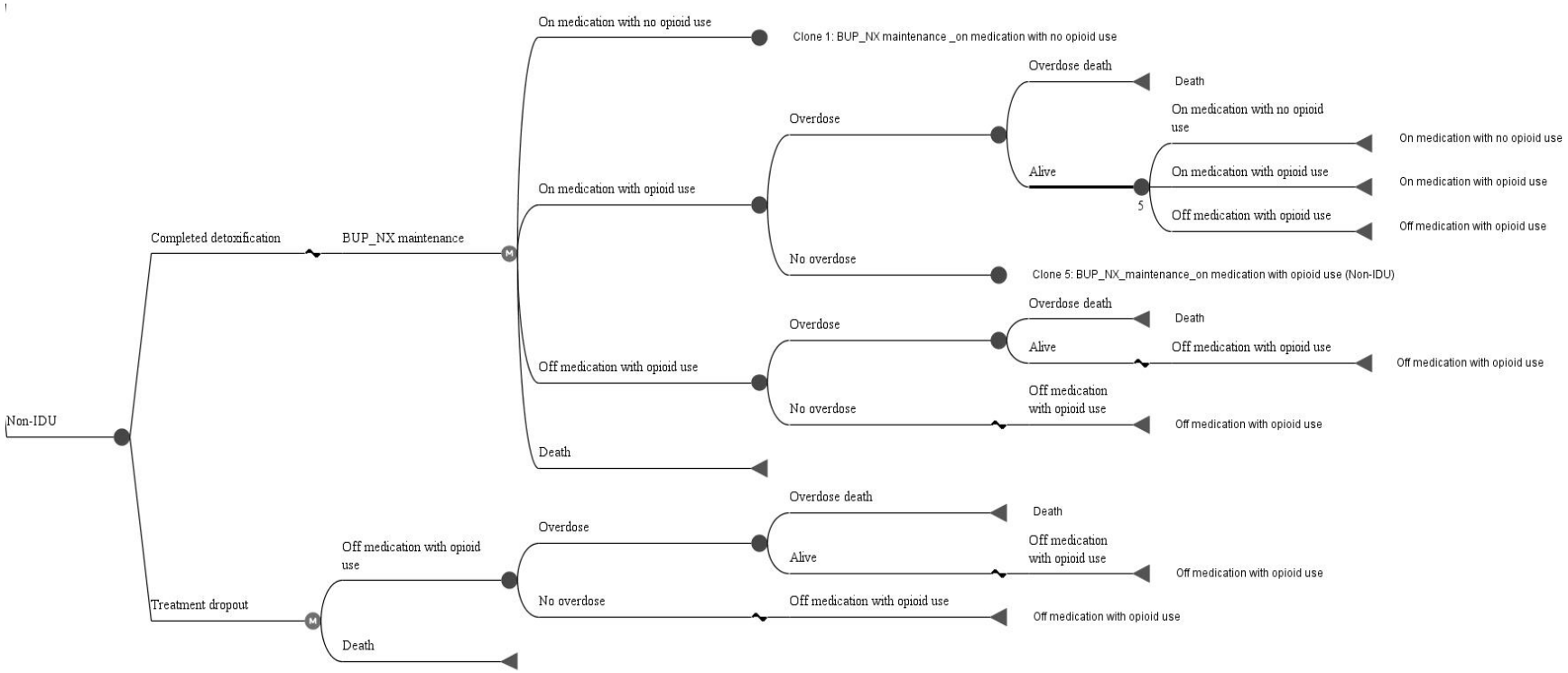
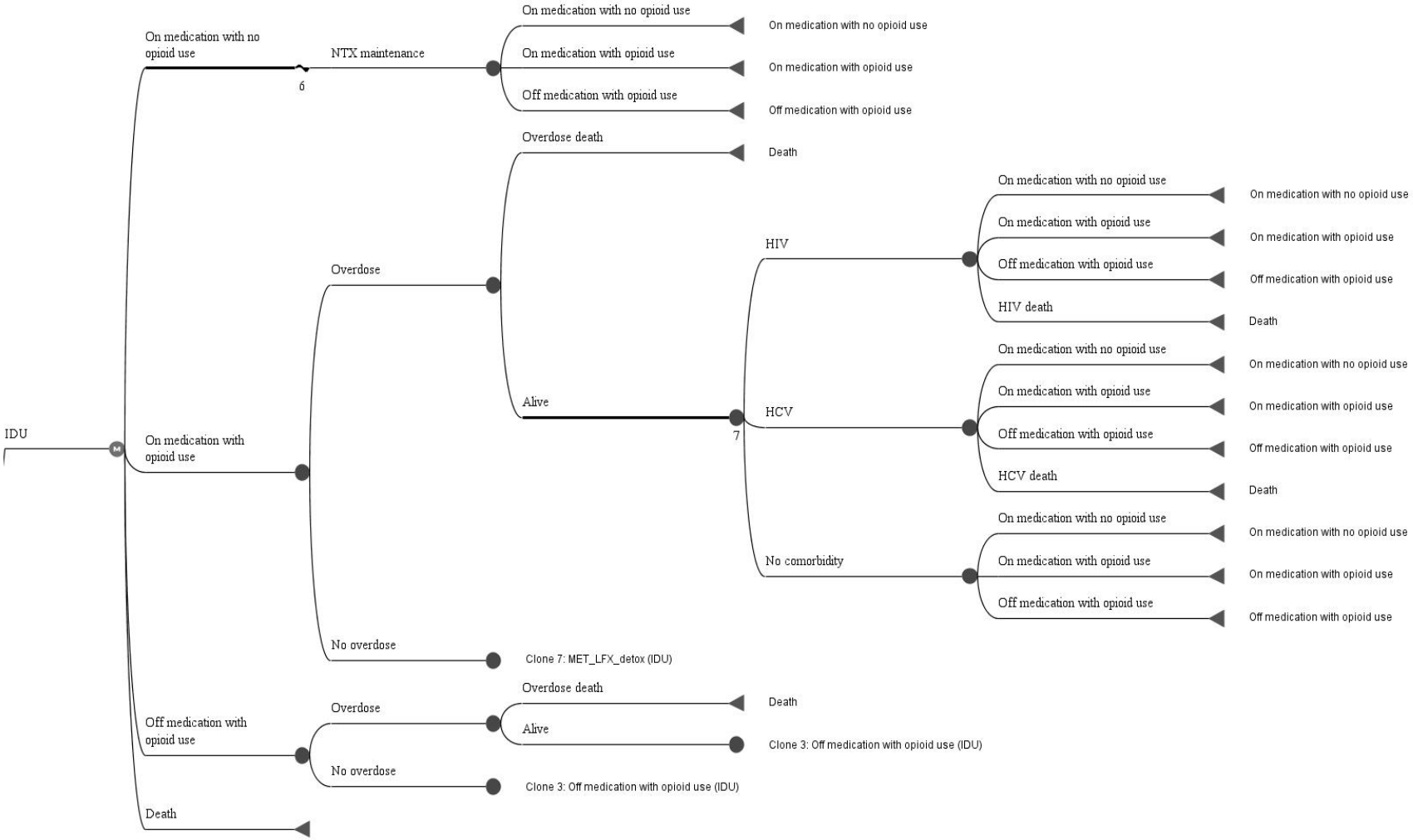
Appendix IIII Clinical pathways with the OUD pharmacotherapies

1) Strategy A (Methadone-lofexidine detoxification and buprenorphine-naloxone maintenance): Injection drug users (IDU)

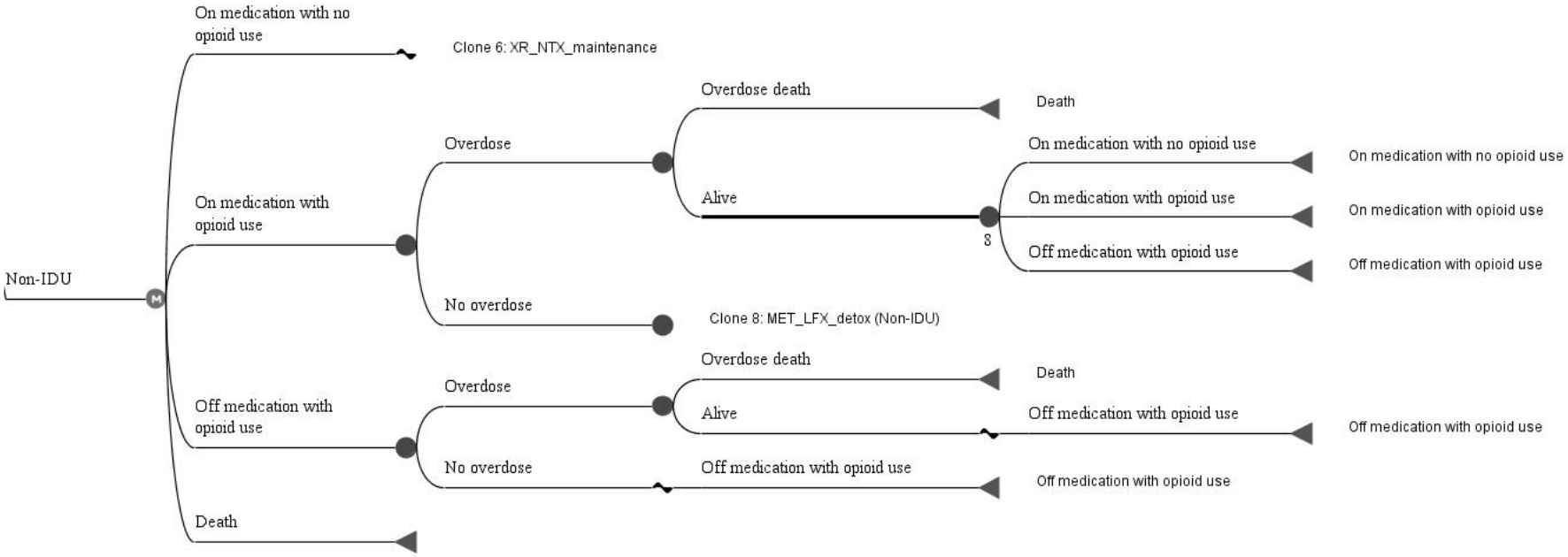
1) Strategy A (Methadone-lofexidine detoxification and buprenorphine-naloxone maintenance): Non-Injection drug users (Non-IDU)



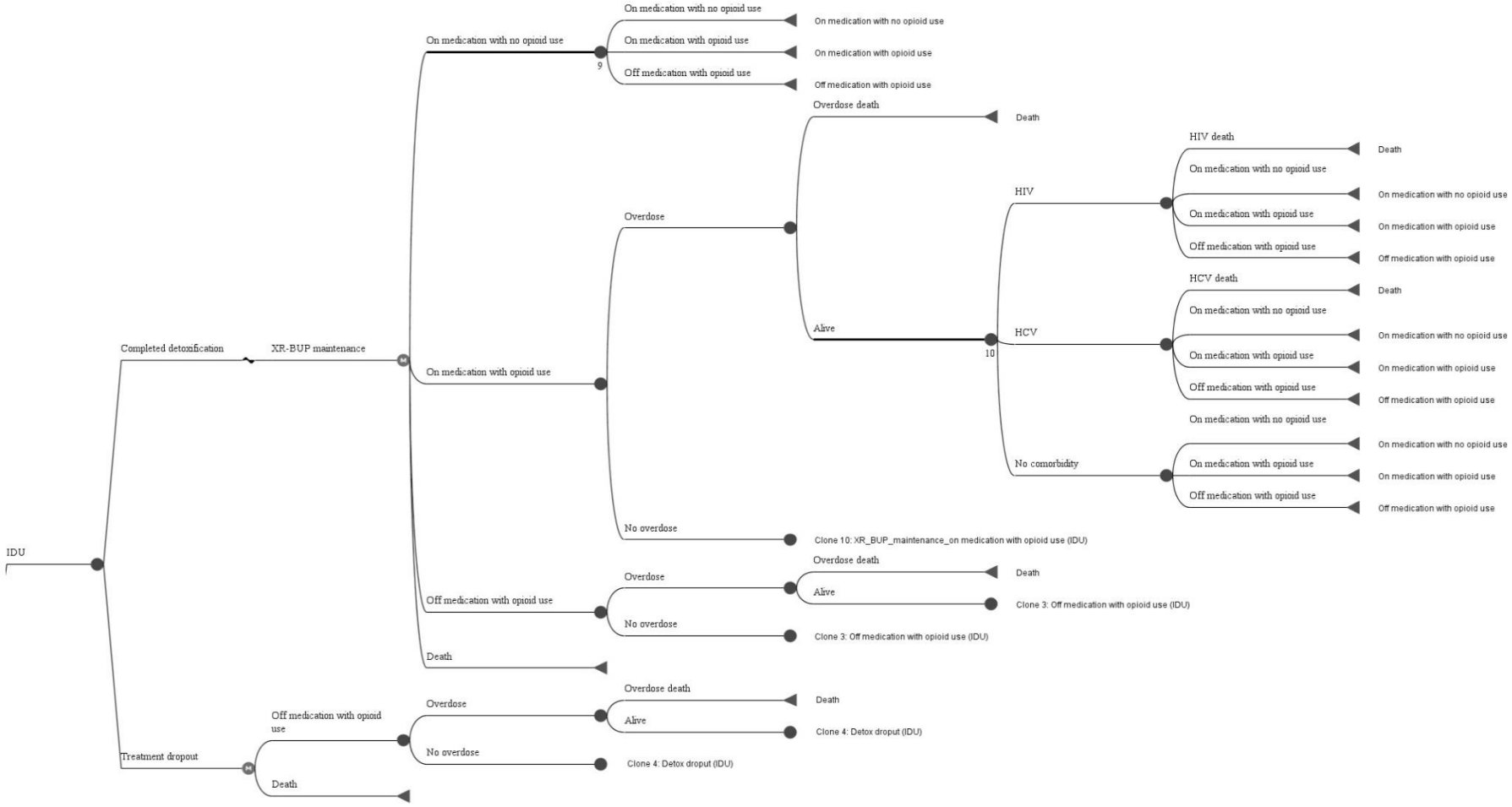
2) Strategy B (Methadone-lofexidine detoxification and extended-release naltrexone maintenance): Injection drug users (IDU)



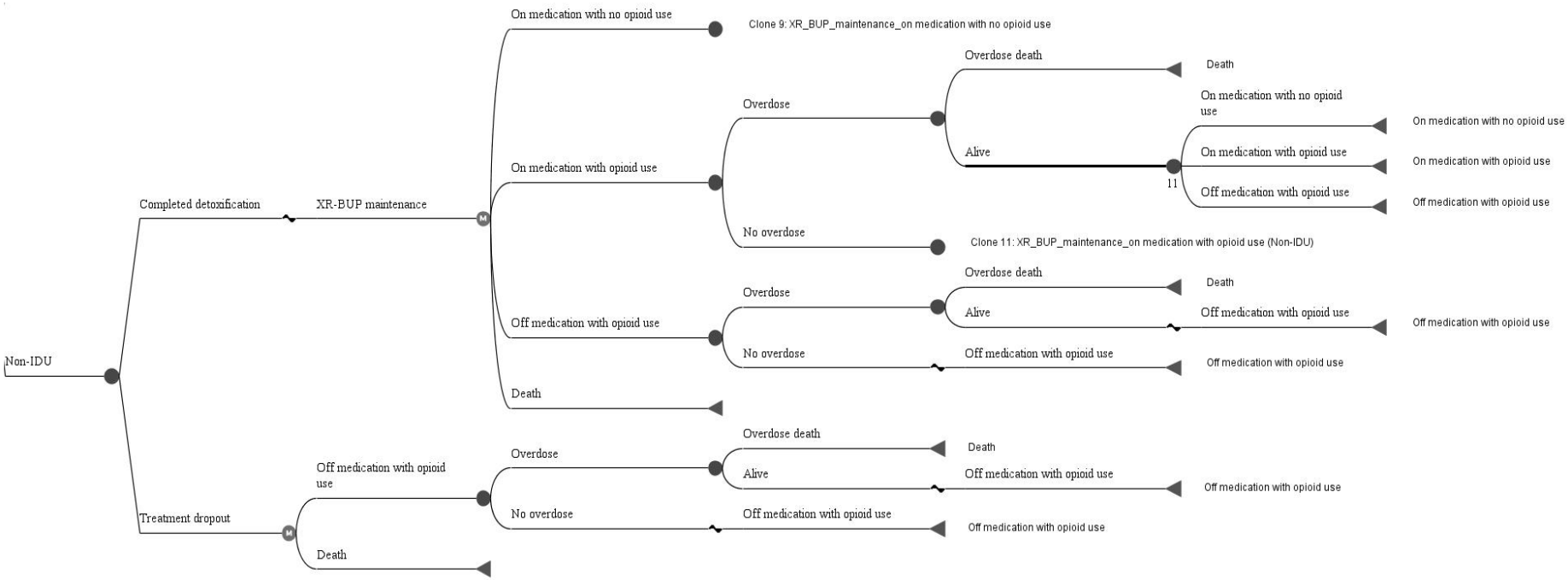
2) Strategy B (Methadone-lofexidine detoxification and extended-release naltrexone maintenance): Non-Injection drug users (Non-IDU)



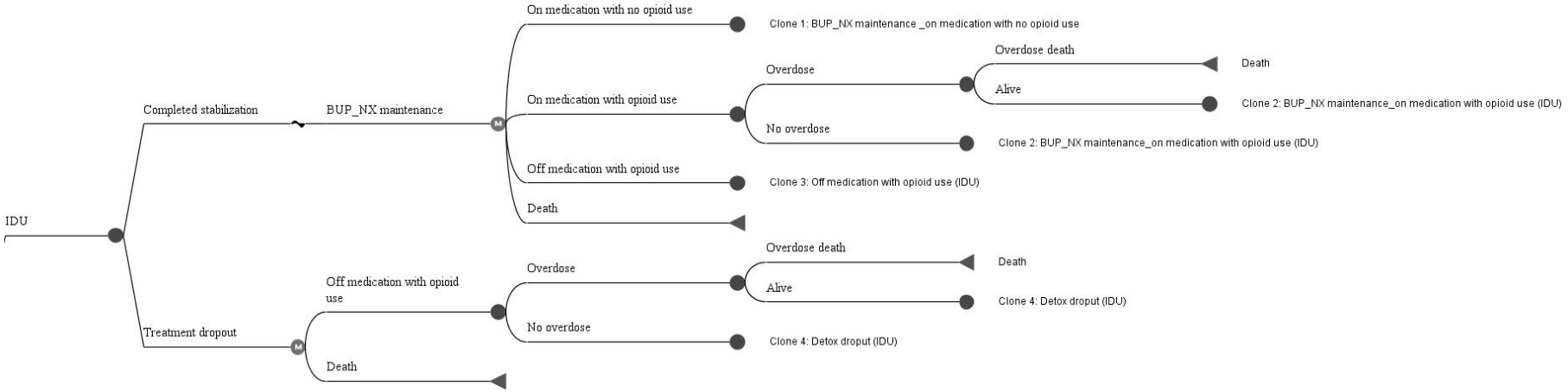
3) Strategy C (Buprenorphine-naloxone detoxification and extended-release buprenorphine maintenance): Injection drug users (IDU)



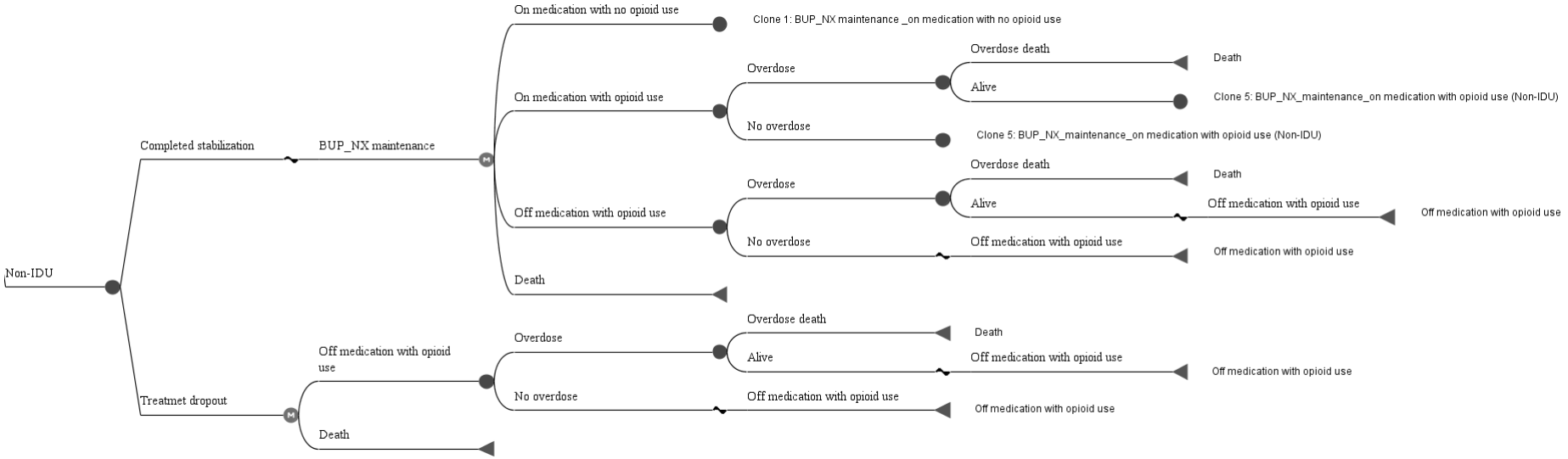
Strategy C (Buprenorphine-naloxone detoxification and extended-release buprenorphine maintenance): Non-Injection drug users (Non-IDU)



4) Strategy D (Buprenorphine-naloxone detoxification and maintenance): Injection drug users (IDU)



Strategy D (Buprenophine-naloxone detoxification and maintenance): Non-Injection drug users (Non-IDU)



5) Strategy E (No treatment): Injection and non-injection drug users