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Stable housing with methadone maintenance therapy and motivational interviewing as a treatment for opioid use disorder

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STABLE HOUSING WITH METHADONE MAINTENANCE THERAPY AND MOTIVATIONAL INTERVIEWING AS A TREATMENT FOR OPIOID USE DISORDER

by

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ABSTRACT

Opioid use disorder (OUD) is a chronic relapsing condition associated with significant patient morbidity and mortality. Patients suffering from OUD have an increased risk of death from suicide, HIV, infectious disease, and trauma, among other causes. Patients suffering from OUD often manage various comorbid psychiatric illnesses and homelessness. From 1999 to 2017, an estimated 400,000 people died from prescription opioid related overdoses. In 2014, there were 28,647 opioid related overdose deaths in the United States.

The current standard of care for treatment of OUD is an opioid receptor agonist methadone or buprenorphine combined with a psychosocial intervention, like cognitive behavioral therapy (CBT), contingency management (CM), or motivational interviewing (MI). MI has proven to be effective in treating OUD when combined with methadone and buprenorphine.

Other studies have found increased rates of opioid abstinence when study subjects were provided recovery housing contingent on urine that was free of opioids and other substances (CM). Among patients with a history of incarceration and co-morbid OUD, stable housing in some form -- private residence or living with a friend or family -- has

been found to be effective in reducing opioid use when compared to homelessness as a control, suggesting homelessness confers a higher risk of opioid use.

This prospective observational study aims to evaluate the effect of stable housing on opioid use disorder treatment and recovery. Study subjects will be Boston area residents who are prescribed methadone. Investigators will follow study subjects over six months while they attend weekly motivational interviewing sessions as part of their treatment regime and attend methadone clinics as usual. Once per week, study subjects will submit urine samples to study affiliated Medical Assistants (MA). Urine samples will be sent to LabCorp for toxicology analysis.

At the conclusion of the study, investigators will examine which patients had longer time to relapse based on their housing status. We hypothesize that subjects with stable housing will have longer abstinence, as measured by urine toxicology, than subjects without stable housing.

Positive findings could be used to help influence policy makers and federal and state legislation to promote stable housing for patients recovering from OUD.

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LIST OF ABBREVIATIONS

AA—Alcoholics Anonymous

AAP—American Academy of Pediatrics

ACOG—American College of Obstetricians and Gynecologists

aOR—Adjusted Odds Ratio

ASAM—American Society of Addiction Medicine

BUMC—Boston University Medical Center

cAMP—Cyclic Adenosine Monophosphate

CBT—Cognitive Behavioral Therapy

CDC—Center for Disease Control

CM—Contingency Management

CNS—Central Nervous System

COX-2—Cyclooxygenase-2

DSM—Diagnostic and Statistical Manual

ED—Emergency Department

FDA—Food and Drug Administration

GABA—Gamma aminobutyric acid

JAMA—Journal of the American Medical Association

MI—Motivational Interviewing

MMT—Methadone Maintenance Therapy

NA—Narcotics Anonymous

NAS—Neonatal Abstinence Syndrome

NEJM——New England Journal of Medicine

NIH——National Institute of Health

OBAT——Office Based Addiction Therapy

OUD——Opioid Use Disorder

PNS——Peripheral Nervous System

RBT——Reinforcement Based Therapy

RH——Recovery Housing

SUD——Substance Use Disorder

CHAPTER ONE

Introduction

Opioids are partial or fully synthetic analogues of naturally occurring opiate products derived from *Papaver somniferum*, commonly known as the opium poppy. Opium, codeine, and morphine are well known examples of opiates, while hydrocodone, hydromorphone and fentanyl are examples of partial or fully synthetic opioids.[1,2]

Opioids are widely prescribed for pain, gut motility, and cough suppression. Opioids have been used globally for their analgesic, euphoric, and central nervous system (CNS) altering effects. Repeated or chronic opioid use induces changes in neuronal circuitry and can lead to a drug-dependent state.[85]

Patients with opioid use disorder (OUD) often go through periods of successful abstinence.[1] OUD is often characterized as a chronic, relapsing condition associated with high patient morbidity and mortality.[3] A 2016 review of OUD concluded that the risk of premature death from suicide, HIV, other infectious disease, trauma, or accidental overdose is 20-fold greater in patients with OUD.[1] Opioid receptor modulators like naltrexone, methadone, and buprenorphine have been widely studied and are effective in the treatment of OUD.[18]

Opium in some form has been used for chronic and acute pain for thousands of years.[2] In 1806 the first opioid drugs were produced after isolation of morphine alkaloid. Opium use began in the 1800s as treatment for “travails” and “boredom”.[2] In 1889, James Adams, a Boston physician, described opium as superior to other

remedies at the time but particularly harmful if misused.[87] After advocacy from Adams and like-minded physicians, a change in prescription practice occurred, leading to a more restrained approach to opioid use.[87]

Limited oversight prior to 1914 allowed physicians to freely prescribe opioids for pain, cough, anxiety, and diarrhea.[86] In the early 1900s, use of opium or its derivatives and cocaine was rampant throughout the United States.[88] The Harrison Anti-Narcotic Control Act of 1914 made writing prescriptions for opioids an ability limited to physicians, dentists, and veterinarians.[6,88] In 1973, physicians at the National Institute of Health (NIH) described a "failure to treat" patients with severe pain with adequate opioid analgesics.[6] A 1980 landmark study in the New England Journal of Medicine (NEJM) concluded that the development of addiction in hospitalized patients was rare in those with no addiction history.[7] Later, a widely cited 1986 article in the journal Pain described treatment successes in cancer pain with opioid analgesics.[8]

Later, ubiquitously prescribed extended release opioid agonist OxyContin was introduced and marketed to medical organizations, lawmakers, and physicians as non-habit forming medication for pain control.[9] Off-label use of the fentanyl lollipop, Actiq[10], pharmaceutical kickback schemes with a fentanyl sublingual spray, Subsys[11], and lucrative speaking and lobbying fees for physicians further contributed to the propagation of the opioid use epidemic in the 1990s and early 2000s.[12,13]

In 2001, the Joint Commission called on providers to assess pain as "the fifth vital sign" in an attempt to address the underassessment and treatment of pain.

Framing pain within the vital sign structure drew attention to it and led to increased assessment by nursing and ancillary staff.[14] In an attempt to eradicate pain, especially post-operative pain, some hospitals began to use sliding scales for administration of pain medications, including opioids.[14]

Today, OUD is a major public health issue. From 1999 to 2017, an estimated 400,000 people died from overdose involving prescription opioid misuse.[15] Deaths from drug overdoses nearly tripled from 1999-2014 (Figure 1.). Among 47,055 drug overdose deaths that occurred in 2014 in the United States, 28,647 (60.9%) involved an opioid.[3] Prescription opioids remain a primary driver of opioid-related fatalities.[4] The rise of OUD is multifactorial. Opioid based approaches to pain control, limited drug treatments, and eroding economic opportunities have contributed to the epidemic.[5]

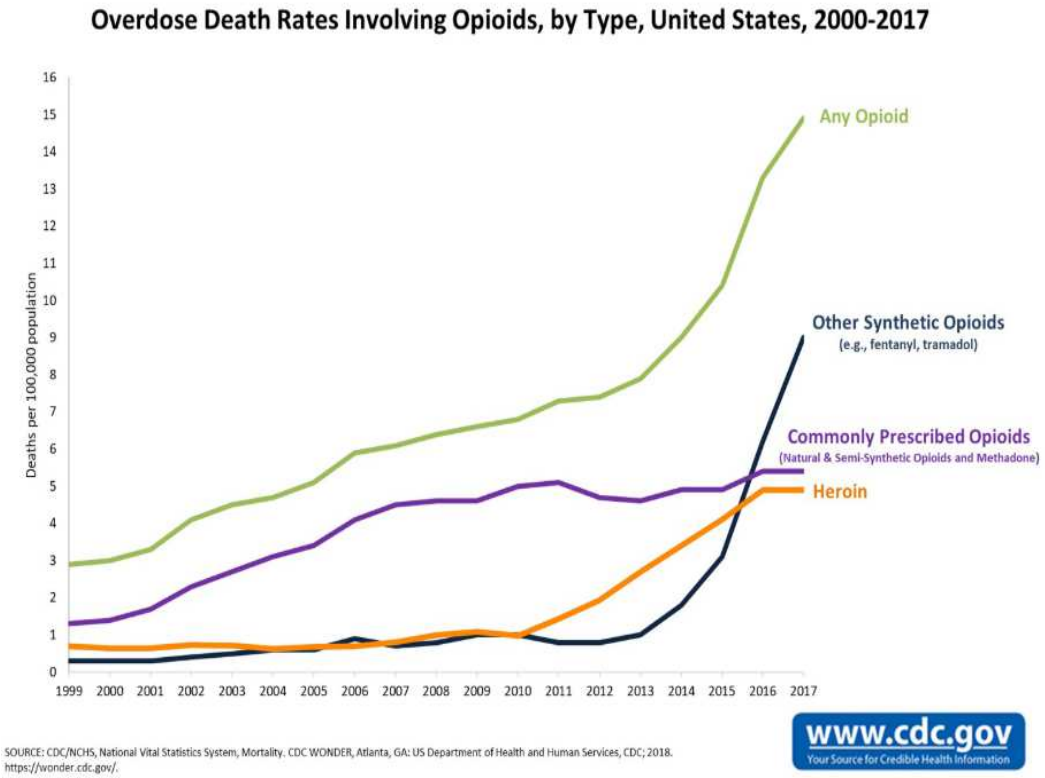

Figure 1. Overdose Death Rates Involving Opioids by Type in the US 2000-2017. Obtained from CDC.gov, A graph of the rate of overdose death rates involving an opioid from 2000-2017. The graph separates incidence of death per opioid involved.

The opioid use epidemic is separated into three stages.[9] Stage one began in the late 1990s and early 2000s with a greater availability and distribution of OxyContin, extended release oxycodone. Patient privacy laws and lack of a formal prescription tracking structure made diversion possible.[9] Stage two began in the early 2010s as updated prescription guidelines made obtaining OxyContin more difficult.[9] Some patients switched to heroin because it was affordable and easier to obtain.[9] Around 2013, the opioid use paradigm shifted a third time. Illicit substance manufacturers began including fentanyl into counterfeit heroin, Norco (hydrocodone), Percocet

(oxycodone-acetaminophen), and the benzodiazepine Xanax (alprazolam).[104] Fentanyl-laced marijuana has also been reported.[103] Fentanyl is a cheap, fully synthetic opioid, 50 to 100 times more potent than morphine.[38] Overdoses from fentanyl, heroin and combinations increased 88% per year from 2013-2016.[9] Poverty and substance use disorders operate synergistically and can be reinforced by psychiatric disorders and social determinants of health like unstable housing.[16] In 2018, investigators at the U.S. Department of Health and Human services concluded that high rates of poverty and unemployment were associated with increased rates of retail opioids sales, utilization, prescription, opioid-related hospitalizations and drug overdose deaths.[111] Additionally, investigators found that, among the counties studied, the ones with worse economic prospects had higher rates of opioid use and other substance use.[111] Psychiatric and other substance use disorders (SUD) are highly comorbid with OUD. Kessler, et al, showed that 27% of patients with a DSM-IV diagnosis of OUD had at least one other psychiatric disorder. Among the 27% of patients with OUD and another psychiatric disorder, 45% of them had two or more.[49] In Massachusetts, overdose -- primarily from opioids -- is the leading cause of death among patients suffering from homelessness.[53]

Statement of the Problem

Opioid agonist therapies like methadone and buprenorphine in combination with psychosocial therapies are effective in the treatment of OUD.[18] Despite effective medication and psychosocial therapies, the OUD epidemic persists. Patients suffering

from OUD experience periods of exacerbation and remission and are vulnerable to relapse.[18] Often social, financial, psychological, and medical issues are intertwined when treating OUD.

The majority of studies on the treatment of OUD have focused on opioid receptor based therapies like methadone and buprenorphine combined with psychosocial therapies. There have been minimal studies on the impacts of social determinants of health – specifically housing and societal integration in OUD. The rise in use of prescription opioid analgesics, ease of access to heroin, fentanyl, and the incidence of opioid use and overdose makes OUD treatment and optimization absolutely paramount.[22]

Hypothesis

Stably housed patients receiving an opioid receptor agonist plus psychosocial therapy for OUD will remain abstinent for longer than unstably housed patients.

Objectives and specific aims

This thesis proposes a prospective observational cohort study of patients with a DSM-V diagnosis of OUD receiving methadone maintenance therapy (MMT). Patients with OUD will be recruited from five methadone clinics in Boston and grouped based on their housing status. Patients will be categorized into four groups: stably housed throughout the study; initially stably housed and transitioned to

unstably housed; initially unstably housed and transitioned to stably housed; and unstably housed throughout the study.

The primary objective is to compare the ratio of abstinent patients at one-, three, and six-month time points between housing groups. The secondary objective will be to measure the mean time to relapse of opioid use between the housing groups. Another secondary objective is to compare relapse of use of other substances beside opioids. Each patient will receive their regular dose of methadone along with weekly one-hour motivational interviewing session (MI) with a social worker. Motivational interviewing, is a communication technique that--through empathetic, non-judgmental, and supportive language--addresses patient ambivalence towards addictive behavior.

Clinical end points of the study will be relapse of opioid use. A secondary outcome will be use of substances other than opioids such as cocaine. Specifically, this study will determine whether:

- Among patients receiving MMT and MI, there is a difference in frequency of relapse and time to relapse of opioids in the four housing groups.
- Among patients receiving MMT and MI, patients with stable housing throughout the study have a lower incidence of and longer time to relapse than patients that are initially stably housed but lose housing, initially unstably house and gain housing, or unstably housed patients.

CHAPTER TWO

Opiate Use Epidemiology

Opiate Use Disorder (OUD) is a global issue associated with staggering rates of mortality and morbidity and has impacted society globally and economic welfare.[19,20] OUD occurs in people from all educational and socioeconomic backgrounds.[1] In 2013, prescription opioid misuse cost the United States $78.5 billion when factoring in health care costs, treatments, and criminal justice costs.[21] Opioids, mainly synthetic opioids, other than methadone are currently the main driver of drug overdose deaths.[1]

According to the U.S. Centers for Disease Control (CDC) opioid use has reached epidemic levels, which they define as an increase, often sudden, in the number of cases of a disease above what is normally expected in a particular area.[23]

In 2017, 70,237 drug overdose deaths occurred in the U.S.[15], 67.8% of which involved an opioid and 45.2% of which involved a synthetic opioid.[15,24]

Drug overdose deaths involving natural and synthetic opioids, increased six-fold since 1999.[24] There has been a dramatic rise in deaths as a result of synthetic opioids like fentanyl, and tramadol (Figure 1). In 2015, an estimated 5.1 million Americans had used heroin at some point in their lives.[3] The age-adjusted rate of overall drug overdose deaths increased by 9.6% from 2016 (19.8 per 100,000) to 2017 (21.7 per 100,000).[25]

In 2016, opioid related deaths were highest among people aged 25-34 (34.6 per 100,000) (Figure 1) The rate of drug overdose deaths involving synthetic opioids other than methadone increased from 0.3/100,000 in 1999, to 1.0 in 2013, 1.8 in 2014, 3.1 in

2015, and 6.2 in 2016.[26] Synthetic opioid related overdose deaths increased an average of 18% per year from 1999-2006, did not statistically change from 2006-2013, then increased markedly to 88% per year from 2013-2016.[26]

Diagnosis of Opioid Use Disorder

Diagnosis of OUD is made clinically. Diagnostic criteria is made through the Diagnostic and Statistical Manual (DSM) of Mental Disorders and has been adopted by the American Society of Addiction Medicine (ASAM) and the CDC.

Mild OUD is described as two or three behaviors out of eleven listed by the DSM as behavior concerning for OUD. Moderate and severe OUD follow with four to five behaviors, and more than six behaviors over a 12 month periods.

The complete list of DSM classified behaviors concerning for OUD can be found Appendix 1.

Opiate Mechanism of Action

Opioid receptors -- Mu, Kappa, and Delta -- are located throughout the central nervous system (CNS). They influence pain and pleasure perception, emotion, respiratory depression, and overall well-being.[28] Mu, Kappa and Delta opioid receptors are coupled to G proteins. Upon binding of an opioid to Mu, Kappa, or Delta receptors, the associated G proteins trigger a signaling cascade, leading to feelings of euphoria, analgesia, and CNS depression.[29] Opioids also bind to CNS dopamine, gamma-aminobutyric acid (GABA), and glutamate. Mu receptor activation leads to depression of secondary protein messengers

such as cyclic adenosine monophosphate (cAMP). Chronic opioid receptor activation leads to chronic upregulation of cAMP and changes in gene expression.[29]

Chronic opioid receptor stimulation and upregulation of cAMP is thought to lead to the physical symptoms of withdrawal.[30] Symptoms of withdrawal from opioids include[1] diarrhea, dilated pupils, generalized pain, restlessness and anxiety, lacrimation, rhinorrhea, and pilo-erection.

Clinical manifestations of opioid receptor activation depend on receptor location in the CNS. Frequency of activation and duration of activation play a role in clinical manifestations or withdrawal. Peripheral nervous system (PNS) Mu receptor activation in the bronchioles and intestines can lead to cough suppression and opiate induced constipation, respectively.[29] Reward center activation and rapid delivery make opioids easily addictive.[28]

Research into neural connectivity regulating addiction, binge/intoxication, cravings, and withdrawal reveals that the process of addiction involves overlapping networks. Positive reinforcement of the mesolimbic reward circuitry is thought to be responsible for learning associations between substance use and relief of undesirable states or situations.[90]

Clinical Manifestations of Opiate Use Disorder

Patients suffering from OUD present in a clinical spectrum depending on the length of dependence, severity and abstinence and include – acute intoxication, opioid withdrawal, or minimal symptoms. Acutely intoxicated patients may present with slurred

speech, sedation with head nodding, miotic pupils, decreased respiratory rate, decreased tidal volume, decreased bowel sounds, and fresh injection sites.[29] Opioid overdose requires emergency medical treatment.[78] Severe opioid overdose is characterized by respiratory depression and requires emergency naloxone to reverse symptoms.[31]

Long-term opioid use can lead to rapid development of opioid analgesia tolerance.[91] User tolerance to opioid induced nausea and respiratory depression develops slowly.[91] Patients with opioid tolerance will require increased dosing to achieve desired analgesic and euphoric effects.[1] Patients who resume opioid use from a period of abstinence have reduced tolerance and are prone to respiratory depression should they resume at a previously tolerated dose.

Opioid use, misuse, abuse, and dependence are important distinctions.[31] Opioid use encompasses use per prescription guidance, misuse, and use because of dependence. Misuse of opioids is defined as use beyond prescription guidance. Patients reporting misuse may obtain opioids from family members, seek opioids from multiple health care providers, and fill prescriptions from different pharmacies.[110] Patients with opioid dependence go through withdrawal without the substance.

Functional impairments develop with normal use or misuse of opioids.[31] Patients with moderate to severe OUD may have impaired social functioning. Patients with DSM-V diagnosed mild OUD are often able to maintain relationships and employment. Normal use of opioids may yield a diagnosis of mild OUD should the patient develop tolerance and withdrawal if the patient is not appropriately tapered off of opioids. The DSM-V

criteria for mild OUD requires just two points out of 11 so long as the patient displays a consistent pattern of use and functional impairment or distress over 12 months.

Prescription Pain Medication Misuse

In the 1990s extended release opioids, transdermal patches, nasal sprays, oral dissolving strips, and pain medication implant devices were developed and marketed, often illegally.[16]

OxyContin was marketed to medical organizations, lawmakers, and physicians as a non-habit-forming medication for pain control.[9]

Cephalon, the manufacturer of Actiq, an oral transmucosal fentanyl citrate[10], trained its sales staff to promote Actiq for use beyond its FDA approval. Actiq was approved by the FDA for treatment of refractory pain for opioid tolerant patients. Despite warnings from the FDA, Cephalon marketed Actiq as pain control for opioid naïve patients.[91] Cephalon paid a $425-million settlement to resolve the allegations in 2008.[91]

In 2012, Insys introduced Subsys, a sublingual fentanyl spray. Its FDA approval was for use in patients with persistent breakthrough pain, refractory to previous opioid therapy. From 2012 to 2015, Insys used speaker programs to raise brand awareness and provided lunches and dinners to practitioners prescribing Subsys. Insys paid kickbacks and bribes to increase prescriptions and dosages of Subsys.[92] Insys agreed to pay $225 million to resolve its illegal promotion of Subsys in 2019.[92]

Many patients with OUD were exposed to a prescription opioid like Actiq and Subsys prior to opioid misuse and seeking of ilicit opioids like heroin.[35] From 2013 to 2016, deaths from fentanyl and its analogs increased by 540% nationally.[16] Since 2013, illicit fentanyl has been included in formulations of cocaine and counterfeit Norco, Percocet, Xanax, heroin, and even marijuana, with or without the user's knowledge.[37,38] Fentanyl is 50 to 100 times[38] more potent than morphine.[38]

In the U.S., use of prescription opioids has been associated with a dramatic rise in overdose death and transition to other opiates and opioids.[39]

Opiate Use in Pregnancy

Prenatal exposure to opioids increases the risk of preterm labor, stillbirth, neonatal abstinence syndrome, and maternal mortality.[40] From 1999 to 2014, the prevalence of OUD among pregnant women increased from 1.5 to 6.5 cases per 1000 delivery hospitalizations.[40] This trend was found across all 50 states.[40]

Loss of custody of their children, among other consequences imposed on pregnant women for opioid use, may prevent many from seeking OUD treatment and prenatal care.[42]

Opioid detoxification in pregnancy is not recommended.[42,43] Maternal detox prior to delivery of the newborn does not reduce the incidence of neonatal abstinence syndrome (NAS).[105] Additionally, patients often relapse prior to the completion of detox[105] with continued use of intravenous opioids potentiating the risk of infectious disease transmission to the expecting mother or baby. Despite the stigma, methadone

maintenance therapy (MMT), however, minimizes risky behavior, reduces transmission of infectious disease, and reduces withdrawal.[44] The American College of Obstetricians and Gynecologists (ACOG) recommends methadone or buprenorphine as optimal treatments for OUD in pregnancy.[105]

Prenatal exposure to opioids including methadone and buprenorphine increases the risk for neonatal abstinence syndrome (NAS).[93] Infants with NAS are at risk for increased morbidity.[93] Symptoms of NAS include high-pitched crying, irritability, exaggerated reflexes, tremors, seizures, vomiting, loose stools, poor feeding, constant sucking, failure to thrive, diaphoresis, sneezing, temperature instability, nasal stuffiness, and yawning.[94] NAS screening should be completed on all infants exposed to pre-natal opioids every few hours until discharge.[107]

Non-pharmacological approaches to treating NAS should be considered before pharmacological ones and should not be considered substitutes.[107] A multidisciplinary team of psychiatrists, obstetricians, mid-wives, mental health therapists, pediatricians, nurses, and social workers is necessary for the optimal treatment of NAS.[107] The goal of treatment in NAS is principally to reduce symptoms. Treatment of NAS begins with a non-pharmacological approach. For example, if the infant presents with tremors associated with NAS, positioning and swaddling should be considered to help the infant calm down. Non-pharmacological interventions for the treatment of NAS should be considered for short-term improvement of symptoms (Appendix 2).[106] NAS symptoms may be scored using the Johns Hopkins NAS scoring form (Appendix 3).[109] According to the Academy of Pediatrics (AAP), morphine or methadone should be considered as

pharmacological interventions for NAS.[106] Infants with severe NAS refractory to morphine or methadone may be started on clonidine or phenobarbital in addition to morphine or methadone.[106] Clonidine is a reasonable alternative to phenobarbital due to the risk of sedation in phenobarbital. Naloxone should be avoided because it may precipitate rapid withdrawal. As the infant begins to improve clinically and exhibit fewer symptoms from the Johns Hopkins NAS scoring form (Appendix 3), drug therapy is weaned.[107]

Risk Factors for OUD

Chronic Pain

Chronic pain often leads to anxiety, depression, problems with mobility, limits daily activity and reduces the quality of life.[46] In 2016 the CDC estimated 50 million Americans suffer from chronic pain. More than 40% of older Americans deal with chronic pain and its sequelae.[28] Opioid pain regimens for cancer related pain have increased over the past two decades.[45] As many as 11.5 million people are prescribed long-term opioids for chronic pain.[47] Balancing chronic pain while reducing the risk of opioid abuse, misuse, and diversion is critical in the prevention of OUD.[45]

Co-morbid Opioid Use Disorder and Psychiatric Disorders

OUD and psychiatric disorders are often co-morbid but their relationship is not fully understood.[48] The American Society of Addiction Medicine has hypothesized that there is a genetic vulnerability in the dysregulation of dopamine and glutamine in schizophrenic patients which may make them more vulnerable to substance use

disorders.[48] Opioids have also been seen as a way of self-medicating.[48] SUDs and anxiety related disorders, such as post-traumatic stress disorder and obsessive compulsive disorder, commonly co-occur.[49] Studies have found that prescription opioids can be used to cope with psychological and emotional discomfort and distress.[50] A 2013 study in the American Journal of Addiction found that, among 85 patients with prescription opioid dependence, 47.1% were diagnosed with a co-morbid anxiety or mood disorder.[51]

Housing

As many as 3.5 million Americans experience periods of homelessness annually.[52] People experiencing homelessness have a higher prevalence of medical and psychiatric illness and substance use.[53] A 2013 study in Boston found that opioid overdose was responsible for more than 80% of deaths among people suffering from homelessness. In the same study, unstably housed male patients aged 25 to 44 were nine times more likely to die of overdose than similar patients who had stable housing.[53]

Neighborhood and social networking are contributing factors to substance use.[54] Economically disadvantaged neighborhoods are prone to disinvestment, abandonment, and crime. Inadequate living situations may lead to higher levels of psychological distress.[54] Abandoned homes and buildings can be convenient locales for substance use behaviors and can be sanctuaries for other illicit behaviors. [54] Substance use abstinence has been shown to improve when people move to less economically disadvantaged neighborhoods.[11] A 2015 study investigating predictors for adherence to extended release

naltrexone found that patients suffering from homelessness and co-morbid mental illness were less likely to adhere to naltrexone.[55]

Opiate Use Disorder Treatment

OUD treatment consists of both pharmacological and psychological approaches. Cognitive behavioral therapies (CBT) and motivational interviewing (MI) are methods of communication that foster healthier thinking and living. Longer treatment retention and MI is associated with greater likelihood of abstinence.

Medication-assisted treatment combined with a psychosocial intervention is the most effective treatment option for OUD.[56] Incarceration is negatively related to abstinence and is not a treatment on its own.[19]

Medicinal Treatment Options for OUD

According to the American Psychiatric Association, in patients with an extended history of opioid use, methadone or buprenorphine maintenance is appropriate.[31]

Methadone

Methadone (METHADOSE, DOLOPHINE) is a long-acting synthetic opioid receptor agonist. It is used to minimize opioid craving and withdrawal.[18] A 2009 Cochrane review found that methadone in conjunction with psychosocial therapy reduced opioid use, potential infection, and crime.[57] Methadone maintenance programs have been shown to reduce mortality by 50% among people with OUD, decrease HIV infection,

decrease hepatitis infection, decrease crime, decrease illicit-substance use, improve social functioning, and increase the rate of retention to rehabilitation programs.[1] Patients taking methadone were found to have reduced opioid use even without counseling services.[58]

Conveniently, patients may receive methadone without risk of withdrawal. Additionally, methadone has been shown reduce psychiatric distress.[48] Induction and stabilization of methadone begins with a 15-30mg oral dose. Dosage is increased by 10-15mg every three to five days up to an average daily dose of 50-80mg. Dosing may be adjusted to minimize side effects and cravings, and optimize adherence.[1] Methadone steady state should be at a level that avoids euphoria, sedation, prolonged QTc interval and opioid craving.[1] Patients may remain on methadone for life. Tapering may be done, usually 5mg daily.[31], however, a 2003 Cochrane review found that despite its efficacy in the prevention or minimization of opioid withdrawal symptoms, tapering methadone led to a majority of patients relapsing to heroin use.[59]

A caveat to methadone treatment is that it currently must be dosed in specialized dispensing centers. At a methadone clinic, all patents must be evaluated by a physician to determine whether MMT is indicated. Providers should explain the rationale for MMT, the course of treatment, side effects, and other treatment options.[60]

Buprenorphine

Buprenorphine is a long-acting opioid partial agonist. It is available in a variety of forms -- oral sublingual (SUBOXONE, SUBUTEX), parenteral (BUPRENEX), patch (SUBOXONE) --and can be combined with naloxone, a potent opioid antagonist.

Buprenorphine may be used once the patient is in mild-moderate withdrawal. Patients must be in mild to moderate acute withdrawal; otherwise buprenorphine will precipitate rapid withdrawal.[18]

Use of buprenorphine to rapidly suppress opioid withdrawal is termed induction.[95] Failure to alleviate withdrawal symptoms may lead to the patient resuming use of opioids.[95] Induction begins with a 4 to 8mg dose on day one, and up to 16mg daily on day two with dosing increases on subsequent days up to day seven.[1] Dosage should be adjusted to minimize cravings and side effects.[1]

To avoid diversion, naloxone is added to buprenorphine to discourage injection. Naloxone, an opioid antagonist, will prevent feelings of euphoria should buprenorphine be crushed and injected in an opioid naïve patient. Injection of buprenorphine/naloxone in a patient with recent opioid receptor activation will trigger sudden, unpleasant withdrawal.[62]

Buprenorphine does not require a specialized clinic for distribution. Buprenorphine is a safer medication at induction than methadone because it does not carry the risk of QTc prolongation.[1] Buprenorphine is prescribed only in medical offices, limiting access to patients with a primary care provider. Furthermore, federal law limits the number of patients a provider can "carry" in one year to 250.

Naltrexone

Naltrexone (VIVITROL, REVIA) is a long-acting mu receptor antagonist. Naltrexone works by blocking opioid agonists and assists in maintaining abstinence in

motivated patients.[1] Effects of subsequent opioid agonists are minimized or extinguished.[18] Oral and intramuscular naltrexone (VIVITROL) has been found to be more effective than placebo in the treatment of OUD.[64]

Patients should be abstinent from opioid agonists for at least 7 to 10 days prior to starting oral naltrexone or risk rapid withdrawal.[96] Naltrexone induction and stabilization involves verifying opioid use status by an opioid negative urine sample. Upon opioid negative urine, a low dose oral naltrexone challenge may be administered. After 24 hours without withdrawal, intramuscular VIVITROL may be given.[1] Similar to methadone and buprenorphine, patients taking naltrexone should receive psychosocial therapy.

Studies of OUD patient adherence to oral naltrexone have found that 50% of patients discontinue it in six weeks and 15% continue after 25 weeks.[63] Naltrexone adherence is notoriously low, worse than methadone and buprenorphine. Thus, due to these issues in adherence, naltrexone is primarily a second-line strategy.[31] Non-adherences is dangerous because of the risk of loss of opioid tolerance while on naltrexone and subsequent overdose.[98]

Psychological Treatment Options

Cognitive Behavioral Therapy (CBT)

CBT can help a patient identify distorted, maladaptive beliefs.[17] CBT uses thought exercises, relaxation techniques, and stress exercises or real experiences to facilitate symptom reduction and improve patient functioning. Patients may improve through a better understanding of the problem or by repeated exposure to the stimuli.[17]

CBT has been found to be effective for a variety of psychiatric disorders, including substance abuse, generalized anxiety, depression, panic disorder, and posttraumatic stress disorder. CBT for substance use disorder has been found to be effective as monotherapy and in combination therapy with social and family support.[65] However, CBT alone did not improve abstinence rates for primary heroin users.[66]

Contingency Management (CM)

CM is a behavioral therapy where individuals are reinforced or rewarded for evidence of a positive behavioral change.[67] Reinforcement of positive behavior will promote further good behavior, in this case, abstinence. CM has been found to improve opioid abstinence[71] and medication compliance.[72] Multiple studies have found CM to be effective in reducing stimulant misuse.[68,69] Interestingly, CM was effective in patients receiving MMT.[69] Meta-analyses of clinical trials in patients with varied SUDs have found CM to increase rates of drug abstinence during treatment compared to control interventions.[70] However, 6 to 12 months after treatment the effects of CM were found to have not been sustained.[70] In a clinical trial of 116 patients with OUD receiving methadone, those receiving CM were found to have greater percentage of opioid and cocaine free urine over the course of the study.[73]

Motivational Interviewing

While patients experience euphoria while taking a substance, ambivalence follows after resolution of a high. In withdrawal, patients often yearn for a life not dependent on

substances. MI is a communication style that guides patients in resolving this ambivalence. Patients are encouraged to make changes to their lives through enhancing inner motivation.[74] MI uses empathetic, nonjudgmental, and supportive approaches to address patient ambivalence towards addictive behavior. MI has been found to reduce DSM-IV diagnosed SUD.[75]

In 2005, investigators at Boston University Medical Center (BUMC) investigated the effects of brief MI on substance use in an emergency department (ED) population.[76] At the conclusion of the study, 40.2% of follow up patients (82% follow up rate) were abstinent from heroin after six months. Within the group that did not receive MI, only 30.6% were abstinent from heroin. Similarly, 22.3% of the intervention group was abstinent from cocaine after six months compared to 16.9% within the group that did not receive MI (aOR = 1.51-1.57).[76]

Providers should help build awareness, support the patient in self-discovery, in their values and goals, and support the changes that the patient is ready for. Providers should be aware of patient readiness for change. Readiness for change is separated into six nonlinear stages: pre-contemplation, contemplation, preparation, action, maintenance, and relapse.[31]

Motivational interviewing was built on four key tenets, highlighted in appendix 4[77]. In summary, providers should aim for collaboration with the patient, to be compassionate in understanding patient feelings, promote patient autonomy, and to evoke patient ideas rather than to assert opinions. A provider's ability to use MI relies on four key skills. Providers should ask open ended questions which encourage further

elaboration and consideration. They should positively affirm patient feelings and actively reflect on patient feelings to ensure to the patient that they are heard. Lastly, providers should summarize patient concerns and foster an environment of progress and build an interest in changing behavior.[77]

Self-Help Groups

In a longitudinal prospective cohort study of 142 opioid dependent patients attending Narcotics Anonymous (NA) and Alcoholics Anonymous (AA) found improved abstinence rates at five-year follow-up.[78] Pre-treatment opioid abstinence was 19% and was 47% at five-year follow-up ($p<0.001$). Attendees were more likely to be abstinent to both opiates and alcohol than non-attenders of NA and AA.[78]

Programs:

In 1995, Boston Medical Center (BMC) created Project ASSERT, an ED-based program aiming to connect substance dependent patients to primary care providers and preventative medicine programs.[85]

The original study by Bernstein et al screened 7,118 ED patents for illicit substance use. Substance use was detected among 41% (2931) of patients and 37% (1,096) of patients with a positive substance screen enrolled in Project ASSERT. Health promotion advocates screened patients on their readiness to change. Patients were given the opportunity to be referred to a substance use treatment program.[80] Among the enrollees, a large number of referrals were made: 3,189 to primary care, 2,018 to

substance use programs, 2,253 for smoking cessation, 339 for mammography, and 689 for psychiatry, social work, or for housing assistance.[80] Some patients had multiple referrals made. Among 245 follow-up patients, there was a 45% reduction in severity of drug use and 56% reduction in alcohol use. Project ASSERT has been adopted in various EDs across America as a way to improve access to healthcare in the substance use population.[80]

Project ASSERT continues to facilitate connections to support programs and mitigate social determinants of health. Its health promotion advocates have offered 60,000 referrals to alcohol and drug screening and treatment programs since 1994.[99] Project ASSERT is an invaluable resource in connecting patients with SUDs to primary care, health and social services, assisting in obtaining health insurance, transportation, and temporary housing.

Faster Paths to Treatment is a substance use urgent care center started in 2016 at BMC. Faster Paths provides referrals to addiction treatment, overdose education, Narcan, substance use counseling, MMT, buprenorphine, and referrals to primary care doctors at BMC.[81]

BMC's office-based addiction treatment (OBAT) program was created in 2003 to address the lack of clinical support for doctors in addiction medicine and addiction psychiatry.[82] At OBAT, registered nurses minimize the barrier to receive buprenorphine by seeing substance use patients. OBAT has expanded patient access to healthcare professionals, and access to buprenorphine.[82]

A 2018 12-year retrospective study within BMC's OBAT program investigated the effectiveness of a voluntary buprenorphine taper.[82] Primary outcomes were completion of a buprenorphine taper. Secondary outcomes were re-engagement of care and resumed buprenorphine treatment after the voluntary taper. Among 1,308 OBAT patients, 48 attempted the buprenorphine taper (22 were medically supervised tapers) and 13 patients resumed buprenorphine maintenance therapy.[82] 35 completed the taper. A 2014 study in the Journal of the American Medical Association (JAMA) investigated the effectiveness of a buprenorphine taper in 113 patients over 14 weeks. Patients were randomized to a three-week buprenorphine taper after six-weeks of buprenorphine stabilization. Investigators found the buprenorphine taper much less efficacious in maintenance of opioid abstinence than continued use of buprenorphine.[108]

Existing Research

Review of the Standard of Care in the Treatment of OUD

A 2016 systematic review by Dugosh et al in the Journal of Addiction Medicine investigated the use of various psychosocial interventions with buprenorphine or MMT in the treatment of OUD.[18] Dugosh et al reviewed the standard of care for OUD. They aimed to find the optimal psychosocial intervention in achieving the highest rates of abstinence combined with either methadone or buprenorphine. They reviewed CBT, 12-step programs, MI, family therapy, group and individual counseling, and social skills training. Each psychosocial therapy varied in format and treatment modality but used common

therapeutic elements. Therapies aimed to modify underlying addictive behavior, encourage the use of pharmacotherapy, and treat psychiatric co-morbidities.

Reviewers followed the PRISMA guidelines.[100] Reviewed journal articles were found through PubMed and PsycINFO databases. Reviewers broadened search terms to include all articles that described experimental trials investigating the efficacy of pharmacotherapy plus any psychosocial treatment for OUD. Search terms included special populations like pregnant women and adolescents. Editorials, commentaries, and overlapping articles were excluded.

1128 studies were reviewed; 190 duplicates were removed. Studies were excluded if they included non-human (5), editorials/obituaries/commentaries (N=32), Non-MAT + Psychosocial related (N=348), Not RCT (N=461), small sample size (N=3), Lacked control/comparison group (N=9), already updated articles (N=8), and not opioid-treatment focused (N=45).

At the conclusion of the study, investigators found significant gaps in research still existed in quality of data, and special populations. The majority of studies examined psychosocial therapy plus methadone treatment. Buprenorphine was studied less. There was little empirical evidence to favor one psychosocial therapy over another when combined with methadone/buprenorphine. There were few comparison studies of psychosocial therapies for OUD treatment effectiveness.

Investigators examined two studies that compared CBT and methadone maintenance therapy to MMT alone in the treatment of OUD. Kouimtsidis et al compared outcomes for patients randomly assigned to MMT and CBT or MMT alone. Patients in

the CBT group received 50 minutes of weekly counseling for the six-month study period. Investigators found no significant difference in the number of days abstinent, heroin use, psychosocial problem severity, quality of life, or MMT compliance.[101] Moore et al randomized patients into MMT only or a phone-line based voice interactive system using CBT. In their four-week study, the two groups experienced no difference in self-reported substance use and urinalysis-verified opioid and cocaine use.

Nyamathi et al investigated MI when combined with MMT for patients with OUD. The study was broken down into three subgroups: one on one MI, MI in a group, and a nursing-led hepatitis health promotion group. There was no significant difference among the three groups in drug use during the intervention phase. At the six-month follow-up, patients receiving individual MI and group MI reported less substance use. A major caveat in the study was that substance use was self-reported. There was no follow-up data after six months.

Dugosh and authors reviewed four studies that utilized CM as part of their treatment regimen for OUD. Two of the four CM studies were performed in China, the other two were performed in the United States. In each of the studies, prizes were awarded to patients who produced morphine negative urine samples biweekly over 12 weeks. All patients received MMT and were encouraged to abstain from morphine if they produce a morphine-positive urine sample. The MMT+CM group consistently outperformed the MMT-only group. They were abstinent longer and had a greater number of overall opioid-free urine samples. This study was conducted in China and thus possibly not generalizable to the population in the U.S. Authors collectively saw subjects

receiving CM provided more morphine-free urine samples than the group receiving methadone maintenance.

Another weakness of the study is that it is a systematic review, thus each of the populations that individual investigators draw on is different. A few of the examined control groups did not include methadone or buprenorphine only groups. The major weakness in the study is that none of the studies compared one type of psychosocial therapy to another one. In order to get an idea of the optimal psychosocial therapy for OUD, psychosocial therapies must be compared across diverse groups. Furthermore, among the studies examined in this systematic review, none were examined for weakness or bias.

Given Dugosh and authors' findings, there is significant work remaining as to the comparative effectiveness of one psychosocial therapy over another. Insufficient work has been done to assess the effectiveness of one psychosocial therapy over another. Given the litany of psychosocial therapies available for the treatment of OUD, differentiating one therapy versus another is essential to finding the optimal treatment regimen for OUD. Additionally, work should be done to elucidate whether buprenorphine or methadone is more effective given the patient's situation and optimal psychosocial therapy. Dugosh's chosen literature reviews did not mention any studies that looked particularly at substance abuse co-morbid with psychiatric illness. The effect of homelessness and psychiatric illness, common comorbidities in OUD, would have been particularly interesting to investigate.

Generally, Dugosh et al found that MMT in combination with a non-specific psychosocial intervention to be effective in treating OUD. Nine out of 14 studies found improvement in treatment retention and opioid use. Five out of 14 found improvements in opioid use only.

Housing in the treatment of OUD

Tuten et al in 2012[83] conducted a randomized prospective control trial studying the effect of abstinent contingent recovery housing (RH) plus abstinence reinforcement-based therapy (RBT), RH alone, or usual care (UC) on opioid abstinence times.[83]

The study screened 801 patients and investigators were able to recruit 243 opioid abstinent patients in Baltimore who received medical services from Johns Hopkins Bayview Medical campus. Patients were diagnosed with OUD by the DSM-IV criteria and were appropriately detoxed at the time of initiation of the study. Patients with psychiatric illness, pregnant patients and those receiving opioid agonist therapy and pregnancy were excluded. The primary outcomes of the study were opioid and cocaine use or abstinence at one-, three-, and six-month follow-ups measured in ratios.

The UC group was referred to substance use treatment programs and community resources alone. The RH group were provided drug-free housing, contingent on biweekly negative urine specimens in addition to UC. The study paid patients $105 a week for up to 12 weeks. Patients were required to submit urine samples biweekly. A positive urinalysis for cocaine or heroin was a primary endpoint. Upon submitting a cocaine or opioid positive urine sample, patients were removed from recovery housing and placed into unspecified alternative housing. Re-entry into drug-free housing was arranged by

therapists once the patient submitted substance negative urine samples. The RBT+RH group received transportation to and from therapy for the course of the study. RBT+RH was based on community reinforcement therapy and also included CBT, recreational activities, vocational assistance, and intense individual counseling. Patients received daily treatment for the first three weeks and treatment four days per week for weeks four through 12.

Post-hoc comparisons of the data found each of the treatment conditions varied at the one- and three-month time points. The outcome did not change as a result of the varying treatment conditions. The RBT+RH group was significantly more likely than the UC group to abstain from opioid and cocaine use at six months. In the RBT+RH group, 37% abstained at six months versus 20% in the UC group ($p<0.016$). RH+RBT groups were 10 times more likely than the UC group to abstain from opioids at each time point (25.9% versus 2.5%; $p<0.001$). The UC group was significantly more likely to be non-abstinent at any time point. The UC and RH groups, as well as UC and RH+RBT groups, were significantly different as a result the addition of housing ($p<0.001$ for both) but RBT+RH and RH groups did not differ in abstinence times. Of note, the patients in the RBT+RH group had longer stays in recovery housing than the RH patients, 49.5 days for RBT+RH compared to 32.2 days for RH alone ($p<0.002$).

Tuten et al reported their data at one and three months as a ratio, limiting analysis at these times. For abstinence at one and three months, data was extrapolated from an included graph, which showed that at one month, about 60% of RH+RBT patients, 45%

of RH, and about 5% of UC patients were abstinent. At three months, about 55% of RH+RBT patients, 40% of RH patients, and 15% of UC patients were abstinent.

Tuten et al investigated psychosocial therapy in combination with stable housing in the treatment of OUD in patients that have completed medication assisted detoxification. Patients psychiatric illness, those who were pregnant, and those prescribed opioid agonists were excluded. The exclusion criteria made about 500 patients from the original screened population ineligible for the study. Furthermore, by excluding the patients taking opioid agonist medication including methadone and buprenorphine, the study is not taking into account the many patients that stay on methadone or buprenorphine and suffer from homelessness. The patients suffering from comorbid psychiatric conditions and patients taking methadone and buprenorphine while recovery from OUD would have been of particular interest to study. The exclusion of patients with co-morbid psychiatric illness is a major limitation given that psychiatric illness and substance use are often co-morbid.

There was an incentive to be abstinent from opioids and cocaine given that recovery housing was contingent on opioid and cocaine free urine. Patients were placed in alternative housing upon an opioid or cocaine positive urine. Tuten and authors never disclosed the details of the alternative housing. There were no adverse outcomes described except the act of physically moving. If housing were not contingent on opioid negative urine samples, it is unclear how effective the psychosocial intervention would be. Treatment conditions varied at the one- and three-month time point but the investigators did not elaborate on the difference. Additionally, standard deviations for

abstinence time for RBT, RH or UC groups were not provided. In the analysis portion of the work by Tuten et al, they declined to include values for abstinence at one and three months. The data did not include a standard deviation or effect size between any of the groups.

Tuten and authors concluded after analysis of their data that abstinent-contingent recovery housing improves abstinence in patients suffering from OUD following a medication assist detoxification. They found patients benefited from the reinforcement based behavioral counseling. Lastly, they found behavioral counselling improves patient outcomes by lengthening recovery housing stays.

Housing stability as a part of Treatment of OUD

Wooditch et al[84] conducted a randomized retrospective clinical trial on residential mobility, housing stability, opioid and alcohol use in 504 patients with OUD for the prior 30 days in Washington D.C. Each patient had a history of criminal justice involvement. The 504 patients were screened for OUD prior to the study.

To be included in the study, patients had to be older than 18, able to provide informed consent, able to understand English, have medical entitlements in Washington, DC, and at the beginning of the study be abstinent from opioid medications for chronic pain and Suboxone. Patients were 51.7 years old on average, 98% African American, 78% male, 73% unmarried, and 52% were on parole or awaiting trial.

Of interest to this study, investigators found that living in shelters and halfway houses was associated with a decreased frequency of substance use. The investigators found that a sober living environment with behavior-governing regulations was

associated with a lower likelihood of substance use. These findings suggest that a structured living environment may influence behavior and reduce OUD.

Patients self-reported risky behavior, crime, treatment, housing status and incarceration. Patients were categorized into specific housing groups based on where they had spent at least 15 days over the 30-day study. Regression modeling was used to examine illicit substance use days. Living in regulated transitional housing (shelters or halfway homes) were related to fewer days of illicit substance use ($B = -0.105$, $P<0.05$). Patients in correctional facilities or drug treatment programs had fewer substance use days ($B = -0.774$; $p <0.001$). The residential transitions ($B = -0.094$) and days of homelessness ($B = 0.100$) were not associated with decreased substance use.

Wooditch and authors concluded that stable housing and its associated structure is an essential resource when treating motivated patients with OUD. Of note, patients on methadone/buprenorphine were excluded from the study, thus, highlighting the effectiveness of stable housing alone in treating OUD.

Wooditch and authors were very selective in their inclusion criteria. They included only English-speaking patients over 18 years old with criminal backgrounds. The patient population was 98% African American which makes this study not as generalizable to the broader population. Housing group categorization was based on the location at which patients stayed for more than 15 days of the study 30 days is a relatively short time to see a robust effect. Patients had up on average 23.2 (SD = 12.8 years) years of non-continuous heroin use. Prior to the study, the patients had, on average, 20.8 days of heroin use (SD = 11.1 days).

Investigators reported modest positive data for incarcerated patients and study subjects living in halfway homes. Since this study was retrospectively done, patients that were lost to overdose were not included in this study. Retrospective studies introduce significant bias into the study because selection criteria can be manipulated to include patients with positive outcomes.

Patients receiving more than 30mg of methadone or buprenorphine per day were excluded, limiting patients to those that are taking just <30mg methadone or buprenorphine excludes many subjects. Regarding data on patients that were actively incarcerated at the time, it stands to reason that the supply of substances is sparse in a prison or jail, a barrier to use. Secondly, there are patrolmen and guards presumably surveilling for any substance use behavior which is another barrier to use. However, this study's most robust data comes from jails where opioid access is limited and where prison guards are on surveillance for substance use.

Summary of Literature Review

Dugosh et al showed MI to be an effective psychosocial intervention when combined with methadone and buprenorphine as treatment for OUD. Tuten et al, showed that patients with OUD when given stable housing had improved abstinence rates at six months. Patients showed improved rate of abstinence when provided psychosocial therapy in combination with stable housing. Wooditch et al showed stable housing in some form whether it being half-way homes or jails/prisons were associated with fewer opioid use days. Each of the studies individually have shown positive outcomes to a degree reducing OUD with some form of "stable" housing. A study investigating the

effects of stable housing on the standard of care – psychosocial therapies plus methadone maintenance -- would make sense to fill a gap in the literature.

CHAPTER THREE

Methods

Project Design

Investigators will conduct a prospective cohort study of patients receiving methadone enrolled in a MMT clinic for OUD. We hypothesize that patients with greater housing stability will be more likely to be abstinent at one-, three- and six- months and have a smaller number of relapses and longer time to relapse than patients with less housing stability.

Project Population and Sampling

Investigators will recruit study subjects at methadone clinics in the city of Boston over a six-month period.

A 2005 study by Bernstein and authors at BMC profiled racial and ethnic diversity among heroin and cocaine users by system utilization in Boston.[114] Conveniently, the proposed study population will be drawing from the same city albeit two decades apart. In 2005 the survey population was 61.7% Black, 23.1% Hispanic, 14.1% White, and 1.1% Other. Blacks were 67.6% male, and 32.4% female. Hispanics were 82.4% male, and 17.7% female. Whites were 66.7% male, 33.3% female. According to the 2019 state census, Bostonians identifying as "White" alone not Hispanic, "Black", "Asian", "Hispanic or Latino", and "more than one race" represented 44.5%, 25.3%, 9.6% 19.7% and 5.1% respectively.[112]

Study subjects will be assumed to have a diagnosis OUD based on status as a patient in a methadone clinic.

A study affiliated BU employed medical assistant will be present at each methadone clinic for three months to complete OUD secondary screening. Secondary screening will cover days of opioid dependence, methadone use history and dosage and opioid dependence time frame. The medical assistants will be present for an additional six months during the study to collect urine samples.

The sample size of the proposed study will be calculated with UCSF sample size calculator and based on work done by Tuten et al, who studied a population of 243 patients, separated into three housing groups: 80 in recovery housing (RH) + reinforcement based training (RBT), 83 in RH only, and 80 in usual care (UC). A total of 163 patients were exposed to housing in the study. The Tuten study was designed to include 67% of patients in the exposed group, RH+RBT and 33% of patients in the UC group. Thus, 67% and 33% ($q1 = 0.670$, $q0 = 0.330$) represent the proportions in the sample size calculations. Alpha level will be adjusted from 0.05 to 0.0127 using the Bonferroni because of multiple comparisons and beta level 0.80. Tuten and authors concluded at six months, that only 20% of UC patients remained abstinent. In contrast, the over six months, RH+RBT housing group was 37% abstinent (OR = 2.349, RR = 1.850).

To account for drop out, investigators will attempt to recruit 447 total patients with a minimum of 385 patients overall. Recruitment numbers adjustments were based on a 2000 randomized control trial by Sees and Authors.[113] Sees and authors compared treatment outcomes in patients receiving MMT or psychosocial therapy over six months in San Francisco, California. In the study, Sees and authors saw a 16% patient drop out

over six months. The study will need 300 housed patients to account for drop out with a minimum of 258 and 148 unhoused patients with a minimum of 127. Significant patient dropout is common in prospective cohort studies. Total number of patients approached, recruited, and drop out will be recorded.

Treatment, Intervention or Exposure Groups

All patients will receive identical treatments: MMT dosed as usual per individual patient methadone maintenance regime and weekly one-hour MI with a social worker trained at least the bachelor's level. Prior to the study beginning, each social worker will be trained on the nuances of motivational interviewing by a study affiliated psychiatrist, nurse practioner, or physician assistant. Social workers will be taught to use non-judgmental, empathetic and supportive language to address any ambivalence towards abstinence.

Patients will be asked about opioid use in the previous week by social workers while completing their weekly MI sessions. In addition, social workers will reinforce pro-abstinence and pro-stable housing thoughts.

Patients will receive a $25 Visa ClinCard for initial screening and for each subsequent MI therapy session as compensation for the subject's time and transportation to and from methadone clinics.

The study will aim to determine if there is a significant difference in the frequency of abstinence and time to abstinence between patients who are primarily living in stable housing and those in unstable housing. Patients will be grouped at the conclusion of the study based on their living situation during the six-month study.

Patients will be separated into stably housed throughout the study, stably housed initially and then unstably housed, unstably housed then stably housed, and unstably housed throughout the study. Patients will be considered stably housed group if they are living in a place where they are named on the title or lease of the residence or if they live with family or friends. Patients living in halfway homes, shelters, abandoned buildings, or suffering from homelessness will be considered unstably housed.

Project Variables and Measurement Tools

An intake survey completed by the medical assistant (MA) at initial recruitment will determine age, sex, race, employment status, housing status, education level. Patients may make multiple changes in housing status over the course of the study. In the event of multiple housing transitions, the patient will be reclassified into the group where they spent the most time over the course of the study.

The MA will complete an OUD screening survey with the study subject including the following: days of opioid use in the past 30 days, days of opioid dependence, methadone use history, methadone dosage, take-home status, opioid dependence time frame, and prescription drugs the patient is taking. These variables are important to define the baseline treatment characteristics of the cohort.

This study will principally investigate frequency of abstinence and time to relapse for patients receiving MMT and MI with variable shelter status over six months. Patients will submit weekly urine samples for toxicology screening. The urine samples will be collected by an MA and sent out to LabCorp for expanded urine toxicology, including amphetamines, barbiturates, benzodiazepines, buprenorphine, cocaine, fentanyl, opiates,

oxycodone, and THC. Patients will be asked about their substance use and housing status by a social worker during weekly MI sessions. An expanded urine substance panel was chosen as it helps us characterize the patient substance use patterns. The study design includes patients suffering from psychiatric comorbidities, these patients may be taking benzodiazepines or other substances as part of their treatment regime. These patient will be included for analysis of opioid use but the patients will not be counted as relapsed, if the patient uses a medication as prescribed.

Recruitment

MAs will approach patients presenting to five methadone clinics in the city of Boston for three months Monday through Friday in an attempt to recruit patients to the study. These patients will be regular patients of the methadone clinic. Additionally, patients will be recruited via referrals from primary care providers. Flyers will be posted throughout Boston to assist in recruiting.

Participants in the proposed study will include minors, adults, patients with psychiatric comorbidities, homeless, and pregnant patients. Patients taking opioid pain medication will be excluded. Patients will be included regardless of their length of opioid abstinence. Patients receiving take home methadone will be included.

Under BUMC IRB guidelines, investigators must obtain parent or guardian permission for subjects under the age of 18 to be able to participate. The proposed experiment must either be directly beneficial to the subject or be of minimal risk.

MAs will follow a recruitment script based on and approved by the BUMC IRB guidelines. A BUMC approved pamphlet detailing study information will be handed to

all prospective patients. Questions will be answered by study staff. Participants will complete an informed consent to participate in the study and will receive a copy of the consent form. Once consented, participants will complete a brief paper survey on their age, race, employment and housing status, educational level, and perceived social barriers. Screening guidelines will follow approved BUMC screening guidelines.

Upon completion of recruitment screening, the patients will be compensated with pre-card $25 Visa ClinCard. All study personnel will maintain privacy per HIPAA guidelines. Patient information access will be password protected and encoded for additional protection of sensitive information.

Data Collection, and Data Safety and Monitoring

All data collection will be completed on paper and transferred to electronic patient logs. Subjective opioid use screening will be documented in electronic patient files by social workers. LabCorp urine toxicity will be accessed via LabCorp servers and uploaded to electronic patient logs. All physical documentation of patient information will be destroyed at the conclusion of the study. Electronic records of study data will be saved for seven years per BU and BUMC policy and encoded for patient privacy and protection.

Analysis

Patient housing status will be determined at the conclusion of the study. The primary outcome of the study is to determine the ratio of relapsed patients at the one-, three-, and six- month time points. Due to the primary outcome of the Tuten and authors paper reporting data as a ratio and sample size for this study being calculated as a ratio,

analysis for the time to relapse will be compared using Chi-square assuming parametric data. The Fisher exact test will be used if there are less than five variables in the contingency tables.

The secondary outcome of the study will be to determine the difference in mean relapse time between the housing groups. Assuming normal distribution of data, the mean time to relapse of opioid use per housing group with standard deviation will be calculated and compared using one way-ANOVA analysis. If the distribution of frequency of relapse and time to relapse is not normal, a Kruskill-Wallace analysis will be attempted. If a difference in the relapse times between housing groups is found, then we will proceed with further testing to compare the difference between groups. This is a prospective cohort study with independent patients, thus frequency of relapse and time to relapse will be compared in an non-pair wise fashion using an unpaired t-test assuming a normal distribution. The Mann-Whitney U test will be used should the data prove not parametric.

Another secondary outcome of the study will be an analysis of the frequency of relapse for other substances included in the expanded urine toxicology screening. To compare whether there is an overall difference in the populations, ANOVA will be used. The non-parametric analogue used would be the Kruskal-Wallis test. If there is a difference in the relapse rate of substances in the expanded urine toxicology screen, each population will be compared to the control using the unpaired T test if parametric, and Mann-Whitney U Test if non-parametric.

Similarly, investigators will assess for frequency of relapse and time to relapse in patients living with family versus patients suffering from homelessness.

The population data collected at the initial screening of the study subjects will be used to further analyze patients. For example, time to relapse for patients that marked living with family can be compared to the homeless population. Another example could be comparing time to relapse in patients with a greater than ten years' history of intermittent opioid use compared to those who have started within the last year. Demographics will allow for further analysis of the population rather than simply between housed and homeless. For analysis of one subpopulation versus another, investigators may use an unpaired t-test if the data be regularly distributed. If the data is not regularly distributed, investigators may use the Mann-Whitney U Test.

If patients relapse, we will note them as relapsed and exclude them from the overall data. The number of patients lost to follow-up will be noted in the study results. In recruitment, we will aim to have subjects in excess so that if patients are lost we can still have sufficient participants.

Timeline and Resources

Investigators will break the study down into four phases: an experimental outline must be written and submitted and approved by the BUMC IRB, a three-month recruitment phase, a six-month experimental phase, and an analysis phase. Recruitment will take place Monday through Friday for three months at five methadone clinics in the city of Boston. If investigators are unable to recruit the adequate number of patients for the study, the recruitment phase may be extended. The experimental stage will take a total of six months. The data will then be analyzed over several weeks.

For this study to occur, investigators will need significant funding at each of the methadone clinics. Five MAs need to be accounted for to handle the initial screening and collection of urine samples over the recruitment and experimental stages. The recruitment and experimental stages should take nine months. Similarly, two social workers per methadone clinic should be present throughout the duration of the experimental stage, nine months. For each patient, $25 Visa ClinCard should be allocated for initial screening and for each subsequent MI session.

Institutional Review Board Statement

The study principal investigator supervisor will submit a detailed outline of this study to the BU IRB via BU's Integrated Network for Subject Protection in Research (INSPIR) software. Investigators will file the study under expedited review status under category three due to the investigators procurement of urine in a non-invasive fashion. Investigators will also file under category seven – use of psychiatric interviews.

Under BUMC IRB guidelines, a separate IRB does not need to be filed with non-BU facilities if study staff are BU affiliated.

The study will include research on individual characteristics, behavior and the subjects will be interviewed. This will not be a clinical investigation of a drug, device, or other product regulated by the Food and Drug Administration (FDA).

All study personnel in direct contact with study subjects will complete human subject's protection training per BUMC protocol. Non-BUMC affiliated study personnel in direct contact with study subjects will complete a study authorization agreement per

BUMC protocol. Unanticipated problems, adverse events, protocol deviations will be reported to the IRB as required by BU IRB protocol.

CHAPTER 4

Conclusion

Previous studies have found psychosocial interventions along with opioid receptor therapies like methadone and buprenorphine to be effective in treating OUD.[94] Despite the effective treatment, OUD persists and is a major public health issue and has become more prevalent in the recent past.

Prior studies identify housing status as a significant social co-morbidity but few studies have addressed it as part of a treatment regimen for OUD. Among the studies that have addressed housing with OUD, none used patients actively receiving methadone in an observational study. The study aims to capture patients already living in stable housing rather than providing new housing as a way to save costs.

The study principally compares the ratio of patients suffering from opioid use disorder that relapse at one-, three- and six- month time points. Patients will be separated into four populations receiving the same standard care of treatment, MMT + MI. Secondary outcomes will be measuring a difference in the mean time to relapse between the populations. At the conclusion of the study, patient housing status will be compared to see if stable housing is associated with reduced frequency of relapse and longer time to relapse.

Sourcing patients from five Boston area methadone clinics will provide a large generalizable population. Boston, Massachusetts is a large metropolitan city and will

allow investigators to have patients from a diversity of backgrounds, races, and cultures. The population of Boston still may not be generalizable to all of the United States.

The study design was intended to be as generalizable as possible and will include minors with parent or guardian permission, adults, patients with psychiatric comorbidities and pregnant patients. This study will include all patients receiving methadone and not using other opioid agonist therapies. This study in its design aims to minimize exclusions. Maximizing inclusion criteria makes the data generalizable and applicable to a wide variety of patients but may dampen the effect in a population that sees greater benefit to stable housing may be cancelled by a population that is not affected as much by stable housing.

Prospective observational cohort studies are inherently limited due to their lack of randomization and potential for confounding. A significant barrier for homeless patients is public transportation and the availability of public health programs like shelter or health insurance. Fortunately, in Massachusetts, methadone is covered by MassHealth. Availability of free methadone is not a guarantee throughout most of the United States. Public transportation like subways makes traveling to methadone appointments easier in Boston because of its robust network of trains.

This study will likely see a significant drop-out of patients. It will be difficult to follow up with patients should they decide to drop out of the study. In the proposed study design, patients who drop out for any reason will be excluded. Patients may decide to not continue the study for a variety of reasons unrelated to relapse. Investigators will recruit

more patients in an attempt to keep the necessary sample size for statistical analysis. The total number of relapse patients will be noted and listed as a caveat.

Patients regardless of their methadone use history or length of substance dependence will also be included. We chose to include patients regardless of their last relapse time to make the study more generalizable to the OUD population as a whole. As a result, the study may include patients who have been on methadone for a prolonged period of time. A 2016 Canadian study of 250 patients on MMT showed a mean relapse time of 99.04 days (74.4).[115] Prolonged times of methadone use may suggest the patients are stable and less likely to relapse.

Investigators will exclude only patients taking opioid receptor agonists for chronic pain control. This decision was made because opioid pain control plus opioid maintenance therapy would confound the study.

Due to the study design of including patients with psychiatric comorbidities, patients may be prescribed substances that will be positive on the expanded urine toxicology, benzodiazepines for example. These patients will not be marked for relapse because they are prescribed medications for medical need. Similarly, patients that self-prescribe marijuana will not be marked as substance users or relapse should they decide to use.

Summary

OUD is a chronic relapsing illness associated with significant medical and social morbidity and mortality.[3]

Opioid receptor modulators, such as naltrexone, methadone, and buprenorphine, have been well studied and are effective at treating OUD.[18] Today, the standard of care in the treatment of OUD is a psychosocial intervention plus an opioid receptor modulator. Despite the existence of effective treatment, OUD has persisted.

Over the past 20 years, deaths from complications of OUD including overdose have increased nearly 20-fold (Figure 1). OUD prevalence has reached epidemic levels. Prescription opioids are the primary driver of opioid-related fatalities.[4] The rise of OUD is multi-factorial. Opioid approaches to pain control, limited drug treatments, and eroding economic opportunities have contributed to the epidemic.[5]. Overdoses from fentanyl and heroin combinations increased by 88% per year from 2013 to 2016.[9]

A 2016 systematic review by Dugosh et al found psychosocial interventions combined with MMT or buprenorphine to be effective in the treatment of OUD. Few studies have evaluated the efficacy of one psychosocial intervention over another. A 2012 study by Tuten et al found that abstinent contingent recovery housing improves abstinence in opioid dependent patients and that the addition of reinforcement-based treatment counselling further improved abstinence. A 2018 prospective cohort study by Wooditch et al. found that regulated housing and sober-living environments were associated with lower illicit substance use.

Building on the findings of Dugosh, Tuten and Wooditch, a prospective cohort study is planned exploring the effects of stable housing among patients who receive the current standard of care, MMT plus MI. Thus far, there has not been a study on patients receiving the standard of care plus stable housing. Wooditch et al found that housing can

positively influence abstinence times but their study used patients who were not receiving MMT or Suboxone. The proposed study is innovative by including patients who receive the MMT, buprenorphine, and stable housing as a way to improve abstinence times.

Clinical and/or Public Health Significance

Upon conclusion and analysis of the study data, we expect investigators to find stable housing to have a positive influence on abstinence times in patients receiving the standard of care treatment for OUD. This study is of particular interest due to prevalence of OUD and its intransigence to treatment.

We hope to include stable housing as part of a treatment regimen for patients suffering from OUD.

Positive findings could be used to influence U.S. federal and state legislation to provide additional resources for patients struggling with OUD and homelessness. Additionally, future randomized controlled trials studying OUD with MMT + MI and stable housing would be warranted to fully understand the effects of stable housing on OUD.

APPENDIX

Appendix 1: Opiate Use Disorder DSM-V Criteria

The severity of OUD is graded on the number of positive symptoms listed below:

A. Mild OUD – 2-3 items.

B. Moderate OUD – 4-5 items.

C. Severe OUD – 6+ items over 12 months.[27]

The severity of OUD influences treatment modality.

1. Opioids are often taken in larger amounts or over a longer period of time than intended.

2. There is a persistent desire or unsuccessful effort to cut down or control opioid use.

3. A great deal of time is spent in activities necessary to obtain the opioid, use of the opioid, or recover from its effects.

4. Craving, or a strong desire to use opioids.

5. Recurrent opioid use resulting in failure to fulfill major role obligations at work, school, or home.

6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.

7. Important social, occupational or recreational activities are given up or reduced because of opioid use.

8. Recurrent opioid use in situations in physically hazardous situations.

9. Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.

10. Tolerance as defined by either of the following:

A. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.

B. Markedly diminished effect with continued use of the same amount of an opioid.

11. Withdrawal as manifested by either of the following:

A. The characteristic opioid withdrawal syndrome.

B. The same or closely related substance is taken to relieve or avoid withdrawal symptoms.

Appendix 2: Non-Pharmacological Treatments for Neonatal Abstinence Syndrome

- Non-Pharamacological Treatments for Neonatal Abstinence Syndrome as adapted from Velez and Jansson, 2008[106]Irritable infants may be soothed with gentle rocking.
- Frequent small feedings. Breast feeding is encouraged but only in if the mother meets the following criteria:
  - Mothers must be able to provide consent to discuss treatment progress with a substance use disorder treatment counsellor
  - Mothers must plan to continue SUD treatment postpartum
  - Mothers must be abstinent from illicit substances for greater than 90 days prior to beginning breast feeding.
  - Mothers must have a negative urine toxicology at delivery
  - Mothers have received consistent prenatal care
  - Mothers should have no medical contraindication to breast feeding
  - Mothers should not be taking a medication that is contraindicated during lactation.
- Pacifiers may be beneficial to calm down oral hypersensitivity.
- Maternal education on soothing her irritated infant is beneficial in promoting dyadic synchrony.
- Rooming-in (ie, placing the mother and infant in the same room)
- Barrier creams to minimize skin excoriation.

Appendix 3: Johns Hopkins Neonatal Abstinence Syndrome Screening Tool

Name: _____

Nursing instructions:

1. If infant scores >8, rescore in one hour.
2. Notify clinician if two scores, one hour apart, >8.
3. Give medication as prescribed by clinician every three to four hours. Do not exceed four hours in dosing.
4. All opioid-exposed infants are monitored and scored for a minimum of 96 hours before discharge.

Categories	Score	Morphine (morphine sulfate oral solution 0.4 mg/mL)
0	0 to 8	0.00 mg
I	9 to 12	0.04 mg
II	13 to 16	0.08 mg
III	17 to 20	0.12 mg
IV	21 to 24	0.16 mg
V	≥25	0.20 mg

Signs and symptoms	Score	Date/time											
		- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -
Excessive cry	2 to 3												
Sleep <1 hour after feeding	3												
Sleep <2 hours after feeding	2												
Sleep <3 hours after feeding	1												
Hyperactive Moro reflex	1												
Markedly hyperactive Moro reflex	2												
Mild tremors: Disturbed	1												
Moderate-severe tremors: Disturbed	2												
Mild tremors: Undisturbed	1												
Moderate-severe tremors: Undisturbed	2												
Increased muscle tone	1 to 2												
Excoriation (specific area)	1 to 2												
Generalized seizure	8												
Fever >37.2°C	1												
Frequent yawning (>3 to 4 times)	1												
Sweating	1												
Nasal stuffiness	1												
Sneezing	1												
Tachypnea (respiratory rate >60/minute)	2												
Poor feeding	2												
Vomiting	2												
Loose stools	2												
Failure to thrive (weight gain ≥10% below birth weight)	2												
Excessive irritability	1 to 3												
Total score													
Initials													

Morphine sulfate solution (0.4 mg/mL) dosing schedule:												
Time morphine												
Dose morphine (in mg)												
Route												
Initials												

Comments:

Appendix 4: Motivational Interviewing Tenets

Motivational Interviewing spirit rests on four key tenets:[77]

A. Collaboration between practitioner and the patient in contrast to assuming the role of a treatment expert and confronting the patient.[77]

B. Compassion – in MI aims to better understand how the patient feels and to promote what is in the best interest of the patient.[77]

C. Autonomy – MI recognizes that making the choice to change is up to the patient.[77]

D. Evocation or drawing out the client's ideas about change rather than inserting the practitioner's ideas and opinions. The practitioner must work on drawing out the patient's motivations rather than to follow the practitioner's opinion.[77]

Motivational Interviewing rests on four key skills, explained by OARS:

O – Open questions that encourage further elaboration and consideration.

A – Affirmations that foster positive feelings in the consultation.

R – Reflections that indicate that the clinician has heard and accurately understood the patient.

S – Summaries that extend the basic reflections to include a sense of momentum or build interest in changing direction.

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