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Cost Effectiveness of Buprenorphine when Used Long Term versus Short Term Use

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BY

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A doctoral project submitted to the faculty of the Medical University of South Carolina
in partial fulfillment of the requirements for the degree
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Since 1999, nearly 841,000 people have died from a drug overdose (CDC, 2022), and substance use disorder (SUD) continues to be a crisis that faces communities across the country. As the crisis continues across communities, the need for medication-assisted opioid use disorder (MOUD) therapy continues to surge.

This was a retrospective analysis of archival data from large national data sources. We constructed well-matched cohorts of patients with short and long-term use of MOUD using propensity score matching of 3 months of baseline data. To measure the cost effectiveness of short-term buprenorphine use verse long-term buprenorphine use.

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CHAPTER I INTRODUCTION

1.1 Background and Need

Since 1999, nearly 841,000 people have died from a drug overdose (CDC, 2022), and substance use disorder (SUD) continues to be a crisis that faces communities across the country. As the crisis continues across communities, the need for medication-assisted opioid use disorder (MOUD) therapy continues to surge. In this study opioid use disorder (OUD) is the primary disease that will be examined. Opioids have been used to manage pain for centuries. However, today's opioids can be either natural or synthetic chemicals that bind to opioid receptors in an individual's brain. Unfortunately, both natural and synthetic opioids have the potential for misuse and may cause addiction (Hoffman et al., 2019). Prescription opioid misuse by adults in the US is common with an estimated economic burden of $76.5 Billion and affect family stability with an increase in child welfare cases (Jacobson et al., 2020).

Medication-assisted treatment for opioid use disorder has shown clear evidence of improvements in treatment retention, reduction of opioid use, reduction of overdose deaths due to OUD, and improved outcomes for neonates born to females with OUD (Jacobson et al., 2020). MOUD consist of a two-prong approach, medication and psychosocial treatment and support. Currently, there are three different kinds of medication that can be used for MOUD: methadone, buprenorphine, or naltrexone, with buprenorphine being the one most commonly used today (Hoffman et al., 2019). Access to MOUD can be in a variety of settings, for example the emergency department (ED), inpatient detoxification facilities (IPDetox), and the outpatient (OP) setting. While each access point provides a different level of care and setting to the patient being served, each access point can play a vital role in linking patients to MOUD services across

settings. However, MOUD is not easy to access, or even available in all geographic areas, so efforts to increase access and improve provider ability to provide MOUD services to individuals with OUD would be expected to decrease the economic burden that OUD places on society.

1.2 Problem Statement

Use of MOUD is increasingly common, but it is not clear how large potential cost savings may be at the population level. Currently, data are sparse on the cost and effectiveness of MOUD so it is difficult for health systems and policy makers to identify costs and benefits of developing additional MOUD services. To successfully argue for more complete MOUD service networks across EDs, IP Detox and OP facilities, we must have good measures of outcomes and cost for patients receiving MOUD compared to well-matched controls with no services.

The objective of this study is: to compare the short-term (60 days) use of buprenorphine versus the long-term (12 months) use of buprenorphine for patients with an opioid use disorder.

Once such data are available, they can inform key stakeholders in the fields of behavioral health, SUD, and ED providers. Local, state, and federal policy makers may find this study of interest as SUD does not discriminate who it affects and has left many policy makers trying to provide solutions to the crisis.

1.3 Research Questions and Hypotheses

Is there a measurable cost savings realized by long-term use of MOUD (operationalized as buprenorphine for this study) as compared to shorter use? The hypothesis is that patients who are long-

term buprenorphine users compared to those that are short-term users have better health outcomes and lower cost to the health care system.

1.4 Population

The population that is being used in the research are individuals that have either a primary or secondary diagnoses of OUD and have received a prescription for buprenorphine as recorded in billing data sets.

CHAPTER II SCOPING LITERATURE REVIEW

This review of the literature is limited to using recent published works as examples of a larger body of evidence which we have examined, but which does not by itself add to our summary and examples of evidence used in this "scoping" review.

There are two types of interventions that can be used for individuals with OUD, psychosocial and medication interventions. Psychosocial intervention when used alone should not be considered the first line of intervention for individuals with OUD (Bart,2012). Historical data has shown that individuals only receiving psychosocial intervention have poor outcomes, 80% of individuals relapse within 2 years of their treatment (Bart,2012). Medical intervention for treatment of OUD consists of using medications also called MOUD. There are three types of medications that are typically used for MOUD: methadone, buprenorphine, and naltrexone. Figure 1 in the appendix illustrates the different types of medication treatments available.

Methadone

Methadone is a synthetic, full opioid agonist and has been used for years to treat OUD and the oldest drugs on the market, and correct dosing can be complicate at best (Koehl et al., 2019). A patient using methadone to treat OUD may experience some adverse effects from the medication; constipation, respiratory depression, and/or prolongation of the heart rate (Koehl et al., 2019). Federal regulations mandate that methadone is dispensed in federally qualified opioid treatment programs (OTP), and patients must be dosed daily, a patient cannot receive take home medication until program adherence is established (Koehl et al., 2019). In the recovery community, methadone is often referred to as a "liquid leash" because of the requirement to go to the clinic daily for dosing.

Buprenorphine

Buprenorphine is a partial opioid agonist with a celling effect, which makes the drug safer to use, clinically the effects are like those of full agonist, like morphine or methadone, however it has maximal opioid effect, providing a wider safety margin (Koehl et al., 2019). The long receptor half-life of buprenorphine does not provide the patient with a euphoria like other medications used for OUD (Koehl et al., 2019). Buprenorphine is available in several different formulations, including tablet, extended-release injections, and implantable rods (Koehl et al., 2019). Buprenorphine is not recommended for patients that have severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment (Koehl et al., 2019). Unlike Methadone, Buprenorphine only requires a prescription from a qualified provider rather than daily dosing at a clinic.

Naltrexone

Naltrexone is an opioid antagonist that is similar to Naloxone and has a high binding affinity for μ opioid receptors (Koehl et al.,2019). Naltrexone is an opioid blocker it prevents prescription or illicit opioid agents from binding to μ receptor that causes an individual to experience a euphoria like effect, since naltrexone only blocks the euphoria effects, it does not assist with the cravings an individual may have, unlike methadone and buprenorphine (Koehl et. al. 2019). Naltrexone is FDA approved to be used both for alcohol and opioid use disorders and is available in extended-release injection or an oral tablet, however, the oral tablet is not the preferred method for the treatment of OUD, because of low adherence rates (Koehl et. al., 2019).

Cost

When comparing cost-effectiveness of inpatient treatment options versus outpatient treatment options, Winser et al. study showed that participates in outpatient services utilized less

services than those receiving inpatient services. In Winser et al. randomized control trial, it was found that inpatient patients cost three times more than those in the outpatient setting, $747.57 versus $257.21. King et al. reviewed the annual health care cost of Medicaid population with OUD and found a significantly higher cost for patients with OUD, $14,537 vs. $8,663; P <.001.

In Barnett et al. examined the cost-effectiveness of buprenorphine maintenance therapy with special attention to the effects it has on the human immunodeficiency virus (HIV) epidemic. In Barnett et al. A dynamic model was used to capture the effects of adding buprenorphine maintenance to the current OUD treatments systems, the research evaluated incremental costs, including all health-care cost, incremental effectiveness and measured in quality adjusted life years (QALYs). It is estimated that there are 600,000- 800,000 individuals in the United States with an OUD, of those only 115,000 are in methadone treatment (Barnett et al., 2001).

In Jennings et al. a retrospective chart review that consisted of patients that presented to a single ED, the study site had a volume of approximately 50,000 visits per year. The study of Jennings et al. examined the effects of readmission rates to the ED for people with substance use disorder (SUD) when medication assisted treatment (MAT) is provided in the ED setting along with referral to continued outpatient care. The findings in Jennings et al. suggest that ED initiated MAT services would significantly increase the patient volume in the ED, especially individuals that are only seeking MAT services. Jennings et al.'s research had several limitations, one being that the study only examined utilization patterns at a single ED visit, the ability to replicate the findings are generalized to the ED in which the study was conducted, the results cannot be used for other like programs.

In Beauchamp et al.'s studied whether implementation of a SUD linkage program from the hospital to outpatient services can improve the care for individuals with SUD. In

Beauchamp's et al.'s research it was found that implementing MAT programs in the hospital with linkage to outpatient clinics were feasible, however community and funding partnerships were crucial to successful implementation. A limitation of Beauchamp's et al.'s study which could also impact my study is the lack of access to outcome data for the linkage of patients to clinics due to privacy concerns.

Fairley et al. studied the cost effectiveness of treatments for opioid use disorder (OUD) and determined that MAT combined with contingency management and overdose education was associated with significant health benefits and cost savings compared with no treatment. Fairley et al.'s research used three medications that was considered for MAT: methadone, oral buprenorphine, and injectable extended-release naltrexone; all three medications that I will be considering in my study as well. Fairley et al. had limitations with their study, availability of data and the need for more refined cost data for treatment.

With outpatient treatments options including three medications options, King et al. studied the cost effectiveness of each type of outpatient treatment and found that methadone maintenance on average cost more per a year than buprenorphine maintenance, $4,613 vs. $4,155, but was more effective at retaining patients in treatment, 20.3% vs. 15.9%.

Kaucher et al. conducted an evaluation of an emergency department medication assisted treatment induction and referral program and found that patients that started treatment in the emergency had more success reaching recovery than those that did not receive treatment. They found 75% of patients induced in the emergency department and received a referral to an outpatient clinic were still engaged in treatment 60 days after induction, compared to 50% that only received a referral to a clinic (Kaucher et al.,2019).

Not only is outpatient services and treatment more affordable and healthier patient outcomes compared to inpatient treatment. The literature also suggests that by inducing patients while in the emergency department, patients are more likely to continue treatment than those that only receive referral sources for outpatient services.

Policy Issues

In efforts to address to the opioid epidemic policy makers have placed guidelines and policies in the prescribing habits of opioids for providers. Hoffman et al., explain the prescriber guidelines when prescribing opioids, which address the prescribing guidelines based on three facets:

1. Determining when to initiate or continue opioids for chronic pain outside of active cancer treatment, palliative care, and end of life care.
2. Opioid selection, dosage, duration, follow up, and discontinuation.
3. Assessing the risk and addressing harms of opioid use.

The guidelines also provide instructions and risk to patients regarding the use of opioids, while the guidelines are helpful to the both the provider and the patient, providers are struggling to find a balance in prescribing and individual clinical decision.

Hoffman et al., explains that another strategy that could be used in the reduction of the opioid crisis, is requiring opioid manufactures to fund continuing medical education (CME) to providers at low or no cost. Policy makers can also review coverage options for non-pharmacological pain management like cognitive behavioral therapy, physical therapy, and rehabilitative exercise (Hoffman et al., 2019).

Utilizing methadone as a treatment option for maintenance has barriers for patients based upon existing polices. There are states that prohibit methadone treatment, along with some

private health insurance plans and government sponsored Medicare programs do not included methadone as a covered benefit (Barnett et al., 2001).

Prescription Drug Monitoring Programs (PDMPs) are databases that providers and pharmacies can gain information that can help identify individuals that are drug seeking, patient safety, or patients at risk for OUD (Hoffman et al., 2019). PDMPs are a tool to record and track opioid prescriptions so that they can be monitored, and intervening steps can be taken if problems or "hot-spots" arises (Hoffman et al.,2019).

A number of authors have used archival data, including the MarketScan® data set that we propose to use to examine dimensions of OUD and use of buprenorphine. However, these papers do not include time periods during the COVID-19 pandemic. There are key points that these papers have raised that will inform our design, data extraction and analysis. The most important ones are as follows:

1. Subjects in the different study types are identified by age, ICD-diagnosis codes for OUD, and by patient prescriptions specifically used to treat OUD. Figure 2 in appendix illustrates the different types of ICD codes used to capture subjects for the study. Subjects are also identified in some studies if they have experienced an overdose in the United States.
2. Authors define treatment by individuals receiving prescriptions for OUD. This is identified through pharmacy claims that included an appropriate National Drug Code.
3. Time horizon is defined by at least a 12-month cohort study group
4. Researchers used propensity scoring technique to address the selection bias.
5. Issues raised by other researchers are that younger adults and those still covered by their parent's insurance plan are more likely to receive inpatient treatment rather than MOUD

services because of the stigma associated with MOUD. There is also a similar preference for individuals with comorbid mental health conditions. Both of these factors have shown a negative outcome such as overdose.

CHAPTER III METHODOLOGY

1.5 Research Design

This is a retrospective analysis of archival data from large national data sources. We constructed well-matched cohorts of patients with short and long-term use of MOUD using propensity score matching of 3 months of baseline data.

1.6 Population and Data Sources

We identified patients with at least two ICD diagnosis codes of OUD, who also have at least one prescription of bupropion, in the MarketScan® data for 2018-2020 for patients ages 18-45. We classified patients based on the length of time for which they have filled prescriptions for buprenorphine. All patients with less than 60 days of coverage were classified as short-term patients, and patients with 12 months or more of continuous coverage were classified as the long-term treatment group. Patients with prescription coverage between 60-365 days were excluded to increase the contrast between our target groups. Patients were matched on characteristics available in the first 30 days of coverage, along with age, sex, geographic location, and comorbid conditions. The matching was performed using SAS (version 9.4) PROC matching using a greedy algorithm.

1.7 Data Analysis

We compared the groups on demographics using univariant descriptive analysis, t-test and chi square where appropriate. Our hypothesis testing was performed using multivariable modeling, controlling for baseline variables, we will use two-side test with an Alpha of .05.

Chapter IV Results

4.1 Results

Since 1999 nearly 841,000 people have died from a drug overdose (CDC, 2022), and substance use disorder (SUD) continues to be a crisis that faces communities across the country. As the crisis continues across communities, the need for medication-assisted opioid use disorder (MOUD) therapy continues to surge. While the use of MOUD is increasingly common, high large the potential cost savings are at the population were not known.

The objective of this study was to compare the short-term (60-days) use of buprenorphine versus the long term (12 months) use of buprenorphine for patients with opioid use disorder. This study was a retrospective analysis of archival data from large national data sources, in which well-matched cohorts of patients with short and long-term use of MOUD were constructed using propensity score matching of 3-months of baseline data.

We identified patients with at least two ICD diagnosis codes of OUD, that also had a least one prescription of buprenorphine, in the MarketScan® data for 2018-2020 for patients ages 18-45. Patients that had less than 60 days of coverage were classified as short-term patients, and patients that had 12 months or more of continuous coverage were classified as the long-term treatment group.

Table 1: Demographic and Unadjusted Medical Care Utilization Measures for Patients Matched based on 90-days Pre-Buprenorphine Initiation Records by Propensity-Scores.

Variable Name	Long Term Use of Buprenorphine N=9,817	Non-Long-Term Use of Buprenorphine N=9,817	Statistic
Age Mean (SD)	43.6(11.5)	42.2 (12.9)	
Sex N (%)			<.001
Male (%)	5,787(58.9)	5,134(52.3)	
Female (%)	4,030(41.1)	4,683(47.7)	
Geographical Location (%)			<.001
Rural (%)	1,773(18.1)	1,340(13.6)	
Urban (%)	8,044(81.9)	8,477(86.4)	
Days in Hospital Mean (SD)	1.4(7.7)	3.2(10.2)	
Annual Admission Mean (SD)	0.214(1.0)	0.448(1.2)	
Annual Medical Cost Mean (SD)	$15,904(41,931)	$25,419(63,158)	
Annual Buprenorphine Cost Mean (SD)	$3,898.50(2,447)	$331.82(287)	
Annual Patient Cost for Buprenorphine Mean (SD)	$571.76(645)	$44.60(66)	
Death or Incarceration Number (%)	117 (1.2)	291(3.0)	<.001

Table 1 above describes the study populations by treatment category after the selection by matching and show population resource use for the 12 months after initiation of buprenorphine treatment. Univariate statistics are used to examine difference between the groups. The long-term use group is slightly older, with more male patients and more rural residents, despite the successful matching. To control for the effects of the variations we will examine all outcomes using multivariable regression models. However, it is clear from the univariate comparison that patients with long-term use of buprenorphine have lower rates of death or incarceration in the 12 months of follow up. Thy also use fewer medical resources measured by hospital admissions, days in the hospital and total medical care costs. As expected, the cost of buprenorphine is greater for patients with 12 months of use than that observed for patients stopping after 60 days or less.

The population selected for this comparison is described in Table 1. We extracted patient characteristics from all bills for 90-days preceding the initiation of buprenorphine, and matched patients by year of treatment start, age, sex, rural/non-rural residence, US region, admission to hospital during the period (yes/no) using propensity-score matching (SAS Proc March greedy algorithm) specifying a maximum of 0.2 mean standardized difference for the analysis. We achieved excellent matching for 9,817 patients, as shown by the green circles all clearly located within the cutoff bands on Figure 1 below. The group comparisons before the match (shown as an x with a red circle in the Figure) clearly show large difference in baseline characteristics in the two groups before the matching took place.

Figure 1: Characteristics of Population Before and After Propensity-Score Matching

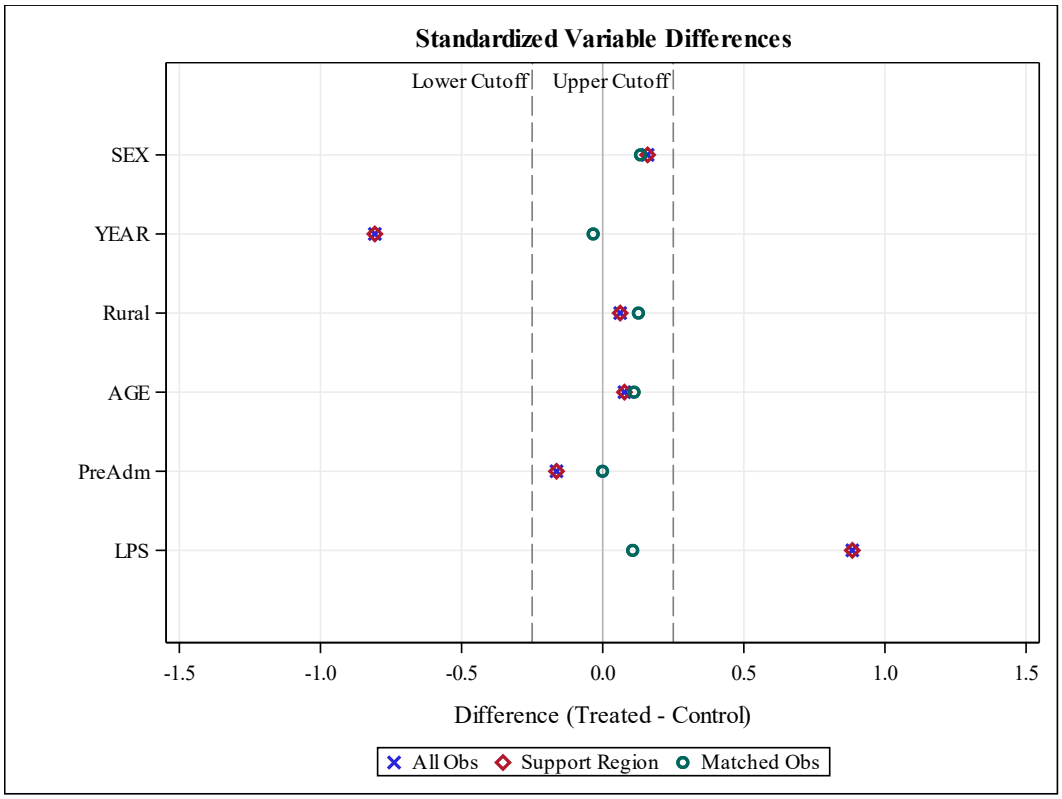

Table 2: Likelihood (Odds Ratio) of Hospital Death or Discharge from Hospital to a Correctional Facility for Patient's with 12+ Months of Buprenorphine Refills Compare to < 60 Days of Refills

Predictor	**OR (95% CI)**	**p-value**
Long use vs. Short Use	0.435 (0.349-0.541)	<.0001
Age	0.972 (0.964-0.980)	<.0001
Male Sex vs. Female	0.877 (0.719-1.071)	0.1995
Rural vs. Urban Residence	0.719 (0.526-1.071)	0.0387
Region of country		
North Central State	0.646 (0.452-0.923)	0.0052
Northeastern State	0.916 (0.658-1.276)	0.7193
Southern States	1.029 (0.782-1.356)	0.0456
Western States (comparison)	Reference group	

Table 2 above shows 57% lower odds of dying during a hospital admission and of being discharged to a correctional facility during the 12 months of treatment compared to short treatment. The adjusted odds ratios and 95% confidence interval of event risk for patients with Long versus Short treatment time is statistically significant after controlling for effects of age, sex, rural residence, and region of the country. The model further shows that rural patients have lower odds of these events that urban residents, that the odds of events is lowest in the North Central US, and highest for residents of Southern states.

Table 3: Mean Annual Medical Care Cost, Number of Days in the Hospital and Number of Hospital Admission for Long Term Buprenorphine Users vs. Non-Long-Term Users of Buprenorphine, Controlling for Difference Between the Groups of Age, Sex, Rural Residence and Region of the US.

Variable	Annual Medical Care Cost Mean (95% CI)	Annual Hospital Days Mean (95% CI)	Annual Hospital Admissions Mean (95% CI)
Long Buprenorphine Use	$16,191 ($15,678-$16,720)	1.28 (1.17-1.40)	0.208 (0.20-0.22)
Non-Long-Term Use of Buprenorphine	$25,745 ($24,909-$26,608)	2.92 (2.66-3.21)	0.415 (0.39-0.44)

Table 3 above shows the mean cost of medical care for the patient group receiving long-term buprenorphine is $16,191 vs. $25,745 for patients on non-long-term use of buprenorphine, for a mean savings of $9,554 per treated patient. These saving are associated with a mean cost for patients that used long-term buprenorphine was $16,191 compared to non-long-term users which was $25,745. Patients using long term buprenorphine have a mean of hospital days of 1.2 per a year compared to non-long-term users of 2.9 days per year. They also have fewer hospital admissions 0.208 vs. 0.415. These differences are all statistically significant after controlling for any differences in age, sex, rural residence or area in the country, as reflected by the lack of overlap of the 95% confidence intervals.

Chapter V Discussion

5.1 Discussion of Results

We performed retrospective analysis of patients that used buprenorphine for opioid use disorder comparing short term use verses long term use of the medication. There was a total of 19,634 patient's data used in the study, evenly distributed among both test groups. Long term buprenorphine users on average have a yearly medical cost of $15,904, which is $9,515 less than those who only use buprenorphine for a short term. Patients that are long term buprenorphine medication not only have lower yearly medical cost, but they are also 57% less likely to die are be incarcerated. Patients that are long term users of buprenorphine also have less hospital admissions and shorter length of stays. While MOUD is becoming increasingly common for patients with OUD, insurance companies would benefit from expanding coverage for buprenorphine medication. Not only does insurance companies have the potential to save money and lower overall health cost for their beneficiaries with OUD, but patient outcomes can be improved.

Policy makers both on federal and state levels should find this study exceptionally intriguing as patients on long term buprenorphine are 57% less likely to die or be incarcerated. Policy makers can use this study to increase awareness of cost benefit of MOUD and pressure insurance providers to increase coverage for patients. Fairley et al. also studied the cost effectiveness of treatments for opioid use disorder (OUD) and determined that MAT combined with contingency management and overdose education was associated with significant health benefits and cost savings compared with no treatment.

5.2 Conclusion

While the opioid epidemic continues to be a wide-spread issue across the United States the need for increased awareness and accessibility to MOUD remains at an all-time high. This study demonstrates that using buprenorphine for MOUD long term not only cost less versus short term but saves lives and decreases chances of incarceration. Future research could potentially include other types of medications, like methadone and naloxone that are also used for MOUD, comparing the short-term verse long term use of the medication with cost outcomes.

This research had the limitation of using other types of medication for a comparison due to billing data. Methadone and naloxone are typically administrated in a clinic and are not always billed at the pharmacy. Since, we used data from pharmacy billing records we were unable to obtain accurate billing data for methadone and naloxone users.

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Appendices

Figure 1: Medications that are used in Treatment of Opioid Use Disorder

Medication	**Pharmacology**	**Advantages**	**Challenges**	**Adverse Effects**
Methadone	Full opioid agonist	• Low risk of precipitating withdrawal symptoms • Administered in opioid treatment programs • Long Half-life	• Dosage adjustment • Administered in opioid treatment programs • Requires QTc monitoring	Opioid toxidrome QTc prolongation Hypoglycemia
Buprenorphine	Partial opioid agonist	• Low risk of respiratory depression • Dispensed at community pharmacy	• Risk or misuse or diversion • Withdrawal symptoms can occur with discontinuation • Prescribers must be waivered providers	Opioid toxidrome, Constipation, vomiting, headache, insomnia, and sweating.
Buprenorphine-naloxone	Partial opioid antagonist	• Low risk of respiratory depression • Dispensed at community pharmacy	• Withdrawal symptoms can occur with discontinuation • Prescribers must be waivered providers	Opioid toxidrome, Constipation, vomiting, headache, insomnia and sweating.
Naltrexone	Competitive opioid antagonist	• Does not cause sedation or respiratory depression • No diversion risk • No waiver needed for prescribers	• Does not reduce cravings • Can precipitate opioid withdrawal • Lack of evidence for treatment retention	Injection site reactions Hepatic enzyme abnormalities, Nasopharyngitis insomnia

[i] *Koehl et al., 2019*

Figure 2: Diagnosis Codes to identify opioid use disorders

ICD-9-CM diagnosis code	Description
30400	Opioid Dependence-Unspecific
30401	Opioid Dependence-Contin
30402	Opioid Dependence-Episode
30403	Opioid Dependence- REMISS
30470	Opioid Other Dep-Unspecific
30471	Opioid Other Dep- Contin
30472	Opioid Other Dep - Episode
30473	Opioid Other Dep- Remission
30550	Opioid Abuse- Unspecific
30551	Opioid Abuse- Continuous
30552	Opioid Abuse- Episodic
30553	Opioid Abuse-In Remission
96502	Poisoning by Methadone
E8501	AAC Poison-Methadone
E8502	AAC Poison-Opiates NEC
E9352	ADV EFF Opiates
E9351	ADV EFF Methadone