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Buprenorphine for Outpatient Treatment of Opioid Dependence (A Clinical Review)

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ABSTRACT

Opioid dependence is a complex health condition that often requires long-term treatment and care. The treatment of opioid dependence is important to reduce its health and social consequences and to improve the well-being and social functioning of people affected. The ultimate achievement of a drug- free state is the ideal and ultimate objective but this is unfortunately not feasible for all individuals with opioid dependence, especially in the short term. Relapse following detoxification alone is extremely common, and therefore detoxification rarely constitutes an adequate treatment of opioid dependence on its own. This makes opioid maintenance treatment an essential component of an effective treatment system for people with opioid dependence. Currently, opioid maintenance treatments like methadone can be dispensed only in a limited number of clinics that specialize in addiction treatment. There are not enough addiction treatment centers to help all patients seeking treatment. Buprenorphine is the first narcotic drug available under the Drug Abuse Treatment Act (DATA) of 2000 that can be prescribed in a doctor's office for the treatment of opioid dependence. This provides more patients the opportunity to access treatment.

KEYWORDS: Buprenorphine, outpatient, opioid, naloxone, methadone, dependence, detoxification

Introduction

Opioids, commonly used as painkillers, have analgesic and euphoric effect. They are either derived from naturally occurring opium (eg heroin) or are made synthetically (eg methadone, buprenorphine). Because of their euphoric effect opioid drugs have a potential for being abused. If used continuously, whether for recreational use or for a medical condition, they have the potential for causing both physical and psychological dependence.

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR) defines opioid dependence as a maladaptive pattern of opioid use, leading to clinically significant impairment or distress. Opioid dependence may be diagnosed if a patient exhibits three or more of the following: 1.Tolerance (need to increase the dose to achieve the desired effect); 2.Withdrawal symptoms when use stops or abruptly declines; 3.Loss of control; 4.Persistent desire or unsuccessful attempts to cut down or control use; 5.Preoccupation with obtaining opioid medications (e.g., multiple doctors, trips to the emergency department); 5.Important social, occupational, or recreational activities forfeited or reduced because of opioid use; 6.Use despite the awareness of adverse physical or psychological problems caused or worsened by opioids [1-2].

Drug dependence can have many negative effects, such as inadvertent overdose, increased risk of infections (e.g. HIV or hepatitis), family distress, disruption at work and involvement in criminal activities. It is difficult to stop using these drugs and remain abstinent due to a combination of craving, unpleasant withdrawal symptoms and the continued or worsening personal circumstances that led to illicit drug use in the first place. Opioid use and dependence are associated with significant medical and psychiatric morbidities, as well as adverse social, familial, vocational, and legal consequences. The risk of criminal activity and legal consequences becomes greater as dependence becomes more severe. Intravenous injection of opioids is associated with increased risk of blood-borne infections such as hepatitis B and C and HIV. Opioid addiction includes not only heroin-related problems, but also the increasingly recognized abuse of prescription pain medications such as hydrocodone, oxycodone hydrochloride, meperidine hydrochloride, and hydromorphone hydrochloride. Rates of addiction to these analgesics have been increasing rapidly.

Epidemiology

Opioid abuse and dependence is increasing because of the availability of opioids through increased global trafficking of heroin and the widespread increase in use of opioid analgesics in the treatment of chronic non cancer pain as well as in acute pain management [3-4]. The estimated worldwide prevalence of opioid use is between 0.3% and 0.5%, equating to 21 to 35 million people [5]. Opioid abuse and dependence are major medical and social concerns throughout the world, contributing to excessive morbidity, mortality, disability, and economic costs [6-7]. The United Nations Office on Drugs and Crime notes that opiates, particularly heroin, are the main problem drugs at a global level, with an estimated 15.6 million opioid abusers globally, including approximately 11.1 million heroin abusers [8].

The number of people aged 12 and older illicitly using prescription pain relievers doubled from 2.6 to 5.2 million between 1999 and 2006. In 2006, 5.2 million surveyed persons had used prescription pain relievers illicitly in the past month, 17 times the number of people who had used heroin. 2.2 million persons aged 12 or older used prescription pain relievers illicitly for the first time in 2006.This is more than any other illicit drug, surpassing marijuana (2.1 million new users), and dwarfing heroin (91,000 new users) [9]. According to the National Survey on Drug Use and Health, there were 140,000 new heroin users older than 12 years of age in 2010 [10]. Nonmedical use of prescription opioids is a cause of increasing concern. Lifetime nonmedical users of pain relievers grew from 31.8 million (13.2%) in 2004 to 34.8 million (13.7%) in 2010; and a 250% increase in oxycodone-related hospital admissions have been observed from 2004 to 2009 [11-14].

From 1999-2002, opioid analgesic poisonings on death certificates increased 91%. During the same period, fatal heroin and cocaine poisonings increased 12.4% and 22.8%, respectively. In 2002, 5,528 deaths were reported from prescription opioid analgesic poisonings, more than either heroin or cocaine. For patients receiving opioid prescriptions, higher opioid doses were correlated with an increased risk of opioid overdose death across diagnoses and regardless of substance abuse status [15].

Treatment

Development / Legislation- From Opioid Treatment Programs to Office Based Therapy

In 1935, U.S. Public Health Services opened a hospital in Lexington, Kentucky, devoted to the treatment of opioid dependence. However, treatment was entirely detoxification-based at that time. In the 1960s, Dole and Nyswander demonstrated that methadone was an effective treatment for opioid addiction**.** In 1963, the New York Academy of Sciences recommended that clinics be established to dispense narcotics to opioid-dependent patients. In 1970, in the Controlled Substances Act (CSA), Methadone was controlled as Schedule II narcotic. Schedule II drugs includes drugs with a high abuse risk, but also have safe and accepted medical uses. These drugs can cause severe psychological or physical dependence. The CSA also creates a closed system of distribution for those authorized to handle controlled substances. The corner-

stone of this system is the registration of all those authorized by the DEA to handle controlled substances. All individuals and firms that are registered are required to maintain complete and accurate inventories and records of all transactions involving controlled substances, as well as security for the storage of controlled substances.

However, till 1974, opioids could not be used for the treatment of opioid addiction as there was significant apprehension among physicians in treating narcotic addicts because of the Harrison Act of 1914 which had the effect of criminalizing addiction. Also, opioids were controlled substances and were subjected to restrictions. In 1974, the Narcotic Addict Treatment Act (an amendment to the CSA) allowed regulated methadone treatment for opioid addiction, but made off-label use of opioids illegal. The resulting regulations amended the CSA to allow methadone to be dispensed for detoxification or maintenance in federally licensed programs, but not in physician's offices. This led to the development of opiod replacement therapy (Methadone clinics-Methadone maintenance treatment). However the major problem of Methadone clinics was its accessibility to the addict population.

To overcome this limited accessibility, the Drug Addiction Treatment Act (DATA) was passed in 2000 which permits qualified physicians to obtain a waiver from the separate registration requirements of the Narcotic Addict Treatment Act to treat opioid addiction with Schedule III, IV, and V opioid medications or combinations of such medications that have been specifically approved by the Food and Drug Administration (FDA) for that indication. Such medications may be prescribed and dispensed. But there was no approved Schedule III, IV, or V drug for the treatment of opioid dependence in 2000. In October 2002, the Food and Drug Administration (FDA) approved buprenorphine monotherapy product, Subutex, and a buprenorphine/naloxone combination product, Suboxone, for use in opioid addiction treatment. These two are currently the only Schedule III, IV, or V medications to have received FDA approval for this indication. On January 5, 2007, the DATA 2000 was amended to allow physicians currently authorized for 1 year to resubmit a notification of intent to treat 100 patients of opioid dependence with buprenorphine. This effectively changed the limit from 30 to 100 patients per physician.

Objectives of opioid dependence Treatment

Opioid dependence is a chronic, relapsing disease that can be successfully medically treated. However, it is a complex physiologic, social, and behavioral disorder that often coexists with psychiatric illness, as well as, co-morbid medical infectious diseases such as the HIV, hepatitis virus infection or tuberculosis [16-17].

The main objectives of treating and rehabilitating persons with opioid dependence are to reduce dependence on illicit drugs; to reduce the morbidity and mortality caused by the use of illicit opioids, or associated with their use, such as infectious diseases; to improve physical and psychological health; to reduce criminal behaviour; to facilitate reintegration into the workforce and education system and to improve social functioning. The ultimate achievement of a drug free state is the ideal and ultimate objective but this is unfortunately not feasible for all individuals with opioid dependence, especially in the short term.

Treatment strategies

Opioid dependence is most effectively treated through a set of comprehensive medical, social, psychological and rehabilitative services that address all the needs of the individual [18-19]. The use of pharmacotherapies in combination with counseling and behavior therapies to provide a comprehensive therapeutic approach to the treatment of opioid abuse and dependence is termed "Medication Assisted Treatment" or MAT. Research studies have shown that the most efficacious treatments for opioid abuse and dependence comprise MAT and include psychosocial counseling, financial, legal, educational services as well as wrap around social services [19]. There are a wide variety of treatment options, both inpatient and outpatient.

A. Methadone maintenance treatment :

At present, there are no direct interventions that are capable of reversing the effects of drugs of dependence on learning and motivation systems [20]. Instead, the management of opioid dependence often consists of pharmacotherapy with methadone and buprenorphine, which do not eliminate physical dependence on opioids. Methadone is a long-acting opioid that is generally administered in an outpatient setting (a methadone maintenance clinic). The methadone prevents the individual from experiencing opioid withdrawal, reduces opioid craving, and enables the individual to have access to other services (such as individual counseling, medical services, and HIV-prevention education). A proper dose of methadone also prevents the individual from getting "high" from heroin. Methadone maintenance therapy can decrease criminal activity, decrease HIV-risk behaviors, and increase stability of employment. Low-dose methadone maintenance treatment is preferable for pregnant individuals who would otherwise use illicit opioids. A longer-acting alternative to methadone is LAAM (levo-alphacetylmethadol). Individuals receiving the proper doses of LAAM only need to take it three times per week, instead of every day as with methadone.

Opioid treatment programs (OTPs), methadone maintenance programs that embrace interventions such as counseling services, vocational resources, referrals, and appropriate drug monitoring, have been shown to reduce opioid use and related crime, increase employment, and decrease the incidence of human immunodeficiency virus (HIV) infection related to needle sharing [21]. In addition, abusers enrolled in such programs gain improved physical and mental health, and decreased overall mortality from opioid addiction. Unfortunately, despite these results, the capacity of the methadone maintenance treatment system has not kept pace with the rise in opioid addiction [21].

However, methadone is only available in specialized treatment programs, called Opioid Treatment Programs (OTPs) that are regulated by Center for Substance Abuse Treatment (CSAT), Substance Abuse and Mental Health Services Administration (SAMHSA). Primary care providers, therefore, are unable to provide this treatment to patients.

B. Opioid antagonist treatment.

An opioid antagonist is a medication that blocks the effects of opioids. Treatment with an antagonist, usually naltrexone, typically takes place on an outpatient basis following an inpatient medical detoxification from opioids. The effects of taking any opioids are blocked by the naltrexone and prevent the individual from getting "high," thereby discouraging individuals from seeking opioids. By itself, this treatment is suitable for individuals highly motivated to discontinue opioid use. However, antagonists can be used in addition to other treatment modalities or with individuals who have been abstinent for some time but fear a relapse.

C. Opioid agonist-antagonist treatment

An opioid agonist is a drug that has a similar action to morphine. Buprenorphine (Buprenex) is an example of an opioid agonist-antagonist, which means it acts as both an agonist (having some morphine-like action) and antagonist (it blocks the effects of additional opioids). Buprenorphine has been shown to effectively reduce opioid use. It is also being studied for opioid detoxification.

Office-based (Outpatient) treatment of opioid dependence:

Rationale for Office-based Opioid Treatment:

The rationale for office based treatment of opioids includes- increased access to treatment as methadone maintainence clinic caters to a very minor population of opioid absuers. Office based approach will improve coordination of general medical, psychiatric, and substance abuse care "under one roof." It will treat opioid dependence like other chronic diseases seen in office settings and avoid stigma. It will limit contact with patients still actively using drugs and recognize and reinforce patient's treatment success. The intent is that office-based treatment with buprenorphine will bring addiction care into the mainstream of medicine by greatly expanding access and providing hope to thousands of drug abusers.

Buprenorphine as Option in Treatment Programs for Opioid dependence:

In an effort to expand access to opioid agonist therapy beyond traditional opioid agonist therapy programs, Congress made an amendment to the Drug Addiction Treatment Act (DATA 2000), signed in 2002, which allows qualified physicians to prescribe and dispense approved buprenorphine (Subutex) and buprenorphine/naloxone (Suboxone) sublingual in office-based practices. Buprenorphine's availability has encouraged opioid-dependent patients who would not otherwise present themselves to an OTP to access treatment.

Pharmacological properties of buprenorphine
Buprenorphine, sold as Buprenex or Subutex, is a long-acting partial opioid agonist that is classified as a Schedule III narcotic, in contrast to methadone and LAAM, which are Schedule II [22]. Opioid partial agonists are drugs that activate receptors, but to a lesser degree than full agonists. Increasing the dose of a partial agonist does not produce as strong an effect as does increasing that of a full agonist. Buprenorphine has unique pharmacologic properties that make it an effective and well-tolerated addition to available pharmacologic treatment modalities for addiction.

Partial agonist- does not induce "High" in opiod dependent patients:
is a partial opioid agonist. Since it is a partial agonist, it helps to treat opioid dependence by activating mu-opioid receptors enough to prevent withdrawal symptoms but not enough to induce a high (though it does so in opioid-naive individuals).

"Ceiling effect" makes overdose less serious:
Buprenorphine has a ceiling effect, meaning that beyond a certain dose (generally considered to be 32mg), no further effect is achieved. Thus, the risk of respiratory depression is lower than full agonists such as methadone, and an overdose is far less likely to have serious consequences.

High receptor affinity prevents 'high" from other opioid abuse:
Buprenorphine has a higher affinity for the mu-opioid receptor than other opioids. If another opioid is taken concurrently, it will have no effect since buprenorphine blocks the receptor site.

Long half life offers once a day dosing:
Buprenorphine has a half-life of 24 to 36 hours. It attaches tightly to opioid receptors and dissociates slowly from them, giving it a 2- or 3-day duration of action. This makes daily or every-other-day dosing possible.

Good safety profile allows office prescription:
Buprenorphine can be prescribed in an office setting on an outpatient basis just like medications for any other chronic disease.

Slow onset of action prevents sedation and euphoria:
Because of its slow onset of action, opioid-dependent patients do not experience sedation or euphoria when taking the appropriate dose.

Partial agonist properties help maintain compliance:
The partial agonist properties of buprenorphine make it a safe and effective option for treatment of patients for opioid addiction. Buprenorphine has sufficient agonist properties such that when it is administered to individuals who are not opioid dependent but are familiar with the effects of opioids, they experience subjectively positive opioid effects. These subjective effects aid in maintaining compliance with buprenorphine dosing in patients who are opioid dependent.

Partial agonist properties mean low abuse potential:
Although buprenorphine can be misused (consistent with agonist action at opioid receptors), its abuse potential is lower in comparison with a full opioid agonist.

Buprenorphine-Naloxone Combination
A new formulation containing buprenorphine in combination with naloxone has been developed to decrease the potential for abuse via the injection route. Buprenorphine is also available as a combined product of buprenorphine and naloxone in a 4:1 ratio. Unlike methadone, which is dispensed in 100 mL of orange juice, buprenorphine is a tablet that can be easily crushed and injected. Adding naloxone to buprenorphine prevents intravenous abuse of buprenorphine. Naloxone is an opioid antagonist and has poor oral bioavailability. Naloxone does not interfere with the pharmacokinetics or effectiveness of buprenorphine when the combination formulation is taken sublingually [23-25]. But, naloxone, when used intravenously, displaces other opioids from endorphin receptors because of its high receptor affinity and precipitates withdrawal in opioid-dependent patients, thereby discouraging intravenous abuse [26,27]. Physicians who prescribe or dispense buprenorhine or the buprenorphine and naloxone combination should monitor for diversion.

Buprenorphine In pregnancy
Buprenorphine has been administered successfully to opioid-dependent pregnant women as a maintenance replacement opioid. Placental transfer may be less than methadone, reducing fetal exposure and subsequent dependence and withdrawal. Buprenorphine has a low incidence of labor and delivery complications and of neonatal abstinence syndrome [28]. However, buprenorphine enters breast milk, and treatment with buprenorphine is strongly advised against during the nursing period [29]. Buprenorphine-naloxone in combination is contraindicated in pregnancy because the safety of naloxone in pregnancy has not been established.

Indications of buprenorphine for opioid dependence
Opioid Dependence: Patient has mild to moderate dependence on opioids (oral, intranasal, or intravenous) [30,31].

Compliance: Patient can be expected to be reasonably adherent to the treatment plan.

Patient education and understanding: Patient has been educated about the risks and benefits of buprenorphine treatment. Explaining to the patient what buprenorphine can do (block illicit opioid effects, decrease craving) and what it cannot do (prevent him or her from ever using drugs again) may help enhance treatment outcomes.

Safety: Patient is willing to follow safety precautions for buprenorphine treatment.

Consent and agreement: Patient has agreed to buprenorphine treatment after a review of treatment options [32].

Intolerance to methadone: Patients who have failed or have adverse effects with methadone.

Early relapse after detoxification: Early relapse after detoxification suggests that the patient needs opioid replacement treatment with either methadone or buprenorphine.

Short term treatment: Buprenorphine is preferred for patients who might be able to successfully taper off buprenorphine after several months as buprenorphine has a milder withdrawal syndrome and might be easier to discontinue than methadone [33].

Methadone toxicity: Older patients, those taking benzodiazepines or other sedating drugs, heavy drinkers, patients with chronic obstructive pulmonary disease or other respiratory illnesses are at increased risk of toxicity to methadone.

Contraindications of buprenorphine for opioid dependence:
Buprenorphine Intolerance: Failed or had adverse effects with buprenorphine or poor response to previous treatment with buprenorphine

Buprenorphine abuse: Intravenous buprenorphine abuse

Poly drug abuse: Comorbid dependence on high doses of benzodiazepines or other central nervous system depressants. Buprenorphine use is contraindicated for patients with alcohol intoxication, delirium tremens, and treatment with monoamine oxidase inhibitors.

Cormorbidity: Significant psychiatric comorbidity

Suicidal Ideation: Active or chronic suicidal or homicidal ideation or intents

Multiple relapses: Multiple previous treatments for drug abuse with frequent relapses

High risk of treatment dropout

Concurrrent medical comorbidities: Some co-occuring medical conditions can be contraindications for buprenorphine use. These could include difficult breathing or lung problems, kidney or gallbladder problems, head injury, severe mental disorders, adrenal or thyroid dysfunction, urination problems, or enlarged prostate. Patients taking

buprenorphine who have hepatitis or impaired liver function should be routinely monitored, especially when taking high doses, because the medication's potential to increase liver damage has not been fully evaluated [35].

Treatment Protocols

Protocols for treatment with buprenorphine for opioid addiction consist of three phases: induction, stabilization, and maintenance.

Induction:

Induction involves medically supervised introduction of a partial agonist – buprenorphine and switching from the full agonist opioid of abuse. The goal is to find the minimum dose of buprenorphine at which the patient discontinues or markedly diminishes use of opioids and has no withdrawal symptoms, minimal or no side effects, and no craving for the drug of abuse. Induction is typically initiated as observed therapy in the physician's office.

When to start buprenorphine induction:

Buprenorphine therapy should be started only after clear and objective signs of opioid withdrawal are present. The reason is that buprenorphine will displace other opioids from the patient's mu opioid receptors. This effect may propel a patient who is not already in withdrawal into withdrawal if buprenorphine does not also provide enough mu opioid receptor stimulation to compensate for what the other opioid was providing. Waiting to initiate buprenorphine therapy until the patient enters withdrawal from the other opioids entails some mild discomfort for the patient, but it provides a good indication that the concentration of other opioids is probably low enough that buprenorphine can be administered safely. For some patients, the period for transition to buprenorphine may be as little as 4 to 6 hours if they have been using shortacting opioids or as much as 24 to 96 hours for longacting opioids [35,36].

Buprenorphine or Buprenorphine- Naloxone combination:

For a patient who is dependent on a short-acting opioid like heroin, Buprenorphine- Naloxone will probably be appropriate for induction. Buprenorphine- Naloxone is also likely to be preferred in cases where medication is dispensed to be taken away from the office or clinic. Patients on long-acting opioid agonists such as OxyContin (oxycodone) or methadone may experience less severe withdrawal symptoms if initially given Buprenorphine but after 3 days can be switched to the buprenorphine-naloxone combination [35].

Stabilization

Stabilization is begun when a patient is having no withdrawal symptoms, minimal or no side effects, and no longer has uncontrolled cravings for opiate agonists. Dosage adjustments may be necessary during early stabilization, and frequent contact with the patient increases the likelihood of compliance: four or five times a month the first month, then once every 2 weeks thereafter.

Maintenance phase

The maintenance phase is reached when the patient is doing well on a steady dose of buprenorphine (or buprenorphine/naloxone). The length of time of the maintenance phase is individualized for each patient and may be indefinite. The alternative to going into (or continuing) a maintenance phase, once stabilization has been achieved, is medically supervised withdrawal. This takes the place of what was formerly called "detoxification."

Training required for burprenorphine prescription by physicians:

To practice office-based treatment of patients with opiate addiction under the auspices of DATA 2000, physicians must first obtain a waiver from the special registration requirements established in the Narcotic Treatment Act of 1974 and its enabling regulations. All physicians must go through a wavier process before they are able to prescribe buprenorphine. A physician must (1) meet the training requirements or be otherwise "qualified"; and (2) complete a waiver notification form and submit it to SAMHSA/CSAT.

Comparision of buprenorphine with methadone

Buprenorphine offers several advantages over methadone, including lower cost, milder withdrawal symptoms following abrupt cessation, lower risk of overdose, and longer duration of action, allowing alternate-day dosing [22,38]. Identifying subpopulations of opioid addicts who differentially respond to buprenorphine versus methadone has not been clearly established. However, patients with less chronic and less severe heroin dependence benefit more fully from buprenorphine than from a pure opioid agonist like methadone [38].

One study comparing buprenorphine and methadone-maintained patients observed that, unique to buprenorphine patients, those with histories of sedative dependence stayed in treatment longer and used less cocaine [39]. Other research has reported differential responses to buprenorphine between men and women, with women showing greater or lesser drug use than did men or methadone-maintained women [39-41]. Studies support buprenorphine as a viable alternative for opioid maintenance therapy. However, its mixed agonist/antagonist action entails special considerations. Buprenorphine may precipitate opioid withdrawal, and patients being switched from short-acting opioids must abstain from illicit opioid use for at least 24 hours before initiating buprenorphine therapy [22]. Another drawback is associated with the sublingual route of administration. This administration presents some difficulties because the tablet is relatively large and slow to dissolve under the tongue and swallowing diminishes its effectiveness. Also, the transition to buprenorphine from long-acting opioids is difficult [20].

Flexible dose buprenorphine versus Flexible Dose Methadone is more likely to retain patients than Flexible dose buprenorphine [42,43]. Low dose methadone is more likely to retain patients than low dose buprenorphine [44]. Medium dose methadone is more likely to retain patients than low dose buprenorphine [45]. Medium dose buprenorphine and low dose methadone are eqally likely to retain patients [44,46]. Medium dose methadone is superior to low dose buprenorphine in suppressing heroin use [46].

Higher doses of buprenorphine (12 mg or greater) are more effective than lower doses in reducing illicit opioid use, with some studies reporting similar efficacy to methadone on major treatmentoutcome measures. However, incidence of relapse was greater with buprenorphine than methadone in a 2011 study of 34,000 Massachusetts Medicaid beneficiaries [38]. The primary advantage of buprenorphine over methadone is its superior safety profile [20]. Large observational studies have found that buprenorphine has a much lower risk of overdose than methadone, and this makes it safer for use in primary care [47-49]. An analysis of French overdose deaths between 1995 and 1998 found an average annual death rate of 0.47% for patients taking methadone, compared with 0.05% for buprenorphine [50]. Studies examining the effectiveness of opioid substitution treatment have found that buprenorphine results in superior retention rates (in comparison to abstinence only treatment), reduces the amount of illict and nonprescribed opioids used by patients, decreases criminal activity, and helps to reduce the transmission of HIV among drug users and the occurrence of high-risk injection practices [51-53].

In patients treated with buprenorphine/naloxone, a significant improvement has reported in social life status, in the educational level and in the toxicological conditions compared to methadone [54]. A significantly better retention rate has been reported in methadone maintained patients compared to buprenorphine. However, illicit opiate consumption has been reported to be significantly lower in buprenorphine maintained patients [55]. Clinical trials comparing the efficacy of buprenorphine to methadone on the outcomes of retention and illicit opioid use have demonstrated similar results when compared with low doses of methadone (20 to 30 mg) [56]. A clinical trial comparing buprenorphine, the buprenorphine/naloxone combination, and placebo was terminated early because buprenorphine and naloxone in combination and buprenorphine alone were found to have greater efficacy than placebo. Opioid-negative urine samples were found more frequently in the buprenorphine and buprenorphine/naloxone groups (17.8% and 20.7%, respectively) than in the placebo group (5.8%, $p < 0.001$ for both comparisons) [23].

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