OPIATES ADDICTION —IS THERE ANY CURE

Original Research Article

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ABSTRACT

Opiates are some of the world's oldest known drugs. Derived from the poppy plant, the use of natural opiates dates back to ancient times and there is even archaeological evidence that suggests that the opium poppy may have been used by man over 30,000 years ago. [1]Any drug derived from the poppy plant, whether naturally or synthetically, is a type of opioid. This includes illegal drugs like heroin and regulated drugs like morphine, codeine and oxycodone, which are often used by healthcare professionals for pain management. Opiates are drugs in the opioid family that are derived directly from the poppy plant and not processed synthetically. There are over 50 known types of opioids, which are often known by their brand name rather than their scientific name. For example, oxycodone is the scientific name for one type of opioid, which is sold under several brands that use oxycodone as the main ingredient, including OxyContin and Percocet. Often prescribed by healthcare professionals to address acute, episodic and chronic pain, opioids can create a powerful psychological addiction that can develop from the use of licit (legal) or illicit (illegal) forms of the drug. Early identification and drug use management is essential. Use of opiates is the fastest growing substance used throughout the world. Morbidity and mortality related to HIV, hepatitis C, and overdose. Treatment for opiate addiction requires long-term management. Their use in the management of acute severe pain and chronic pain related to advanced medical illness is considered the standard of care in most of the world. In contrast, the long-term administration of an opioid for the treatment of chronic non-cancer pain continues to be controversial. Behavioral interventions alone have extremely poor outcomes, with more than 80% of patients returning to drug use. Similarly poor results are seen with medication assisted detoxification. This article provides a **topical review** of the **three medications** approved for long-term treatment of opiate dependence: the opioid agonist **methadone**, the opioid partial agonist **buprenorphine**, and the opioid antagonist **naltrexone**. **Results** indicate that maintenance medication provides the best opportunity for patients to achieve recovery from opiate addiction. Either methadone or buprenorphine is associated with retention in treatment, reduction in illicit opiate use, decreased craving, and improved social function. Oral naltrexone is ineffective in treating opiate addiction but recent studies using extended release naltrexone injections have shown promise. While no direct comparisons between extended release naltrexone injections and either methadone or buprenorphine exist, indirect comparison of retention shows inferior outcome compared to methadone and buprenorphine. **Further work is needed** to compare directly each medication and determine individual factors that can assist in medication selection. Until such time, selection of medication should be based on informed choice following a discussion of outcomes, risks, and benefits of each medication.

Keywords: Review, opiate, addiction, methadone, buprenorphine, naltrexone, pharmacotherapy

I. INTRODUCTION

Most medical practitioners will see patients who have become addicted to illegal drugs. In addition, with increasing opioid prescribing, [1] more patients are developing prescribed opioid addiction. Opioid addiction or dependence syndrome is synonymous terms which refer to a state of compulsive drug use despite related harm. This is exemplified by continued opioid injecting despite sustaining overdoses or infections. In other opioid dependent patients (for example with prescribed opioid dependence) excessive or unsanctioned use may be correlated with drug-related impairment (such as sedation or overdose) and accidents. Addiction can be considered as a chronic disease, with a relapsing and remitting pattern, significant long-term morbidity and an increased risk of death.[2] One approach to managing addiction is the use of opioid substitution therapy with drugs such as methadone. This therapy has a substantial evidence base for improving physical and social health outcomes (reducing drug crimes, blood-borne viral spread and overall mortality).[4–8] The provision of opioid substitution therapy is not simply maintaining addiction, because it also significantly reduces harm. It is therefore appropriate that methadone is included in the World Health Organization's Essential Medicines List for treating opioid addiction.[9]

II. CAUSES

1. Trauma or Other Physical Injury, Mood changes affect performance like: Street brawls and gang fights are often initiated and carried out under the influence of drugs and alcohol. , Driving vehicles or operating machinery under the influence of alcohol/ drugs, Poor judgment, delayed reaction, poor coordination and a disregard for safety guidelines due to intoxication. The user may participate in high-risk behavior like climbing high places or handle fire recklessly under the notion that nothing can happen to him.

2. Perceptual Distortions Perceptual distortions can also result in accidents. He may step off a fast moving bus under the mistaken impression that it is moving slowly, or may step off the parapet of a terrace and fall, as his sense of judgment related to space is also affected.

3. Acute Intoxication Reaction when he is under the influence of a high dose of the drug, he may react in an unusual manner. Narcotic analgesics can cause apathy, sedation, and psychomotor retardation. He may remain unmoved and not respond even to a crisis like a fire. If he is agitated, he needs to be watched carefully as he may harm himself or others. Forcing him to eat or drink when he is in the stage of intoxication is risky. As his swallowing reflexes are poor, food particles can go down the wind pipe.

4. Coma and Overdose Deaths Users steadily increase the drug intake as tolerance grows. While tolerance develops to effects like euphoria, the increased drug intake may be dangerously high and may lead to respiratory depression, coma and death. IV (intravenous) narcotic abusers are highly prone to overdose deaths of this kind. A combination of alcohol and sleeping pills is particularly dangerous. While alcohol is readily absorbed and the effect is felt immediately, sleeping pills take longer to act. The user may continue to drink alcohol under the impression that he is not 'high' enough. Later, when the sleeping pills begin to take effect on the brain, the resulting overdose can cause death.

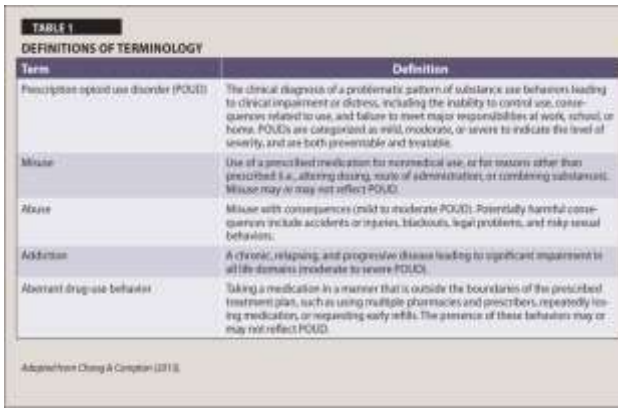


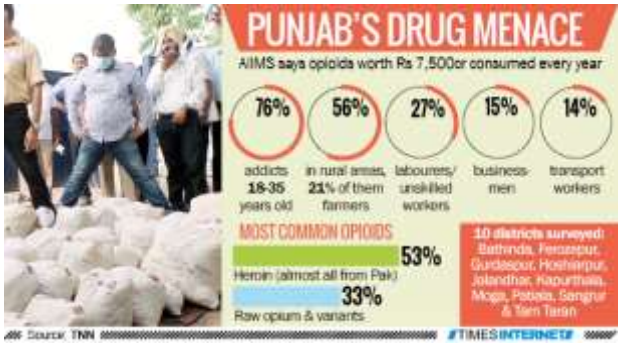
TABLE 1

DEFINITIONS OF TERMINOLOGY

Term	Definition
Prescription opioid use disorder (POUD)	The clinical diagnosis of a problematic pattern of substance use behaviors leading to clinical impairment or distress, including the inability to control use, consequences related to use, and failure to meet major responsibilities at work, school, or home. POUDs are categorized as mild, moderate, or severe to indicate the level of severity, and are both preventable and treatable.
Misuse	Use of a prescribed medication for nonmedical use, or for reasons other than prescribed (i.e., altering dosing, route of administration, or combining substances). Misuse may or may not reflect POUD.
Abuse	Misuse with consequences (mild to moderate POUD). Potentially harmful consequences include accidents or injuries, blackouts, legal problems, and risky sexual behaviors.
Addiction	A chronic, relapsing, and progressive disease leading to significant impairment in all life domains (moderate to severe POUD).
Aberrant drug-use behavior	Taking a medication in a manner that is outside the boundaries of the prescribed treatment plan, such as using multiple pharmacies and prescribers, repeatedly losing medication, or requesting early refills. The presence of these behaviors may or may not reflect POUD.

Adapted from Chang & Compton (2013).

Abuse/Misuse Of Opiates



Opiates Have Become Necessity

Opioid maintenance therapy & Discussion

Pharmacologic therapy for heroin addiction has focused on ameliorating withdrawal symptoms and reducing cravings. By replacing heroin with legally obtained opioid agonists, many risk factors of the drug-abusing lifestyle can be mitigated.

Methadone maintenance therapy [14] (MMT) has been the standard of care for more than **30 years**. However, the recent advent of buprenorphine maintenance therapy (BMT) is changing the landscape of treatment for opioid-dependent patients. [3, 5]

Methadone, a long-acting synthetic opioid agonist, can be dosed once daily and replaces the necessity for multiple daily heroin doses. Methadone is a highly regulated Schedule II medication, only available at specialized methadone maintenance clinics.

Buprenorphine is a mu-opioid partial agonist that, like methadone, suppresses withdrawal and cravings. However, the property of partial agonism confers a "ceiling effect," at which higher doses of buprenorphine cause no additional effects. Buprenorphine has been combined with Naloxone [3, 6] in a 4:1 ratio. Naloxone is an opioid antagonist that is poorly absorbed sublingually and orally but is well-absorbed intravenously. As a result, an opioid-dependent patient injecting buprenorphine/Naloxone will suffer a withdrawal syndrome due to naloxone's occupation of mu-opioid receptors. Buprenorphine/Naloxone sublingual tablets in July **2013** were tried for the maintaining treatment of opioid dependence. The new formulation has high bioavailability, a fast dissolve time, a small tablet size, and a menthol flavor to encourage patient adherence with treatment. [4] Zubsolv's indication was expanded to include induction dosing for patients dependent on short-acting opioids (eg, heroin) in **2015**. For patients dependent on long-acting opioids (eg, methadone), buprenorphine Monotherapy is recommended for induction.

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In **June 2014**, buccal form of buprenorphine/Naloxone (Bunavail) for opioid dependence maintenance therapy was introduced. The film was shown to be safe and effective with less constipation than with Suboxone. [4]

In **August 2015**, in patients maintained on buprenorphine were treated with clonidine. Those given clonidine maintained initial abstinence for longer periods suggesting that clonidine could be a useful adjunctive maintenance treatment alongside buprenorphine. Office-based treatment of opioid addiction is now possible with BMT. [4] or practiced in a qualified practice setting. [4] In **2016**, the try was given to the first buprenorphine implant (Probuphine) for opioid dependence. The implant, which is comprised of four, one-inch-long rods that are implanted under the skin on the inside of the upper arm, provides a constant, low-level dose of buprenorphine for six months. Each rod contains approximately **80 mg of the drug for a total of 320 mg** implanted at once. The implant is designed for use in patients who are already stable on a low dose of the drug, because it must be inserted and removed surgically. Only health care providers who have completed the training called as the Probuphine could use this. Risk Evaluation and Mitigation Strategy **(REMS)** program should insert and remove the implants. [5]

Ling et al studied the efficacy of buprenorphine implants over a 6-month period in patients with opioid dependence. Initial induction with sublingual buprenorphine-Naloxone tablets preceded implant placement. Less opioid use was observed (as assessed by urine samples) in patients using the buprenorphine implants.

In 2017, the FDA approved a once-monthly SC injection (Sublocade) for opioid use disorder (**OUD**). When injected, it forms a solid mass upon contact with body fluids from the Atrigel delivery mechanism. The drug must be administered in a healthcare setting to avoid inadvertent IV administration that could result in death. Treatment with a transmucosal buprenorphine-containing product has been given on a stable dose of transmucosal buprenorphine treatment for ≥7 days. [47]

Historically, l-alpha-acetylmethadol (LAAM) has also been used for opioid-dependence maintenance pharmacotherapy. However, LAAM is associated with prolonged QT interval, and several cases of cardiac arrhythmia and death have been reported. Therefore, LAAM was recently removed. Several ***Cochrane Database Systematic Reviews*** about the efficacy of opioid agonist therapy have been published in recent years. While all of these reviews stress the need for larger, multicenter, randomized clinical trials of longer duration, some conclusions can be drawn from existing data. A review of *Cochrane* reviews found that high-dose MMT (60-109 mg/d) is more effective in retaining patients in treatment than low-dose MMT (1-59 mg/d). Moreover, methadone at flexible doses was more effective in retaining patients in treatment (RR, 1.23) than buprenorphine. A second systematic review of databases found that low-dose methadone (20 mg/d) was less effective than buprenorphine (2-8 mg/d) and that high-dose methadone (>50-65 mg/d) was more effective than buprenorphine (2-8 mg/d).

Another ***Cochrane* review** found that oral substitution treatment was associated with significant reductions in heroin injection. Although pain is common among opioid-dependent patients, pharmacologic approaches are limited. Tsui et al found that treatment with escitalopram, a selective serotonin reuptake inhibitor, was associated with clinically meaningful reductions in pain severity and pain interference during the initial 3 months of treatment. [9]

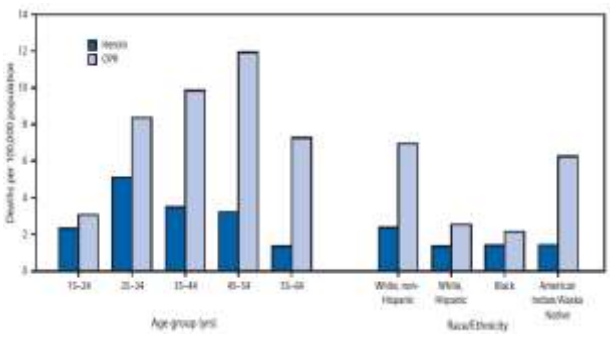
Preventing opioid dependence relapse

A randomized, placebo-controlled trial suggested that an Injectable, sustained-release form of naltrexone (Depotrex) increased retention of patients in treatment for opioid abuse. [5] Further studies are necessary to evaluate the efficacy of this treatment modality.

Once monthly treatment with extended-release IM naltrexone showed statistically significant higher rates of opioid-free urine screens compared. A trial demonstrated that naltrexone-assisted detoxification increased the likelihood of a successful transition to extended-release injection naltrexone (XR-naltrexone) by almost threefold compared with those given a buprenorphine taper. In a study 250 patients with opiate dependence were given monthly injections of an extended-release formulation of 380 mg of naltrexone or placebo. [2] The study found substantial benefit in the actively treated group, with abstinence rates of 90%. Other measures confirmed this benefit, with a median retention of 168 days in the naltrexone group compared with 96 days in the placebo group, and reduced craving in the naltrexone group. Given the poor therapeutic efficacy of oral naltrexone in most opioid-dependent populations, this intramuscular formulation may be a valuable.

The use of naltrexone was shown to be effective in fostering sobriety in heroin- and amphetamine-dependent outpatients in a 10-week randomized, double-blind, placebo-controlled trial. A long-acting buprenorphine subdermal implant (Probuphine) was approved **May 2016** for use in opioid tolerant patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product. Four implants (80 mg/implant of buprenorphine HCl) are inserted in the upper arm for **6 months** of treatment and removed by the end of the sixth month. Treatment with **catechols-O - methyltransferase (COMT)** inhibitors may improve adherence to buprenorphine maintenance treatment for opioid addiction. [5] In a study remained abstinent for longer than 6 months when they received the COMT inhibitor entacapone (200-1000 mg/day) were given in addition to buprenorphine. Another 61 patients (24.1%) remained abstinent for 12- to 24 months and 41 (16.2%) remained abstinent for 24- to 30 months. Forty-one (16.2%) patients were able to achieve abstinence using long-acting naltrexone. [5] This is the first study of its kind to demonstrate COMT-inhibitors' anticraving effects.

Stress has been associated with impaired decision making and increased risk for relapse, even after long periods of abstinence. In a double-blind, placebo-controlled, randomized protocol, the negative effects of stress on performance were prevented by the beta-adrenoceptor antagonist propranolol as early as after 30 days and as late as 24 months after abstinence began, suggesting a potential role for beta-blockers in decreasing the risk for relapse. [6]



Heroin Overuse Deaths

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III. OPIATE WITHDRAWAL

Opiate withdrawal is generally considered less likely to produce severe morbidity or mortality compared with barbiturates and benzodiazepines. Safe withdrawal from opioids is termed detoxification and can be performed as outpatient or inpatient therapy., depending upon presence of comorbid medical and psychiatric problems, availability of social support, and polydrug abuse.

First device designed to reduce the symptoms of opioid withdrawal introduced in 2017. The NSS-2 Bridge device is placed behind the patient's ear and emits electrical pulses to stimulate branches of certain cranial nerves. The device can be used for up to 5 days during the acute phase of opioid withdrawal. Approval was based on a single-arm study of 73 patients undergoing physical withdrawal from opioids. Within 30 minutes of using the device, all patients showed a reduction in Clinical Opiate Withdrawal Scale (COWS) score of almost 31%. The device is available by prescription only. [8], buprenorphine & Methadone, and alpha-2 agonists, such as clonidine and lofexidine, are commonly used pharmacologic methods of detoxification. The use of methadone and buprenorphine is based on the principle of cross-tolerance in which one opioid is replaced with another and then slowly withdrawn. Alpha-2 agonists appear to be most effective in suppressing autonomically mediated signs and symptoms of abstinence [9], but they are less effective for subjective symptoms.]Patients experienced decreased side effects and stayed in treatment longer using tapered methadone compared to the alpha-2 agonists clonidine or lofexidine. Buprenorphine was associated with fewer adverse effects than clonidine, and patients were more likely to complete withdrawal with buprenorphine compared with clonidine. Moreover, a second multicenter randomized trial demonstrated that buprenorphine-Naloxone was more effective than clonidine for opioid detoxification. Buprenorphine was equally effective as methadone for withdrawal completion, but withdrawal symptoms appeared to resolve more quickly with buprenorphine.

IV. SUMMARY

Data to date suggest that buprenorphine and methadone are more effective than alpha-2 agonists, such as clonidine, for opioid detoxification, with buprenorphine associated with a shorter duration of withdrawal symptoms. However, all of these medications are effective, and the choice may depend in part on availability. Kunoe et al described use of an investigational naltrexone implant in 56 abstinence-oriented patients who completed inpatient treatment for opioid dependence compared with patients who received usual care instead of the implant. The implant group had an average 45 days less heroin use and 60 days less opioid use than the usual care group over a 6-month period ($P < 0.05$). The naltrexone implant significantly reduced opioid use compared with usual care. [62]

Psychotherapies and support groups

Detoxification alone, without ongoing treatment, is not adequate to manage patients. [6] Patients in methadone programs often benefit from cognitive behavioral, supportive, or analytical-oriented psychotherapies if they are added to standard drug counseling. Cognitive behavior psychotherapy primarily focuses on the patient's thoughts and behaviors. Cognitive behavior–based models are widely used in drug rehabilitation programs. Two major cognitive behavior theories of substance abuse are the following:

Relapse prevention: Based on the work of Marlatt and Gordon, important relapse prevention concepts and techniques include identification and avoidance of high-risk situations, understanding the chain of decisions leading to drug use, and changing one's lifestyle.

Cognitive therapy of substance abuse: Developed by Beck and colleagues, cognitive therapy of substance abuse is based on the concept that drug abusers engage in complex behaviors and thought processes, such as positive and negative drug-related beliefs and spontaneous flashes related to drug use before giving in to the actual drug use.

Dynamic psychotherapy is based on the concept that all symptoms arise from underlying unconscious psychological conflicts. The major goal of this therapy is to help the patient become aware of these conflicts and develop more adaptive coping mechanisms and healthier methods of resolving intrapsychic conflict.

Group therapy is argued to be especially effective because it can target the social stigma attached to having lost the ability to control one's self with regard to the use of a substance. Aversion therapy involves pairing aversive stimuli to cognitive images of opioid use and conversely conjuring images of socially appropriate behaviors such as employment, education, and nondrug behavior. Although psychosocial therapy is likely to be beneficial in the treatment of opiate withdrawal, the specific type of psychosocial therapy may not be important. A Cochrane review assessed 11 studies involving 1592 patients and explored the effectiveness. Five different psychosocial interventions (including behavioral, counseling, and family therapies) were added to treatment with either methadone or buprenorphine. The addition of the psychosocial intervention (regardless of the specific psychosocial approach) to the pharmacological treatment significantly reduced dropouts, use of opioids during treatment, use of opioids during follow up, and clinical absences during treatment. [5]

V. CONCLUSION

Opioid substitution therapy is a highly effective component of comprehensive drug rehabilitation for opioid addiction. It reduces mortality and morbidity. All states and territories provide services to support opioid substitution therapy, including detailed treatment guidelines. However, the numbers of patients seeking treatment are increasing, while the numbers of prescribers are decreasing. Different opioid substitution therapy formulations allow treatment selections better suited to the individual patient. It is important to try and keep the patient in therapy. Regular follow-up is advised to monitor the patient's progress.

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