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Current and Potential Pharmacological Treatment Options for Maintenance Therapy in Opioid-Dependent Individuals

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Abstract

Opioid dependence, manifesting as addiction to heroin and pharmaceutical opioids is increasing. Internationally, there are an estimated 15.6 million illicit opioid users. The global economic burden of opioid dependence is profound both in terms of HIV and hepatitis C virus transmission, direct healthcare costs, and indirectly through criminal activity, absenteeism and lost productivity. Opioid agonist medications, such as methadone and buprenorphine, that stabilize neuronal systems and provide narcotic blockade are the most effective treatments. Prolonged provision of these medications, defined as maintenance treatment, typically produces improved outcomes when compared with short-duration tapers and withdrawal. The benefits of opioid agonist maintenance include decreased illicit drug use, improved retention in treatment, decreased HIV risk behaviours and decreased criminal behaviour. While regulations vary by country, these medications are becoming increasingly available internationally, especially in regions experiencing rapid transmission of HIV due to injection drug use. In this review, we describe the rationale for maintenance treatment of opioid dependence, discuss emerging uses of opioid antagonists such as naltrexone, and sustained-release formulations of naltrexone and buprenorphine, and provide a description of the experimental therapies.

Opioid dependence is a chronic, relapsing medical condition with multiple potential complications. Treatment of this complex disease process requires understanding of the neurobiology and social context of the patient with this disease. Here we review the definition, epidemiology, neurobiology and current and potential future pharmacological treatment options for opioid dependence.

1. Definition of Opioid Dependence

An important challenge for clinicians treating any chronic disease is to verify the diagnosis, and this is no different for opioid dependence. Opioid dependence is defined by the Diagnostic and Statistic Manual of Mental Disorders, Fourth Edition (DSM-IV)^[1] as a condition characterized not merely by physical dependence on opioids (e.g. tolerance, having to take more to get the desired effect; and withdrawal, manifested by a set of characteristic symptoms upon abrupt cessation or decreased amount of a substance) but also including a loss of control over use (table I). Physical dependence, resulting in tolerance and withdrawal, are commonplace with extended exposure to opioids (e.g. treatment of chronic pain) but what differentiates DSM-IV-defined opioid dependence, commonly referred to as addiction, from physical dependence, is the loss of control over opioid use with resultant adverse consequences (preoccupation, excessive amount of time in pursuit, continued use despite adverse consequences such as illegal dealings).^[2]

2. Epidemiology of Opioid Use and Misuse

Internationally, there are an estimated 15.6 million illicit opioid users in the world, with 11 million who use primarily heroin.^[3] It is estimated that globally, the misuse of opioids is on the rise. Opioids are the main drugs of abuse in Asia, Europe and much of Oceania. The global economic burden of opioid dependence is profound both in terms of direct healthcare costs as well as indirectly through absenteeism, lost productivity, etc. Studies in industrialized countries have shown that opioid dependence accounts for 0.2–2.0% of gross domestic product.^[3] In certain countries, pharmaceutical opioids are increasingly abused. For instance, in 2009, there were 180 000 new heroin users 12 years of age or older in the US; an increase from 90000 new users in 2002. This is in contrast to over 2million new pharmaceutical opioid users in the same year.^[4] In the US, 5.3 million people used pharmaceutical opioids nonmedically, with 36% meeting DSM-IV criteria for opioid abuse or dependence. In all countries there is a gap between the number of individuals who need treatment for opioid dependence and those receiving such treatment. Greater understanding of the neurobiological basis of opioid dependence, the public health benefits from providing such treatments and refinement of medications that can be delivered in general medical settings have begun to address the gap between numbers of patients and available providers.^[5,6]

3. Neurobiological Basis for Opioid Dependence

As with many addictive substances, opioid exposure affects dopaminergic pathways in the ventral tegmental area and nucleus accumbens of the mesolimbic forebrain. Chronic opioid exposure causes changes in G protein-coupled receptors, second messenger synthetic enzymes and protein kinases that mediate the reinforcing action of opioids.^[7,8] Chronic exposure additionally produces neurochemical and structural neuronal changes that may last long after opioid pressure is removed. These changes result in a hypersensitization of the brain's reward system such that the individual may experience pathological wanting (i.e. craving) independent of the occurrence of withdrawal symptoms leading to a state of compulsive drug-seeking and drug-taking behaviour.^[6] As such, the chronic disease model of opioid dependence, including long-term pharmacological maintenance treatment along with counselling, has emerged.

4. Rationale for Pharmacological Treatment of Opioid Dependence

The neurobiological changes seen in opioid dependence support the construct of incorporating the chronic disease model to explain the phenomenon of opioid dependence. Additionally, they lend support to long-term maintenance pharmacotherapies to stabilize these complex biochemical systems.^[2,9] It is important to recognize that although opioid detoxification strategies may be considered as a component of a comprehensive treatment plan for patients with opioid dependence, these strategies have not proven effective alone to promote long-term abstinence in the majority of patients.^[10,11] Appropriately prescribed and dosed pharmacological maintenance treatment of opioid dependence, however, is associated with reduced illicit drug use, minimal euphoria, decreased adverse consequences resulting from opioid use (e.g. HIV infection, overdose) and reduced opioid withdrawal.^[2,12–14] In this report, we describe the pharmacological agents available to treat opioid dependence and prevent relapse in patients with opioid dependence (table II). It is important to mention that pharmacotherapies for opioid dependence are often applied in conjunction with psychosocial counselling.^[15,16] Some studies have shown substantial improvements in outcomes based on the intensity of counselling services provided along with medication.^[16] However, a recent meta-analysis revealed that adding psychosocial support to standard maintenance treatments does not impact treatment outcomes.^[17] The type, intensity and frequency of such

psychosocial interventions is an area of active research and is beyond the scope of the current review but has been recently discussed.^[17]

5. Opioid Agonist Therapy

Opioid agonist maintenance treatment has revolutionized the care of opioid-dependent individuals and has been associated with increased treatment retention, increased opioid abstinence, improved psychosocial functioning and facilitated treatment of other co-morbid medical and psychiatric conditions. As with all controlled substances, in addition to the benefits, medication interactions, side effects and risks of diversion need to be considered.

5.1 Methadone

Methadone hydrochloride is a synthetic opioid agonist at the μ -opioid receptor. In terms of pharmacokinetics, the compound has a high receptor binding affinity, reaches peak levels in 2–6 hours after oral ingestion, and remains variably receptor bound for 24–48 hours after administration.^[18] The first report of methadone for the treatment of heroin addiction was published by Dole in 1965.^[19] He postulated that patients dependent on heroin had an innate biochemical derangement of the opioid system and noted that treatment with a long-acting opioid agonist seemed to stabilize this instability.^[20] He went on to describe how, at appropriate doses, methadone effectively suppresses opioid craving, blocks the euphoric effects of exogenous opioids (i.e. ‘narcotic blockade’) and stabilizes psychosocial functioning.^[21–23] Narcotic blockade refers to the concept that at adequate once-daily doses, opioid agonist therapy blocks the euphoria induced by opioid administration, stabilizes the cycle of euphoria-seeking compounded by opioid withdrawal, which often leads to loss of control over use, and allows the patient to function in a state of relative normalcy. Clinically, the concept of narcotic blockade is borne out in studies that demonstrate improved treatment retention and decreased illicit drug use in patients receiving higher doses of methadone.^[24] In order to produce narcotic blockade, clinically, tolerance and incomplete cross-tolerance to opioids needs to be taken into consideration. Therefore, in practice, a patient is generally inducted on a relatively small dose of methadone and the dose is titrated with careful attention and assessment to the comfort of the patient and the establishment of narcotic blockade. Once a stable dose is reached, the patient is maintained on this dose without further need for dose titration, in most cases.^[21] Methadone’s efficacy for the treatment of opioid dependence has been established in numerous observational and experimental reports since its initial description in 1965.^[25–27] Data from a longitudinal cohort of 1203 patients with opioid dependence on methadone maintenance treatment followed for 5 years further suggest methadone’s efficacy. Of the 432 patients completing the 5-year follow-up, the prevalence of weekly heroin use decreased from 91% pre-methadone admission to 24% at 1-year follow-up and increased slightly to 31% at 5-years follow-up, although still significantly improved over pre-admission levels.^[27] In a systematic review and meta-analysis assessing the efficacy of methadone over non-opioid treatment options, data from a total of 1969 patients were assessed. These data suggested that methadone was superior to non-opioid agonist treatment options in terms of treatment retention and reduction of heroin use (relative risk [RR] 0.66, 95% CI 0.56, 0.78).^[26] Additionally, methadone treatment has been associated with decreases in criminal behaviour, HIV risk behaviour and HIV seroconversion among injection drug users.^[12–14,25]

Internationally, the availability of methadone as a treatment for opioid dependence varies widely. In Australia and regions like the EU, many countries allow the prescription of methadone in general medical settings with dispensing performed at pharmacies. In response to the prevalence and spread of HIV through injection drug use, China and countries of Central and South East Asia have more recently allowed for the distribution of methadone with dispensing typically limited to specialty opioid treatment programmes. Russia does not

allow treatment with methadone or other opioid agonists. The provision of methadone for the treatment of opioid dependence in the US is restricted to federally regulated opioid treatment facilities. Specific regulations need to be met that include prespecified induction dosing schedules, provision of on-site counselling services, and frequency of urine toxicology testing among other practices.^[2,5] The appropriate maintenance dose of methadone is highly individualized; however, daily doses of 80–120 mg are common and are more likely to produce ‘narcotic blockade’. Data from a 30-week randomized clinical trial of high-(80–100 mg) versus moderate-dose methadone (40–60 mg) showed that patients randomized to high-dose methadone had a greater reduction in illicit opioid use.^[28] With the increasing purity of heroin available, higher doses of methadone are often required to produce opioid cross-tolerance.^[29]

Common side effects noted with methadone maintenance treatment include constipation, excess sweating, drowsiness and decreased libido. More recent studies have suggested an association between methadone treatment and male secondary hypogonadism, decreased vitamin D levels, and bone mineral density.^[30,31] A serious potential side effect noted with methadone treatment may include risk for QT interval prolongation at higher doses.^[32–34] As a potent full opioid agonist there is also a risk of overdose among opioid naive individuals if medication is diverted from its intended use. In addition, due to its unique pharmacokinetics with a prolonged half-life and duration of action, the majority of addiction treatment-related methadone overdoses occur within the first 30 days of therapy due to too rapid dose escalations. Methadone metabolism is initially slow,^[35] and its half-life can vary considerably based on patient factors and co-administration of other medications.^[36] For instance, one study showed a 17-fold variation in blood level for a given dose, highlighting individual variation in metabolism.^[37]

As methadone is metabolized by the hepatic cytochrome P450 (CYP)3A4, medication interactions need to be considered. Some common interactions are noted here. Interactions with HIV medications are known to occur: efavirenz, darunavir and nevirapine may induce opioid withdrawal; zidovudine levels may be increased leading to increased toxicity. Rifampin, used to treat tuberculosis, may induce opioid withdrawal; antifungal and antimicrobial therapies interact with methadone, for instance, fluconazole, voriconazole, clarithromycin and ciprofloxacin increase plasma methadone concentrations; the herbal supplement St John’s Wort increases the metabolism and elimination of methadone and may induce opioid withdrawal; the antipsychotic quetiapine may increase methadone levels resulting in sedation; and anticonvulsants carbamazepine, phenytoin and phenobarbital may be associated with opioid withdrawal.^[38] Clinicians must consider potential medication interactions when prescribing medications to patients receiving methadone.

5.2 Buprenorphine and Buprenorphine/Naloxone

Buprenorphine is a high-affinity partial agonist at the μ -opioid receptor and an antagonist at the κ -opioid receptor that was approved as pharmacotherapy for opioid dependence in 1996 in France and 2002 in the US.^[18,39,40] Two formulations are available for the treatment of opioid dependence, a buprenorphine-only tablet or film and a buprenorphine/naloxone combination tablet or film. Naloxone is an opioid antagonist at the μ -opioid receptor with high receptor affinity and intravenous bioavailability. If taken as prescribed, sublingually, the naloxone component of the buprenorphine/naloxone combination formulation is not appreciably absorbed. The presence of naloxone in this formulation is meant to deter misuse or diversion of this medication through the injection route in subjects with opioid agonists in their system. EU marketing approval for combination buprenorphine/naloxone was granted in 2006. In the US buprenorphine and buprenorphine/naloxone tablets and film for the treatment of opioid dependence are classified as a schedule III narcotic and, therefore, on the basis of the federal legislation enacted in 2000, the Drug Addiction Treatment Act of 2000,

can be prescribed in office-based settings by certified physicians.^[2,41] Because of this, buprenorphine has allowed expanded access to pharmacological treatment for patients with opioid dependence who might not otherwise seek or have access to care. Due to its partial agonist properties, there is a ceiling to common agonist effects including analgesia and respiratory depression. Additionally, because it is a high-affinity μ -receptor partial agonist, if given in the presence of opioids or opioid metabolites, especially among physically dependent individuals, precipitated withdrawal will occur. Nonetheless, despite these favourable attributes, injection misuse of buprenorphine has created concerns in certain countries. For instance, both Malaysia and Finland saw considerable injection misuse of the buprenorphine mono-formulation.^[42,43] As such, this ultimately led to the introduction of the buprenorphine/ naloxone combination, in a 4 : 1 ratio, in the EU and other regions. In the injection scenario, naloxone absorption would be substantial resulting in precipitated withdrawal.^[44–46] However, buprenorphine/ naloxone may still be misused via the intravenous route in opioid-naïve individuals or those receiving buprenorphine maintenance, although to a lesser degree than the buprenorphine mono-formulation. This was demonstrated in a laboratory investigation of abuse liability of buprenorphine/naloxone compared with buprenorphine alone.^[47]

The efficacy of buprenorphine and buprenorphine/naloxone has been established in several early studies of buprenorphine dosing regimens.^[40,48,49] Additionally, numerous clinical trials have demonstrated that buprenorphine is a safe and effective alternative to methadone treatment.^[50–53] In one randomized clinical trial of over 160 subjects, buprenorphine 8mg/ day was found to be similar to methadone 60mg/day and both were superior to methadone 20mg/day in terms of treatment retention and decreased opioid use.^[50]

After the initial patient evaluation and assessment, induction onto buprenorphine or buprenorphine/naloxone treatment takes place in an observed or unobserved manner.^[54] During the induction phase of treatment, clinicians may assess for precipitated opioid withdrawal, which can occur if the patients is not manifesting opioid withdrawal symptoms when the first dose of buprenorphine or buprenorphine/naloxone is administered, clinicians may also assess the need for dose adjustment and discuss relapse prevention and trigger avoidance. Provision of or referral to psychosocial counselling and establishment of a treatment plan is similar to methadone. The maintenance phase follows induction and can consist of physician visits, urine toxicology testing, continued discussion of relapse prevention and trigger avoidance, and screening and management of other co-morbid conditions.^[55] The usual effective dose of buprenorphine or buprenorphine/ naloxone is between 8 and 24mg daily, expressed as buprenorphine concentration.^[48]

Side effects most frequently noted with receipt of buprenorphine or buprenorphine/naloxone include headache, and the common opioid-related side effects of constipation, sweating, and decreased libido. Many of these abate with continued exposure to the medication or dose titration. As a thebaine derivate, one potential side effect of note is elevated liver transaminase values. This is most concerning in patients with chronic hepatitis C infection and most clinical trials have limited exposure to buprenorphine exposure subjects with transaminases below 3–5 times normal at baseline.^[56] However, more recent observational studies have demonstrated hepatic safety in more diverse patient populations.^[57,58] QT interval prolongation does not appear to be an issue with buprenorphine.^[59] Finally, although the naloxone component of the buprenorphine/naloxone combination formulation is not absorbed via the sublingual route of administration, naloxone should be avoided in pregnancy. Therefore, it is important to monitor women of childbearing age receiving buprenorphine/naloxone for pregnancy, and if it occurs, to transition patients to methadone or to buprenorphine-only formulations.

Medication interactions have also been noted with buprenorphine and buprenorphine/naloxone. Respiratory depression and overdose have been reported in patients abusing benzodiazepines while receiving buprenorphine.^[60] Similar to methadone, buprenorphine is metabolized by the CYP3A4 system and, therefore, is vulnerable to medication interactions. While in one study a small number of subjects receiving buprenorphine/naloxone who were exposed to atazanavir had increased buprenorphine and nor-buprenorphine levels and experienced sedation,^[61] a larger cohort study found no reports of sedation or need to adjust doses in patients receiving buprenorphine/naloxone and atazanavir.^[58] Potential interactions with other antiretroviral medications are plausible; however, they do not appear to be clinically significant.

5.3 Levomethadyl Acetate HCl (LAAM)

Levomethadyl acetate HCl (LAAM) is a long-acting opioid agonist that was approved for use in the US for the treatment of opioid dependence in 1993. In 2001 and 2003, respectively, it was removed from the European and US markets over concerns of cardiac QT prolongation and torsades de pointes.^[62] Because of LAAM's long half-life, it can be dosed three times weekly, compared with methadone, which is dosed daily. As LAAM is currently not available for the treatment of opioid dependence, a full description of it is beyond the scope of this discussion. However, because of its long half-life and reports of similar efficacy to methadone in reduction of opioid use, there have been some attempts to reconsider LAAM as an alternative opioid agonist treatment option.^[63,64] A recently published European randomized, open-label trial of LAAM versus methadone found that LAAM was non-inferior to methadone in terms of opioid use, treatment retention and safety.^[64] However, recent data confirms prior concerns over corrected QT (QTc) prolongation and risks for serious cardiac side effects with the use of LAAM.^[59,65]

6. Opioid Antagonists

6.1 Oral Naltrexone

As an opioid antagonist, naltrexone blocks the euphoric effects of opioids diminishing the reinforcing effects of heroin and pharmaceutical opioids,^[66] and potentially extinguishing the association between conditioned stimuli and opioid use.^[67] Opioid antagonists have no addictive potential or tolerance. To date, the oral form of naltrexone has been the primary opioid antagonist used for maintenance treatment of opioid dependence. Naltrexone is a derivative of nalox-one and has an affinity for the μ -opioid receptor that is 20 times that of morphine thereby displacing bound opioid agonists^[66] and blocking the effects of exogenously administered opioids.^[67] Peak plasma concentrations are achieved within 1 hour, and antagonist effects can last for up to 72 hours.^[67]

Despite its potential appeal as a medication for maintenance treatment, the clinical utility of naltrexone as a treatment for opioid dependence has been limited.^[8,50,66,68] Initiating the medication can be difficult for many individuals due to the requirement of attaining prolonged (e.g. 7 days) abstinence. This leads to induction processes that may be complicated by precipitated withdrawal, relapse and early dropout. A Cochrane review concluded that oral naltrexone, with or without psychotherapy, was no better than placebo or no pharmacological treatments with regard to retention in treatment, use of the primary substance of abuse or side effects.^[88] The authors identified 13 randomized controlled trials in 1158 opioid-dependent outpatients following detoxification. Less than a third of subjects were retained in treatment over the duration (mean of 6 months) of the studies. In one study, only 15 of approximately 300 patients chose naltrexone over detoxification or maintenance treatment with methadone. Only 3 of the 15 remained on naltrexone for more than 2 months.^[69] In another, study only 40% of 242 patients remained in treatment over 4

weeks.^[70] While overall naltrexone is of limited benefit over placebo, selected trials of naltrexone have demonstrated some efficacy in the treatment of certain populations (for example, healthcare professionals)^[71] those who are employed, with stable social contacts, and highly motivated patients.^[72] Naltrexone following detoxification has demonstrated some efficacy when delivered as part of a packaged Behavioral Naltrexone Therapy,^[73] when combined with contingency management and observed administration and other various counselling strategies,^[72,74] and in patients who are dependent upon non-heroin opioids.^[75]

Studies have demonstrated that dosages of 50, 100 and 150mg/day of naltrexone can block the effect of 25 mg of intravenous heroin for 24, 48 and 72 hours, respectively.^[67] Standard dosages of naltrexone are 50mg/day, or 100 mg on Monday and Wednesday and 150mg on Friday.^[76] Administration of naltrexone will precipitate opioid withdrawal in opioid-dependent individuals if they have not been abstinent for at least 7 days. In some patients it may be necessary to document abstinence through urine toxicology and/or through a naloxone challenge.

Naltrexone undergoes both hepatic and extra-hepatic metabolism. It is metabolized by CYP3A but is not known to be an inducer or inhibitor of this enzyme making it less likely to have interactions with medications metabolized in this way. Primary metabolic pathways are mono-oxygenation and dioxygenation; minor pathways include glucuronidation, N-dealkylation, and hydrolysis. Medication safety guides list only opioid agonists and yohimbine as contraindicated in patients receiving naltrexone.^[77,78] Potential side effects of naltrexone include epigastric pain, nausea, headache, dizziness, nervousness, fatigue or insomnia. Large dosages (up to 300 mg/day) may be hepatotoxic, although hepatic safety at standard doses has been recently demonstrated in a cohort of patients co-infected with HIV and hepatitis C.^[79]

6.2 Sustained-Release Naltrexone

The overall lack of efficacy seen with oral naltrexone, partly due to low rates of retention and adherence, has led to the development of sustained-release formulations that are expected to help address adherence. These formulations include implants and depot injection formulations. A Cochrane review identified a single trial of sustained-release naltrexone of appropriate quality for determination of outcomes.^[80] This trial compared low-dose (192 mg) and high-dose (384 mg) depot naltrexone to placebo.^[81] The high-dose injection was associated with greater treatment retention compared with placebo (weighted mean difference [WMD] 21.00; 95% CI 10.68, 31.32; $p < 0.0001$) and low-dose (WMD 12.00; 95% CI 1.69, 22.31; $p = 0.02$). The primary adverse effects were fatigue and administration site-related conditions. A recent published study conducted in Russia randomized 250 patients to a depot formulation of naltrexone (Vivitrol; Alkermes Inc.) or placebo.^[84] Primary findings included longer median proportion of weeks of confirmed abstinence, 90% (95% CI 69.9, 92.4) in the depot naltrexone group compared with 35% (11.4–63.8) in the placebo group ($p = 0.0002$). Median retention was greater than 168 days in the depot naltrexone group compared with 96 days (95% CI 63, 165) in the placebo group ($p = 0.0042$). Several subsequent studies have also demonstrated the efficacy of sustained-release naltrexone in various patient-care settings, evaluating a variety of outcomes, and using various comparator groups. A recently published randomized trial evaluating the safety and effectiveness of implantable naltrexone compared with usual care after completion of inpatient detoxification^[82] found that patients randomized to naltrexone had decreased heroin and other opioid use during 6 months of follow-up. In a follow-up to this study, of patients receiving at least one naltrexone implant, 51% went on to continue naltrexone treatment via reimplantation, suggesting good treatment retention with this modality.^[83] A large, double-blind, randomized, placebo-controlled, multicentre study also clearly

demonstrated the efficacy of long-acting naltrexone combined with psychosocial counselling over placebo in terms of opioid use, craving and treatment retention.^[84] A review paper by this same group outlined the efficacy and advantages of sustained-release naltrexone over oral formulations.^[85] The US FDA has approved a sustained-release naltrexone formulation for the treatment of opioid dependence in the US.

7. Investigational Agents

7.1 Sustained-Release Buprenorphine

Sustained-release formulations of buprenorphine have been developed in part to address concerns about adherence and diversion. In the largest study to date, an implantable formulation of buprenorphine designed to provide 6 months of medication was compared with placebo implants.^[86] The 6-month randomized (2:1 active to placebo randomization scheme) clinical trial was conducted in 163 opioid-dependent subjects, all of whom received ancillary drug counselling. Subjects in both groups were allowed to receive sublingual buprenorphine for complaints of opioid craving, withdrawal or as deemed appropriate by a blinded physician. A supplemental implant was also available. The primary outcome was opioid abstinence, over 16 weeks, assessed using thrice weekly urine toxicology analyses. During the first 16 weeks of treatment, opioid abstinence via urine toxicology analysis was seen in 40% of the samples in the buprenorphine group (95% CI 34.2, 46.7; median, 40.7%) compared with 28% (95% CI 20.3, 36.3; median, 20.8%) in the placebo group ($p = 0.04$). Treatment retention was longer in patients who received buprenorphine implants. However, subjects in both treatment arms required supplemental sublingual buprenorphine. This indicates that the implants provided less than adequate doses of buprenorphine. The clinical utility of this agent will likely depend on patient acceptance, demonstrated utility in patients with poor adherence and the extent of diversion and abuse of sub-lingual formulations.

7.2 Diacetylmorphine (Heroin)

In a Cochrane review of diacetylmorphine (heroin) maintenance, authors^[87] identified eight randomized studies involving 2007 patients. Of note, all studies were conducted in subjects with a history of failing prior outpatient treatment, generally with methadone. Those receiving heroin were requested to attend a dedicated clinic to receive and inject prescribed heroin from two to three times a day. The review concluded that the available evidence suggests a small added value of heroin prescription for long-term, treatment-refractory, opioid users. Opioid-dependent subjects who received heroin prescribed along with flexible doses of methadone used fewer illicit substances and had a reduced probability of being imprisoned. Adverse events, including infections and overdose, were consistently more frequent in the heroin group. The review concluded that heroin prescription should remain as a last resort treatment for people who currently or have previously failed other maintenance treatments. In a limited number of countries, heroin is available to treat heroin dependence in highly supervised settings.

8. Conclusions

Opioid dependence is a chronic, relapsing medical condition with a known neurobiological basis. Stabilization of these neurobiological pathways with long-acting opioid agonist medications diminishes opioid withdrawal and blocks the effects of exogenous opioids. We reviewed the currently available pharmacotherapeutic options for the treatment of opioid dependence including methadone, buprenorphine, buprenorphine/naloxone and naltrexone. Agonist-based modalities are effective at reducing opioid use, promoting treatment retention and reducing transmission of HIV; similarly, opioid antagonists have been shown to reduce opioid use, promote retention and enhance relapse prevention. Additionally, the

potential given risks associated with opioid agonist treatment and concerns over diversion, investigation into alternative medications and mechanisms for delivery were reviewed. It is yet unclear the role these agents will take in the landscape of treatment options. Based on available therapies and current research it is likely that the field of addiction medicine will have a range of medications (agonists, partial agonists, antagonists) administered through a variety of routes (oral, sublingual, injectable) for the treatment of opioid dependence.

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Table I**Diagnostic criteria for opioid dependence**

Opioid dependence: a maladaptive pattern of opioid use leading to clinical impairment or distress manifested within a 12-month period by 3 of the following:

1. Tolerance: increased amounts of opioids to achieve intoxication or the desired effect or diminished effects with continued use of the same amount of opioid
 2. Withdrawal: manifested by the characteristic withdrawal syndrome or use of opioids to relieve or avoid withdrawal symptoms
 3. Use of opioids in larger amounts or over a longer period of time than intended
 4. Persistent desire or unsuccessful attempts to cut down or control opioid use
 5. Great deal of time spent obtaining opioids, using opioids or recovering from their effects
 6. Loss of interest in social, occupational or recreational activities
 7. Opioid use despite knowledge of physical or psychological problems
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Table II

Increasingly available options for maintenance therapy for opioid dependence

Medication	Action	Usual effective dose	Frequency	Adverse effects
Methadone	Opioid agonist	20–100mg orally	Daily	Constipation, respiratory depression, dizziness, sedation, diaphoresis
Buprenorphine	Partial opioid agonist	8–24mg sublingually	Daily to thrice weekly	Constipation, headache
Buprenorphine/ naloxone	Partial opioid agonist/ opioid antagonist	8–24mg sublingually	Daily to thrice weekly	Constipation, headache; not to be used in pregnant patients
Naltrexone	Opioid antagonist	50–100mg orally	Daily	Hepatitis, hepatic failure, concomitant use of opioid; not to be used in pregnant patients