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Maintenance Medication for Opiate Addiction: The Foundation of Recovery

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Abstract

Illicit use of opiates is the fastest growing substance use problem in the United States and the main reason for seeking addiction treatment services for illicit drug use throughout the world. It is associated with significant morbidity and mortality related to HIV, hepatitis C, and overdose. Treatment for opiate addiction requires long-term management. 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 by the FDA for long-term treatment of opiate dependence: the opioid agonist methadone, the opioid partial agonist buprenorphine, and the opioid antagonist naltrexone. Basic mechanisms of action and treatment outcomes are described for each medication. Results indicate that maintenance medication provides the best opportunity for patients to achieve recovery from opiate addiction. Extensive literature and systematic reviews show that maintenance treatment with 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

Opiate dependence (hereafter referred to as addiction) is a major public health problem with global reach.[1] The illicit use of opiates contributes to the global burden of disease and can result in premature disability and death.[2] Overdose is a significant cause of death and the incidence and prevalence of blood borne viruses (e.g., HIV, hepatitis B, and hepatitis C) are higher in illicit opiate users, especially injection drug users (IDU), than the general population.[3–7] In the United States, deaths related to opiate analgesic overdose now exceed those caused by both heroin and cocaine combined.[8] Access to, adherence to, and outcome for the treatment of general medical illness and infectious diseases such as HIV, viral hepatitis, and tuberculosis are reduced in opiate addicts.

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Globally, between 24 and 35 million adults age 15-64 years used an illicit opiate in 2010.[9] Throughout Europe and Asia, opiate use is the primary reason for seeking treatment for illicit drugs.[9] While there has been relative global stability in prevalence of illicit opiate use, the United States has seen a significant increase the illicit use of prescription opiates despite stable levels in heroin use.[9,10] In 2009 in the United States, opiates were second only to alcohol as the primary reason for treatment admission.[11] In fact from 1999 to 2009, annual treatment admissions for opiates increased from approximately 280,000 to 421,000 individuals.[11] The increase in prescription opiate use, overdose deaths, and treatment admissions parallels increases in production and distribution of prescription opiates.[8]

The addiction liability of opiates is high with 50% and 11% of people who used heroin or prescription opiates, respectively, last year meeting addiction criteria.[12] The focus of this review is on the pharmacologic treatment options for these opiate addicted individuals. A brief discussion of the neurobiology of opiate addiction will be followed by description of the role current FDA-approved treatments for opiate addiction have in facilitating recovery. Economic, ethical, and regulatory issues surrounding these medications are beyond the scope of this review and will not be discussed.

Neurobiology of opiate addiction

The risk for developing opiate addiction is a complex interaction between genetics, environmental factors, and the pharmacological effects of opiates. For example, selective breeding in rodents has produced strains prone to opiate self-administration; multiple genetic loci associated with opiate self-administration have been identified; and selective disruption of the gene encoding the mu opioid receptor, the principal target of opiates, can eliminate opiate self-administration and conditioned place preference.(for a review see 13) Human family and twin studies have identified increased genetic risk for addiction in the first degree relatives of addicts but also that the genetic risk specific to opiate addiction is second only to that for alcoholism.[14,15]

Environmental factors such as availability of opiates, perceived risk of opiate use, psychosocial stressors, and learned coping strategies all influence the risk of developing opiate addiction. For example, the incidence of opiate addiction has paralleled increased availability opiates. While 75% of high school seniors perceive using heroin once or twice as dangerous, only 40% perceive similar use of prescription opiates as dangerous.[16] Traumatic lifetime experience may increase the risk for opiate addiction. In rodent models, maternal separation early in life increases vulnerability to opiate addiction for both the pup and the dam and, in humans, weak parental bonds increase the risk for illicit drug use during adulthood.[17–19] In humans, there is an association between post traumatic stress disorder and opiate addiction with an over-representation in prevalence of this disorder in opiate addicts compared to the general population and to those with other substance use disorders.[20]

The euphoria and abuse liability of an opiate is related to both its pharmacokinetic and pharmacodynamic properties. The rapidity with which a drug enters and then exits the brain is positively correlated with its rewarding and reinforcing effects.[21–23] This principal is clinically apparent in the transition from oral or intranasal to smoked or intravenous routes of drug administration and through the practice of crushing extended release tablets in order to achieve more immediate opiate absorption. Once in the brain, the primary target for abused opiates is the mu opioid receptor. This receptor is present throughout the brain with highest density in areas modulating pain and reward (e.g., thalamus, amygdala, anterior cingulated cortex, and striatum). Activation of mu opioid receptors inhibits GABA-mediated tonic inhibition of dopaminergic neurons in the ventral tegmental area.[24] This initiates a

cascade of effects in diverse brain regions, including the striatum, amygdala, and prefrontal cortex, that are not only related to reward but influence the risk for repeated opiate use by heightening the saliency of drug related cues and the incubation of drug craving.[25,26]

Repeat opiate administration induces tolerance and imparts the potential for a withdrawal syndrome upon cessation. The unpleasant physical and psychological symptoms of withdrawal produce negative reinforcement whereby opiates continue to be used, often in escalating doses, in order to avoid their onset.[27] Furthermore, short acting opiates modulate stress responsive pathways causing dysregulation and further stress-induced negative reinforcement. This stress dysregulation can continue long after a person has discontinued opiates and, thereby, is a contributing factor to the risk for relapse during stress.

Long term approaches to the treatment of opiate addiction are required because of persistent alterations in dopaminergic, opioidergic, and stress responsive pathways. Human imaging studies have identified ongoing reductions in dopamine D2 receptor binding potential in opiate addicts and that this reduction correlates with the duration of opiate use.[28,29] Animal models of opiate addiction and postmortem studies in human opiate addicts have identified alterations in opioid gene expression in specific brain areas related to reward and behavior.(for review see 13) Finally, stress response is exaggerated in former heroin addicts who are not taking methadone pharmacotherapy.[30] While pharmacotherapy may not correct alterations in dopamine receptor availability and opioid gene expression, it does appear to normalize several aspects of stress responsiveness.[31–33]

The advent of epigenetics has allowed us to gain understanding as to how genetic expression is modified by environmental and pharmacological inputs, thus linking all three main contributors to the risk for addiction. For example, environmental inputs such as maternal care or social hierarchy modulate expression of neuroreceptors that, in turn, influence drug self-administration.[34,35] Opiate administration also modulates expression of several genes including those in opioidergic, dopaminergic, and stress responsive pathways.(for review see 13) The details of how the interaction between genes, environment, and drugs contributes to the development, persistence, and relapse to addiction have yet to be elucidated. This interaction forms the hypothesized foundation for the persistence of addiction vulnerability even in those who have discontinued drug use and indicates that long term relapse prevention strategies need to include both environmental and pharmacological interventions beyond the immediate period of withdrawal.

Psychosocial intervention only

While this review does not comprehensively address non-pharmacological interventions for opiate addiction, when used alone, these approaches should be considered to lie outside the domain of first-line evidence based treatment. Historical data indicate poor outcome in patients provided only psychosocial interventions. Whether compelled or voluntary, return to opiate use approaches 80% within two years of intensive residential treatment.[36,37] While a systematic review by the Cochrane collaboration indicates some psychosocial interventions may be superior to others, a separate review found that psychosocial intervention alone was inferior to methadone maintenance for such outcomes as retention in treatment and reduction in opiate positive urine toxicology tests.[38,39] This later review also indicated a trend for greater mortality in psychosocial versus methadone treatment, a finding supported in other reports from populations that receive no treatment, psychosocial treatment only, or those who voluntarily discontinue pharmacotherapy.[40–44]

Medically assisted detoxification

The negative reinforcement of withdrawal is a primary driver of ongoing drug use. Several strategies to relieve opiate withdrawal symptoms have been evaluated. The short term (first 30 days) effect on relief of symptoms and return to illicit opiate use between alpha adrenergic agonists such as clonidine and lofexidine (and presumably dexmedetomidine) and opiate based regimens are similar.[45] Rapid withdrawal and sedation assisted transition to opioid antagonist therapy has increased risk of serious adverse events when performed under heavy sedation and is too resource intensive to endorse given the limited benefit when performed under light sedation.[46,47] Longer period of detoxification (1–6 months) with methadone or buprenorphine are also ineffective in promoting abstinence beyond the initial stabilization period.[48,49]

Medications used to treat opiate addiction beyond the withdrawal period

Methadone, buprenorphine, and naltrexone are each FDA approved for the long-term treatment of opiate addiction (see Tables 1 and 2). Methadone has been used for the longest period of time and thus has a large body of research supporting its effectiveness. Buprenorphine is similar to methadone in mechanism of action (partial agonist versus full agonist) and effectiveness and thus will be discussed in a slightly abbreviated manner. Naltrexone, and opiate antagonist, has a less of an historical basis for effectiveness but a newly evolving literature warrants attention.

Methadone

Methadone is a synthetic mu opioid receptor agonist originally synthesized in the late 1930's as a congener of atropine.[50] In the treatment of opiate addiction, methadone is administered orally in liquid, tablet, or dispersible tablet formulation and is a racemic mixture whose R-entantiomer is responsible for the opioid effect and both R- and S- entantiomers are NMDA antagonists. Following oral administration, it is rapidly absorbed, undergoes little first pass metabolism, and has moderate bioavailability of 70%–80%. Methadone is approximately 90% bound to plasma proteins such as albumin, globulin fragments, and α_1-acid-glycoprotein. Methadone is also distributed throughout various tissues such as the liver, intestine, lung, muscle, and brain with an apparent volume of distribution during steady state of 3.6 L/kg. Following oral administration, peak plasma levels are reached within 2–4 hours and the elimination half-life at steady state is approximately 28 hours, allowing for once daily dosing. Methadone is hepatically metabolized into inactive compounds primarily by cytochrome P450 3A4 and 2B6 enzymes and is eliminated through both renal and fecal routes. The use of certain medications that induce (e.g., phenytoin, rifampin, efavirenz) or inhibit (e.g., azole based antifungals) these enzymes may impact plasma methadone levels although the clinical effect in terms of precipitating withdrawal or inducing sedation are variable.[51]

Methadone safety is well established.[52] Like other opiate agonists, methadone has the potential to induce lethal respiratory suppression when given in doses that exceed an individual's tolerance. Recent increases in methadone associated deaths are primarily related to its minimally regulated use in the treatment of pain and not due to its use in the treatment of opiate dependence.[53] This may be due to too rapid dose escalations and a differential rate in development of tolerance to the analgesic and respiratory suppressive effects of methadone. In the setting of addiction treatment, higher levels of dosing supervision reduce mortality rates.[54] There has been recent concern regarding potential cardiac safety of methadone. While methadone will increase the electrocardiographic QTc interval, this appears minimal in magnitude and rarely exceeds the 500 msec threshold associated with cardiac arrhythmia and sudden death in those with heart disease.[55,56] Evidence that

preventing cardiac events through electrocardiographic monitoring or use of buprenorphine, which likely does not prolong the QTc, is lacking.[57] It appears, therefore, that the greatest risks in mortality associated with methadone maintenance occur during the induction period, because of multiple drug ingestion (e.g., benzodiazepines), or due to the loss of tolerance upon methadone discontinuation.[43]

Methadone's ability to relieve the opiate withdrawal syndrome was noted as early as 1947 and within two years it became the preferred medication for detoxification at the national narcotics hospital in Lexington, Kentucky.[58] Upon taking methadone, opiate addicts in withdrawal found their symptoms relieved; those with active addiction did not experience euphoria or request their usual and available doses of injected morphine; and, after chronic administration, sudden cessation of methadone produced a milder, albeit longer in duration, withdrawal syndrome than following morphine cessation.[59]

It was not until 1964 when scientists at the Rockefeller Medical Research Institute (now University) began to evaluate methadone maintenance as a means of long-term medication-assisted treatment for opiate addiction. This work helped to establish that not only did methadone relieve opiate withdrawal but, when at steady-state, it also blocked the euphoric and sedating effects of superimposed opiates.[60,61] Thus, with methadone, major components of both the positive and negative reinforcing effects of short-acting opiates were reduced and craving subsided thus allowing the addict to concentrate on non-drug related activities.

Methadone response appears to be dose related with most patients stabilizing at doses between 60mg–120mg daily.[62] Response is most frequently measured in terms of retention in treatment and reduction in illicit opiate use, although improvements psychosocial function and medical status have also been documented.[63] Mean 1-year retention in treatment is approximately 60% and can vary based on adherence to evidence-based dosing practices.[64–67] In terms of retention in treatment and adherence to treatment regimen, the results of methadone maintenance are similar to or exceed results for other medically managed diseases such as hypertension, dyslipidemia, and diabetes mellitus.[68] At any given time in treatment, approximately 15% of patients in methadone maintenance will have ongoing illicit opiate use. While there are some associations between treatment outcome and age, medical comorbidity, criminal justice involvement, ongoing non-opiate drug use, and patient satisfaction with treatment, predicting and then preventing treatment failure has not proved successful.[67,69–72] Providing intensive psychosocial services and counseling may improve treatment outcome during the initial 6 months of methadone maintenance but its benefit diminishes through time such that patients receiving intensive services have similar incidence of drug use at 1-year as those receiving standard counseling.[73]

Methadone maintenance is not the replacement of an illegally used opiate for a legally supervised opiate. Unlike abused opiates, once a stabilization dose is achieved (generally between 60mg–120mg daily), rarely is there need to increase dose due to development of tolerance. The reason for this is unknown but may be related to its NMDA antagonist properties.[74] In addition, at stabilization, methadone binds approximately 30% of mu opioid receptors allowing the remaining receptors to perform their usual physiological function in modulation of pain, reward, and mood.[75] Additionally, the psychosocial problems inherent in opiate addiction are also relieved upon methadone maintenance. Regulation of stress response is one such function that tends to normalize with methadone stabilization. For example, suppression of adrenocorticotropic hormone (ACTH) and corisol caused by administration of short acting opiates, blunted diurnal variation in their release in active addicts, and the increase in these hormones during opiate withdrawal are all corrected during methadone maintenance (see Table 2)[52,76,77] Perhaps most importantly, many of the abnormal hormonal responses to stressors during addiction and even following abstinence

based treatment are corrected once patients are stabilized on methadone.[for review see 78] Thus while methadone relieves withdrawal and blocks the effect of superimposed opiates, it may more importantly be thought of as a relapse prevention drug in that it normalizes many of the physiological stress-related responses that precede and contribute to relapse (Table 3).

Buprenorphine

Buprenorphine is a semi-synthetic mu opioid partial agonist with weak partial agonist effects at both delta and kappa opioid receptors. It was first synthesized in the late 1960's by Bentley et al. as part of analgesic explorations of thebaine congeners.[79] In the treatment of opiate addiction, buprenorphine is administered sublingually in tablet or film formulations. A new subdermal implant that delivers buprenorphine for 6 months is in development and showing promise in the treatment of opiate addiction.[80] Buprenorphine undergoes extensive first pass metabolism and oral administration results in poor bioavailability. Following sublingual administration, however, bioavailability is approximately 50%.[81] Buprenorphine is extensively protein bound to globulin fragments and is distributed to various tissues with an apparent volume of distribution during steady state of 3.7 L/kg. Following sublingual administration, peak plasma levels are reached within 1–3 hours and the elimination half-life at steady state is approximately 37 hours, allowing for once daily, and in some instances every other day, dosing. Buprenorphine is hepatically metabolized by cytochrome P450 3A4 and possibly 2C8 into the weak opioid partial agonist norbuprenorphine, which is eliminated through glucuronidation.[82] Both buprenorphine and norbuprenorphine are eliminated through renal and fecal routes. The use of certain medication that induce or inhibit cytochrome P450 3A4 may impact plasma buprenorphine levels although the clinical effect of this is minimal possibly due to buprenorphine's partial agonism, high receptor affinity, and/or because of the weak opioid effects of norbuprenorphine.[51]

The literature on safety evaluation of buprenorphine maintenance is less developed than that of methadone, but phase III research reports indicate that buprenorphine maintenance is quite safe with equivalent adverse events to methadone and placebo.[64,66,83] Although buprenorphine is a partial agonist at mu opioid receptors, it may induce respiratory suppression but to a lesser extent than full agonists.[84] Additionally, as a partial agonist with high receptor affinity and modest efficacy, many of buprenorphine's effects plateau after approximately 16 mg, although doses of up to 32mg are used clinically.[84] Thus, while it may have similar rewarding properties as methadone in non-tolerate opiate addicts, attempts to increase this effect or achieve intoxication through dose escalation beyond this ceiling are of little avail.[85] Nevertheless, deaths associated with buprenorphine have been reported following its more rapid delivery through injection or when combined with benzodiazepines.[86] In order to reduce the harm associated with buprenorphine injection, it is available in formulations that combine buprenorphine with the opioid antagonist naloxone in a 4:1 ratio. Naloxone undergoes extensive first pass metabolism and is not absorbed into the systemic circulation when taken orally or sublingually. Injection, however, allows naloxone to enter systemic circulation and compete with buprenorphine for receptor occupancy. This competition reduces initial effects of buprenorphine, thus lowering its rewarding properties and the risks of lethal respiratory suppression.[87] As with methadone, deaths in buprenorphine maintenance patients are more likely to occur during the initial induction period or due to loss of tolerance following its discontinuation.[43]

Buprenorphine's ability to both induce and relieve opiate withdrawal was observed by Martin et al. in 1976 and within two year Jasinski et al. hypothesized that it may be used in the treatment of opiate dependence.[88,89] Because buprenorphine is a high affinity and moderate efficacy mu opioid partial agonist, it will displace other high efficacy opiates, if present, and induce withdrawal symptoms. On the other hand, when a patient has stopped

using opiates and is in withdrawal, buprenorphine will bring relief through its partial agonist effect. Because of this dual effect, induction onto buprenorphine has the potential to precipitate withdrawal. It is, therefore, generally advised that the first dose of buprenorphine be given no sooner than 12 hours after the last use of a short-acting opiate and 24 hours after a long acting opiate, which may be difficult for many patients to achieve. Various induction protocols ranging from inpatient, to outpatient monitoring for withdrawal symptoms prior to first dose, to patient driven home-induction are available to help the clinician safely induce patients onto buprenorphine.[90,91] Following chronic administration, sudden cessation of buprenorphine produces a mild yet prolonged withdrawal syndrome.[89]

While there were several early reports that buprenorphine could relieve opiate withdrawal and block the effect of superimposed opiates, it was not used as a maintenance treatment until 1985.[89,92,93] As with methadone, upon relief of withdrawal and craving, patients on buprenorphine maintenance turned their focus from non addiction related activities. Unlike methadone, buprenorphine is not as highly regulated so most studies have evaluated buprenorphine maintenance in a primary care setting.

Buprenorphine response is dose related with most patients stabilizing on at doses between 12mg–16mg daily.[64,94] When adequate doses are used, treatment outcome in terms of retention and reduction in illicit opiate use is similar to that of methadone maintenance.(for review see 95) Unlike methadone, where dose can be increased to facilitate treatment response, buprenorphine's ceiling effect may limit its effectiveness in patients with ongoing opiate use.[96] In these individuals, transitioning from buprenorphine to methadone may allow for improved treatment outcome. Also, the role of intensive counseling does not appear to improve outcome of office based treatment compared to standard counseling.[96,97]

There is little difference in outcome between office based and opiate treatment program settings, although direct comparison of a randomized population has yet to be performed. A weakness in the buprenorphine literature is that most study follow-up periods are between 12–24 weeks. In these studies, retention rates are similar to that of methadone over the same period of time.[98] Whether this similarity persists for 1-year is uncertain. One small but dramatic program based placebo-controlled study found 1-year retention of 75% and 0% for buprenorphine and placebo, respectively.[41] Additionally, all patients receiving placebo dropped out by three months and four out of twenty had died by the end of the year whereas none receiving buprenorphine died.

Aside from ongoing opiate use, predictors of buprenorphine treatment outcome may include depression, income, and ongoing cocaine use.[69] There has been recent attention to the use of buprenorphine for the treatment of prescription opiate addiction.[97] During maintenance treatment, patients have reduced illicit opiate use but following buprenorphine taper, more than 90% of patients return to illicit opiate use.[97] In another study comparing heroin addicts to prescription opiate addicts, the heroin addicted patients had more severe medical and addiction severity and did not do as well in buprenorphine as the less ill prescription opiate addicts.[99] Caution in interpreting this finding is warranted since these two populations are not comparable and the difference in outcome may be more related to addiction severity than to the patient's opiate of choice. There is no neurobiological or pharmacological reason why, after adjusting for these factors, heroin addicts and prescription opiate addicts would have different treatment outcomes and thus require separate consideration in medication choice.

The neurobiological effect of buprenorphine in the treatment of opiate addiction is presumed to be mediated through partial agonism of the mu opioid receptor. The effect at delta and

kappa receptors is likely too weak to contribute to its treatment effectiveness. Buprenorphine binds extensively to mu opioid receptors with over 90% occupancy following doses of 16mg or greater.[100] Buprenorphine can suppress stress responsive hormones such as ACTH and cortisol when administered acutely to healthy controls.[101] When stabilized methadone maintained patients were transitioned onto buprenorphine, basal levels of beta-endorphin remained normal.[102] It appears that most stress responsive markers are normalized in buprenorphine maintained patients and that failure to normalize correlates with craving and relapse.[103,104] Thus, as with methadone, the role of buprenorphine in the treatment of opiate addiction is not simply replacement of an illicitly used opiate for a medically supervised opiate but rather as a medication that corrects many of the neurobiological processes contributing to relapse.

Naltrexone

Naltrexone is a semi-synthetic mu and kappa opioid receptor antagonist synthesized in the mid-1960's as a congener of oxymorphone.[105] In the treatment of opiate addiction, naltrexone is administered either orally in tablet formulation or intramuscularly in an extended release formulation. Following oral administration, it is rapidly absorbed but undergoes significant first pass metabolism with a bioavailability less than 50%.[106] Naltrexone has low protein binding capacity and an apparent volume of distribution of approximately 19 L/kg. Peak plasma levels following oral administration are reached within 4 hours and the elimination half-life at steady state is approximately 9 hours.[107] Naltrexone is reduced to the weak opiate antagonist 6β-naltrexol in the liver. Naltrexone, 6β-naltrexol, and their conjugates are renally eliminated with less than 3% recovered in the feces.[107] There are no known drug interactions that would alter naltrexone metabolism and thus limit its use.

Naltrexone safety is well established. There have been some reports of hepatotoxicity following high dose naltrexone and caution is advised in prescribing naltrexone in the setting of acute hepatitis or end stage liver disease.[108] Unlike methadone and buprenorphine, naltrexone is not behaviorally reinforcing in individuals without opiate tolerance and does not induce respiratory suppression. Since it is an opiate antagonist, naltrexone may precipitate withdrawal in patients with physical dependence on opioids.

The initial hypothesis for the use of opioid antagonists in the treatment of opiate addiction was as a means of eliminating a condition response to use opiates.[109] Based on this hypothesis, return to opiate use following detoxification is caused by negative reinforcement of environmental stimuli (e.g., cues and social stressors) and if an antagonist prevented the addict from relieving this negative state through opiate use, then the behavior of turning to opiates in these situations would eventually cease. Indeed, naltrexone can block the effect of superimposed opiates for approximately 24–48 hours after oral dosing.[110] The plasma levels sufficient to block 25mg of heroin are approximately 1–2 ng/ml, a level maintained for 21–28 days following 380mg of the intramuscular extended release formulation.[111]

As early as 1976, NIDA convened a workgroup to study and promote the development of both oral and extended release naltrexone as a treatment for opiate addiction.[112] Early and successive work found that naltrexone was well tolerated with few adverse effects other than mild nausea. Patients taking naltrexone reported fewer days of heroin use and had few opiate positive urine drug tests.[113] Patient adherence and drop out has been a major stumbling block for oral naltrexone. In multiple studies of either daily or thrice weekly dosing, fewer than 20% of patients remain in treatment for 6 months.[113–115] A Cochrane collaboration meta-analysis found that due to extensive drop-out rates, oral naltrexone maintenance with or without psychotherapy was no better than placebo treatment.[116]

Extended release naltrexone may improve treatment outcome because non-adherence to daily oral regimens is reduced by delivery of a once monthly injection. Currently there are limited data regarding the extended release intramuscular injection. In a two month randomized placebo controlled trial, only 70% of patients were retained for 8-weeks.[117] A larger trial in Russia retained 53% of patients at 6 months compared to 38% for placebo.[118] Patients receiving extended release naltrexone also had significantly fewer days of illicit opiate use. While intramuscular naltrexone is the only FDA approved extended release formulation, literature on subdermal implants capable of maintaining naltrexone plasma levels between 1–2 ng/ml for 6 months, may also contribute to our understanding of the role naltrexone may play in the treatment of opiate addiction. These studies have shown retention of approximately 60% at 6-months, exceeding that of oral naltrexone.[119,120] Illicit opiate use was also significantly reduced, however, in one study, patients receiving the implants had a higher rate of non-opiate drug use than those receiving methadone.[121]

The use of naltrexone in the treatment of opiate addiction is mechanistically quite different from that of methadone and buprenorphine. Each medication can block the effect of superimposed opiates and following steady-state oral administration, naltrexone achieves approximately 95% mu opioid receptor occupancy.[122] Unlike methadone and buprenorphine, naltrexone is without intrinsic opiate activity and poses minimal risk abuse or diversion. What may be most compelling about naltrexone comes from the literature on its use in the treatment of alcoholism where it reduces craving, a frequent predecessor to relapse. In fact, reduction in base-line craving is correlated with its effectiveness.[123] Naltrexone's effect on craving in opiate addicts is less clear. Oral naltrexone may not reduce craving more than placebo and if it does, this reduction does not necessarily correlate with abstinence.[124,125] Failure of oral naltrexone to prevent relapse in opiate addicts may be related to ongoing stress dysregulation and is supported by animal research showing its failure to suppress stress-induced relapse.[126] Whereas both methadone and buprenorphine can normalize stress response, naltrexone maintenance may not. In fact, oral naltrexone administration stimulates ACTH and cortisol, even following chronic administration.[127] This stimulation mimics the hormonal response during opiate withdrawal. It also mimics the response to acute administration of alcohol, which may explain oral naltrexone's effectiveness for alcohol but not opiate addiction.[128] Whether extended release naltrexone has a similar effect on stress response remain unknown but its ability to reduce craving is promising.[118]

Methadone, buprenorphine, naltrexone direct comparisons

There are no randomized double-blind controlled trials comparing all three medications. One randomized trial comparing each of the medications found 24-week retention rates of 84%, 59%, and 21% for methadone 50mg, buprenorphine 5mg, and naltrexone 50mg, respectively, despite suboptimal doses of methadone and buprenorphine.[129] A comparative study between buprenorphine and oral naltrexone found naltrexone response inferior.[130] There are no comparative outcome studies between either methadone or buprenorphine and extended release naltrexone. It has been observed that the 6-month retention rates following extended release naltrexone are similar to 1-year retentions in methadone maintenance and thus non-inferiority studies of extended release naltrexone are needed.[131]

Special populations

End stage liver disease

Decreased hepatic metabolism and plasma protein can lead to increased methadone clearance.[132] Increased methadone clearance may result in onset of withdrawal symptoms and can be prevented by increasing methadone dose. Since this will also increase methadone

peak levels, it may result in sedation. If this occurs, the methadone dose may be split into two doses taken during the course of the day. There are no formal studies of buprenorphine pharmacokinetics in end stage liver disease. Given the long half-life and active metabolites of buprenorphine, it is unclear if dose adjustment is needed in end stage liver disease. FDA labels for both oral and intramuscular naltrexone recommended against their use in the setting of end stage liver disease.

Pregnancy

The placenta is metabolically active and can increase clearance of both methadone and buprenorphine. Since methadone does not have active metabolites, patients may experience early withdrawal and may require increases in or splitting of methadone dose during the second and third trimesters.[133] It is recommended that neither naloxone nor naltrexone be administered during pregnancy, although each are Category C, thus buprenorphine should be administered as the mono product and naltrexone should be avoided. Both methadone and buprenorphine are associated with improved maternal and fetal outcomes compared to abstinence based approaches. While the recent MOTHER trial found that the length, but not intensity, of neonatal abstinence syndrome and the neonates' need for morphine relief was lower in women taking buprenorphine compared to methadone, there was lower retention in the buprenorphine treated group.[134]

Adolescents

Opiate addiction is often a disease of pediatric onset. Early interventions can prevent the associated consequences of addiction such as HIV and hepatitis C.[135] Because adolescents often have shorter addiction history, it is not known whether they would require maintenance pharmacotherapy. Several reports comparing short-term detoxification to buprenorphine maintenance, however, show better results with longer periods of medication and high rates of relapse following discontinuation of medication.(for a review see 136) Comparative research to guide maintenance medication selection in adolescents is needed. Until such research is available the choice of maintenance medication should be based on available evidence and informed choice.

Chronic pain

A significant number of patients in maintenance pharmacotherapy complain of chronic pain.[137] Many of these patients may require daily or intermittent opioid analgesics. Both methadone and buprenorphine have been used in the treatment of moderate to severe pain and their chronic use for opiate addiction does not preclude the regular use of opioid analgesics. Naltrexone can prevent the effectiveness of opioid analgesics. Its antagonist effect can be overridden in setting of acute pain but caution is advised.[138] It is not clear whether naltrexone maintenance can be recommended for the patient requiring ongoing opioid analgesia.

Criminal justice

Methadone and buprenorphine have been used with success in criminal justice populations.[139,140] Each can reduce recidivism and illicit opiate use. Oral naltrexone requires close supervision for adherence and trials of extended release naltrexone in criminal justice populations are forthcoming.[141] No direct comparisons of these medications have been performed in a criminal justice setting. While there is legal precedent for compulsory addiction treatment and medication in offenders, this precedent does not extend to a specific medication and the criminal justice system must avoid requiring one medication in favor of others and respect the informed choice of decisions made between a physician and patient.[142]

Health professionals

Opiate addicted health professionals have excellent treatment outcomes compared to the general population.[143] Behavioral interventions alone have retention rates approaching 80%.[144] While some have reported successful use of naltrexone as an adjuvant treatment in opiate addicted health professionals, in the absence of controlled trials it is difficult to know if it provides added benefit to behavioral interventions alone.[145,146] Without clear benefit of naltrexone over methadone or buprenorphine, the selection of specific pharmacotherapy should be between a physician and patient and based on evidence and informed choice.

Conclusion: Medication and recovery

Extensive research shows that each of the three available medications used to treat opiate addiction have superior treatment outcomes to non medication based therapies. Increased retention reduces mortality, improves social function, and is associated with decreased drug use and improved quality of life. Thus, these medications help patients achieve “recovery” as it is currently defined.[147] While methadone and buprenorphine appear to have superior outcomes to both oral and intramuscular naltrexone, more direct comparisons are needed. Further work is needed to identify and predict treatment response to help individualize medication choice. Until such data are available, it is prudent, and within a patient’s right to informed choice, for treatment professionals to provide information regarding these standard treatment options, their expected outcomes and potential adverse effects, and allow the patient to choose the medication that best suits his or her need.

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Reference List

1. Degenhardt L, Bucello C, Calabria B, et al. What data are available on the extent of illicit drug use and dependence globally? Results of four systematic reviews. Drug and Alcohol Dependence. 2011; 117:85–101. [PubMed: 21377813]
2. World Health Organization. Geneva: WHO Press; 2009. Global health risks: mortality and burden of disease attributable to selected major risks.
3. Salomon N, Perlman DC, Friedmann P, Ziluck V, Des J. Prevalence and risk factors for positive tuberculin skin tests among active drug users at a syringe exchange program. Int J Tuberc Lung Dis. 2000; 4:47–54. [PubMed: 10654644]
4. Nelson PK, Mathers BM, Cowie B, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. The Lancet. 2011; 378:571–583.
5. Mathers BM, Degenhardt L, Phillips B, et al. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. The Lancet. 2008; 372:1733–1745.
6. Paulozzi LJ, Budnitz DS, Xi Y. Increasing deaths from opioid analgesics in the United States. Pharmacoepidemiol Drug Saf. 2006; 15:618–627. [PubMed: 16862602]
7. Degenhardt L, Bucello C, Mathers B, et al. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. Addiction. 2011; 106:32–51. [PubMed: 21054613]
8. Centers for Disease Control and Prevention. Vital signs: Overdoses of prescription opioid pain relievers – United States, 1998–2008. MMRW. 2011; 60:1487–1492.
9. UNODC. World drug report 2011. 2011. United Nations Publication (Sales No. E.11.XI.10).
10. Substance Abuse and Mental Health Services Administration. Rockville, MD: Office of Applied Studies; 2011. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. DHHS Publication No. SMA 11-4658. NSDUH Series H-41.
11. Substance Abuse and Mental Health Services Administration. Treatment episode data set. 2011.

12. Substance Abuse and Mental Health Services Administration. National survey on drug use and health 2010. 2011.
13. Kreek MJ, Bart G, Lilly C, Laforge KS, Nielsen DA. Pharmacogenetics and human molecular genetics of opiate and cocaine addictions and their treatments. Pharmacol Rev. 2005; 57:1–26. [PubMed: 15734726]
14. Merikangas KR, Stolar M, Stevens DE, et al. Familial Transmission of Substance Use Disorders. Archives of General Psychiatry. 1998; 55:973–979. [PubMed: 9819065]
15. Tsuang MT, Lyons MJ, Meyer JM, et al. Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. Arch Gen Psychiatry. 1998; 55:967–972. [PubMed: 9819064]
16. Monitoring the Future. 2011 data from in-school surveys of 8th- ,10th, and 12th-grade students. 2011 http://monitoringthefuture.org/data/11data.html#2011data-drugs.
17. Kalinichev M, Easterling KW, Holtzman SG. Long-Lasting Changes in Morphine-Induced Locomotor Sensitization and Tolerance in Long-Evans Mother Rats as a Result of Periodic Postpartum Separation from the Litter: A Novel Model of Increased Vulnerability to Drug Abuse? Neuropsychopharmacology. 2003; 28:317–328. [PubMed: 12589385]
18. Vazquez V, Giros B, Dauge V. Maternal deprivation specifically enhances vulnerability to opiate dependence. Behav Pharmacol. 2006; 17:715–724. [PubMed: 17110797]
19. Brook JS, Brook DW, Zhang C, Cohen P. Pathways from adolescent parent-child conflict to substance use disorders in the fourth decade of life. Am J Addict. 2009; 18:235–242. [PubMed: 19340642]
20. Mills KL, Teesson M, Ross J, Peters L. Trauma, PTSD, and substance use disorders: findings from the Australian National Survey of Mental Health and Well-Being. Am J Psychiatry. 2006; 163:652–658. [PubMed: 16585440]
21. Volkow ND, Ding YS, Fowler JS, et al. Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in the human brain. Arch Gen Psychiatry. 1995; 52:456–463. [PubMed: 7771915]
22. Volkow ND, Wang GJ, Fischman MW, et al. Effects of route of administration on cocaine induced dopamine transporter blockade in the human brain. Life Sci. 2000; 67:1507–1515. [PubMed: 10983846]
23. Marsch LA, Bickel WK, Badger GJ, et al. Effects of Infusion Rate of Intravenously Administered Morphine on Physiological, Psychomotor, and Self-Reported Measures in Humans. Journal of Pharmacology and Experimental Therapeutics. 2001; 299:1056–1065. [PubMed: 11714895]
24. Johnson SW, North RA. Opioids excite dopamine neurons by hyperpolarization of local interneurons. J Neurosci. 1992; 12:483–488. [PubMed: 1346804]
25. Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F. Addiction: Beyond dopamine reward circuitry. Proceedings of the National Academy of Sciences. 2011; 108:15037–15042.
26. Pickens CL, Airavaara M, Theberge F, Fanous S, Hope BT, Shaham Y. Neurobiology of the incubation of drug craving. Trends in Neurosciences. 2011; 34:411–420. [PubMed: 21764143]
27. Koob GF, Volkow ND. Neurocircuitry of Addiction. Neuropsychopharmacology. 2010; 35:217–238. [PubMed: 19710631]
28. Wang GJ, Volkow ND, Fowler JS, et al. Dopamine D2 receptor availability in opiate-dependent subjects before and after naloxone-precipitated withdrawal. Neuropsychopharmacology. 1997; 16:174–182. [PubMed: 9015800]
29. Zijlstra F, Booij J, van den Brink W, Franken IHA. Striatal dopamine D2 receptor binding and dopamine release during cue-elicited craving in recently abstinent opiate-dependent males. European Neuropsychopharmacology. 2008; 18:262–270. [PubMed: 18077142]
30. Kennedy JA, Hartman N, Sbriglio R, Khuri E, Kreek MJ. Metyrapone-induced withdrawal symptoms. Br J Addict. 1990; 85:1133–1140. [PubMed: 2224193]
31. Schluger JH, Borg L, Ho A, Kreek MJ. Altered HPA axis responsivity to metyrapone testing in methadone maintained former heroin addicts with ongoing cocaine addiction. Neuropsychopharmacology. 2001; 24:568–575. [PubMed: 11282257]

32. Bart G, Borg L, Schluger JH, Green M, Ho A, Kreek MJ. Suppressed prolactin response to dynorphin A1-13 in methadone-maintained versus control subjects. J Pharmacol Exp Ther. 2003; 306:581–587. [PubMed: 12730354]
33. Schluger JH, Bart G, Green M, Ho A, Kreek MJ. Corticotropin-releasing factor testing reveals a dose-dependent difference in methadone maintained vs control subjects. Neuropsychopharmacology. 2003; 28:985–994. [PubMed: 12700714]
34. Hackman DA, Farah MJ, Meaney MJ. Socioeconomic status and the brain: mechanistic insights from human and animal research. Nat Rev Neurosci. 2010; 11:651–659. [PubMed: 20725096]
35. Morgan D, Grant KA, Gage HD, et al. Social dominance in monkeys: dopamine D2 receptors and cocaine self-administration. Nat Neurosci. 2002; 5:169–174. [PubMed: 11802171]
36. Pescor MJ. Follow-up study of treated narcotics addicts. Publ Health Rep. 1943; (Suppl 170):1–18.
37. Vaillant GE. A 20-year follow-up of New York narcotic addicts. Arch Gen Psychiatry. 1973; 29:237–241. [PubMed: 4741515]
38. Mayet S, Farrell M, Ferri M, Amato L, Davoli M. Psychosocial treatment for opiate abuse and dependence. Cochrane Database Syst Rev. 2005 CD004330.
39. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev. 2003 CD002209.
40. Hser YI, Hoffman V, Grella CE, Anglin MD. A 33-year follow-up of narcotics addicts. Arch Gen Psychiatry. 2001; 58:503–508. [PubMed: 11343531]
41. Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. Lancet. 2003; 361:662–668. [PubMed: 12606177]
42. Woody GE, Kane V, Lewis K, Thompson R. Premature deaths after discharge from methadone maintenance: a replication. J Addict Med. 2007; 1:180–185. [PubMed: 21768955]
43. Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. BMJ. 2010; 341:c5475. [PubMed: 20978062]
44. Cushman P, Dole VP. Detoxification of Rehabilitated Methadone-Maintained Patients. JAMA: The Journal of the American Medical Association. 1973; 226:747–752. [PubMed: 4585339]
45. Amato L, Davoli M, Minozzi S, Ali R, Ferri M. Methadone at tapered doses for the management of opioid withdrawal. Cochrane Database Syst Rev. 2005
46. Gowing, L.; Ali, R.; White, JM. Gowing Linda, Ali Robert, White Jason M Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal Cochrane Database of Systematic Reviews: Reviews. Ltd Chichester, UK: John Wiley & Sons; 2010. Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. 2010.
47. Collins ED, Kleber HD, Whittington RA, Heitler NE. Anesthesia-Assisted vs Buprenorphine- or Clonidine-Assisted Heroin Detoxification and Naltrexone Induction. JAMA: The Journal of the American Medical Association. 2005; 294:903–913. [PubMed: 16118380]
48. Sees KL, Delucchi KL, Masson C, et al. Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence: a randomized controlled trial. JAMA. 2000; 283:1303–1310. [PubMed: 10714729]
49. Ling W, Hillhouse M, Domier C, et al. Buprenorphine tapering schedule and illicit opioid use. Addiction. 2009; 104:256–265. [PubMed: 19149822]
50. Kleiderer, EC.; Rice, JB.; Conquest, V.; Williams, JH. Farbenindustrie plant, Hochst am Main. Vol. 981. Washington, DC: Office of the Publication Board Department of Commerce; 1945. Pharmaceutical activities at the I.G.
51. McCance-Katz EF, Sullivan LE, Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. Am J Addict. 2010; 19:4–16. [PubMed: 20132117]
52. Kreek MJ. Medical safety and side effects of methadone in tolerant individuals. JAMA. 1973; 223:665–668. [PubMed: 4739193]
53. Center for Substance Abuse Treatment. Methadone mortality - a reassessment. Division of Pharmacologic Therapies, Center for Substance Abuse Treatment, SAMHSA/DHHS; 2007.

54. Strang J, Hall W, Hickman M, Bird SM. Impact of supervision of methadone consumption on deaths related to methadone overdose (1993–2008): analyses using OD4 index in England and Scotland. BMJ. 2010; 341:c4851. [PubMed: 20847018]
55. Martin JA, Campbell A, Killip T, et al. QT interval screening in methadone maintenance treatment: report of a SAMHSA expert panel. J Addict Dis. 2011; 30:283–306. [PubMed: 22026519]
56. Martell BA, Arnsten JH, Krantz MJ, Gourevitch MN. Impact of methadone treatment on cardiac repolarization and conduction in opioid users. Am J Cardiol. 2005; 95:915–918. [PubMed: 15781034]
57. Bart G. CSAT's QT interval screening in methadone report: outrageous fortune or sea of troubles? J Addict Dis. 2011; 30:313–317. [PubMed: 22026522]
58. Isbell, Harr; Wikler, Abra; Eddy, NB.; Wilson, JL.; Moran, CF. Tolerance and addiction liability of 6-dimethylamino-4-4-diphenylheptanone-3 (methadon). Journal of the American Medical Association. 1947; 135:888–894. [PubMed: 18897594]
59. Isbell H, Vogel VH. The addiction liability of methadone (amidone, dolophine, 10820) and its use in the treatment of the morphine abstinence syndrome. American Journal of Psychiatry. 1949; 105:909–914. [PubMed: 18127077]
60. Dole VP, Nyswander ME, Kreek MJ. Narcotic blockade. Arch Intern Med. 1966; 118:304–309. [PubMed: 4162686]
61. Dole VP, Nyswander M. A medical treatment for diacetylmorphine (heroin) addiction. A clinical trial with methadone hydrochloride. JAMA. 1965; 193:646–650. [PubMed: 14321530]
62. National Institutes of Health. Effective medical treatment of opiate addiction. National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. JAMA. 1998; 280:1936–1943. [PubMed: 9851480]
63. Ball, JC.; Ross, A. The Effectiveness of Methadone Maintenance. New York: Springer-Verlag; 1991.
64. Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. N Engl J Med. 2000; 343:1290–1297. [PubMed: 11058673]
65. Strain EC, Bigelow GE, Liebson IA, Stitzer ML. Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial. JAMA. 1999; 281:1000–1005. [PubMed: 10086434]
66. Ling W, Wesson DR, Charuvastra C, Klett CJ. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. Arch Gen Psychiatry. 1996; 53:401–407. [PubMed: 8624183]
67. Simpson DD, Joe GW, Broome KM, Hiller ML, Knight K, Rowan-Szal GA. Program diversity and treatment retention rates in the drug abuse treatment outcome study (DATOS). Psychology of Add Behav. 1997; 11:279–293.
68. McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. JAMA. 2000; 284:1689–1695. [PubMed: 11015800]
69. Marsch LA, Stephens MA, Mudric T, Strain EC, Bigelow GE, Johnson RE. Predictors of outcome in LAAM, buprenorphine, and methadone treatment for opioid dependence. Exp Clin Psychopharmacol. 2005; 13:293–302. [PubMed: 16366759]
70. Kelly SM, O'Grady KE, Mitchell SG, Brown BS, Schwartz RP. Predictors of methadone treatment retention from a multi-site study: A survival analysis. Drug Alcohol Depend. 2011
71. Belding MA, McLellan AT, Zanis DA, Incmikoski R. Characterizing "Nonresponsive" Methadone Patients. Journal of Substance Abuse Treatment. 1998; 15:485–492. [PubMed: 9845861]
72. Villafranca SW, McKellar JD, Trafton JA, Humphreys K. Predictors of retention in methadone programs: a signal detection analysis. Drug Alcohol Depend. 2006; 83:218–224. [PubMed: 16384657]
73. Kraft MK, Rothbard AB, Hadley TR, McLellan AT, Asch DA. Are supplementary services provided during methadone maintenance really cost-effective? Am J Psychiatry. 1997; 154:1214–1219. [PubMed: 9286179]

74. Davis AM, Inturrisi CE. *d*-Methadone blocks morphine tolerance and *N*-methyl-D-aspartate-induced hyperalgesia. J Pharmacol Exp Ther. 1999; 289:1048–1053. [PubMed: 10215686]
75. Kling MA, Carson RE, Borg L, et al. Opioid receptor imaging with positron emission tomography and [(18)F]cyclofoxy in long-term, methadone-treated former heroin addicts. J Pharmacol Exp Ther. 2000; 295:1070–1076. [PubMed: 11082442]
76. Kreek MJ, Wardlaw SL, Hartman N, et al. Circadian rhythms and levels of beta-endorphin, ACTH, and cortisol during chronic methadone maintenance treatment in humans. Life Sci. 1983; 33(Suppl 1):409–411. [PubMed: 6319894]
77. Facchinetti F, Grasso A, Petraglia F, Parrini D, Volpe A, Genazzani AR. Impaired circadian rhythmicity of beta-lipotrophin, beta-endorphin and ACTH in heroin addicts. Acta Endocrinol (Copenh). 1984; 105:149–155. [PubMed: 6320568]
78. Kreek, MJ.; Borg, L.; Zhou, Y.; Schluger, J. Relationships between endocrine functions and substance abuse syndromes: heroin and related short-acting opiates in addiction contrasted with methadone and other long-acting opioid agonists used in pharmacotherapy of addiction. In: Pfaff, D.; Arnold, A.; Etgen, A., et al., editors. Hormones, Brain and Behavior. San Diego, CA: Academic Press; 2002. p. 781-830.
79. Bentley KW, Hardy DG. Novel analgesics and molecular rearrangements in the morphine-thebaine group. 3. Alcohols of the 6,14-endo-ethenotetrahydrooripavine series and derived analogs of N-allylnormorphine and -norcodeine. J Am Chem Soc. 1967; 89:3281–3292. [PubMed: 6042764]
80. Ling W, Casadonte P, Bigelow G, et al. Buprenorphine implants for treatment of opioid dependence: a randomized controlled trial. JAMA. 2010; 304:1576–1583. [PubMed: 20940383]
81. Schuh KJ, Johanson CE. Pharmacokinetic comparison of the buprenorphine sublingual liquid and tablet. Drug Alcohol Depend. 1999; 56:55–60. [PubMed: 10462093]
82. Picard N, Cresteil T, Djebli N, Marquet P. In vitro metabolism study of buprenorphine: evidence for new metabolic pathways. Drug Metabolism and Disposition. 2005; 33:689–695. [PubMed: 15743975]
83. Fudala PJ, Bridge TP, Herbert S, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. N Engl J Med. 2003; 349:949–958. [PubMed: 12954743]
84. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clin Pharmacol Ther. 1994; 55:569–580. [PubMed: 8181201]
85. Comer SD, Sullivan MA, Walker EA. Comparison of Intravenous Buprenorphine and Methadone Self-Administration by Recently Detoxified Heroin-Dependent Individuals. Journal of Pharmacology and Experimental Therapeutics. 2005; 315:1320–1330. [PubMed: 16144974]
86. Kintz P. Deaths involving buprenorphine: a compendium of French cases. Forensic Sci Int. 2001; 121:65–69. [PubMed: 11516889]
87. Comer SD, Sullivan MA, Vosburg SK, et al. Abuse liability of intravenous buprenorphine/naloxone and buprenorphine alone in buprenorphine-maintained intravenous heroin abusers. Addiction. 2010; 105:709–718. [PubMed: 20403021]
88. Martin WR, Eades CG, Thompson JA, Huppler RE, Gilbert PE. The effects of morphine- and nalorphine- like drugs in the nondependent and morphine-dependent chronic spinal dog. J Pharmacol Exp Ther. 1976; 197:517–532. [PubMed: 945347]
89. Jasinski DR, Pevnick JS, Griffith JD. Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction. Arch Gen Psychiatry. 1978; 35:501–516. [PubMed: 215096]
90. Center for Substance Abuse Treatment. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2004. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. DHHS Publication Number (SMA) 04-3939. Treatment Improvement Protocol (TIP) Series 40.
91. Lee JD, Grossman E, DiRocco D, Gourevitch MN. Home buprenorphine/naloxone induction in primary care. J Gen Intern Med. 2009; 24:226–232. [PubMed: 19089508]
92. Mello NK, Mendelson JH. Buprenorphine suppresses heroin use by heroin addicts. Science. 1980; 207:657–659. [PubMed: 7352279]

93. Reisinger M. Buprenorphine as new treatment for heroin dependence. Drug Alcohol Depend. 1985; 16:257–262. [PubMed: 4092611]

94. Ling W, Charuvastra C, Collins JF, et al. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. Addiction. 1998; 93:475–486. [PubMed: 9684386]

95. Mattick, RP.; Kimber, J.; -Breen-Court; Davoli, M. Mattick Richard P, Kimber Jo, Breen Courtney, Davoli Marina Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence Cochrane Database of Systematic Reviews: Reviews. Ltd Chichester, UKD: John Wiley & Sons; 2008. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. 2008.

96. Fiellin DA, Pantalon MV, Chawarski MC, et al. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. N Engl J Med. 2006; 355:365–374. [PubMed: 16870915]

97. Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive Counseling During Brief and Extended Buprenorphine-Naloxone Treatment for Prescription Opioid Dependence: A 2-Phase Randomized Controlled Trial. Archives of General Psychiatry. 2011; 68:1238–1246. [PubMed: 22065255]

98. Mattick RP, Ali R, White JM, O'Brien S, Wolk S, Danz C. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. Addiction. 2003; 98:441–452. [PubMed: 12653814]

99. Moore BA, Fiellin DA, Barry DT, et al. Primary care office-based buprenorphine treatment: comparison of heroin and prescription opioid dependent patients. J Gen Intern Med. 2007; 22:527–530. [PubMed: 17372805]

100. Greenwald MK, Johanson CE, Moody DE, et al. Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. Neuropsychopharmacology. 2003; 28:2000–2009. [PubMed: 12902992]

101. Rolandi E, Marabini A, Franceschini R, Messina V, Bongera P, Barreca T. Changes in pituitary secretion induced by an agonist-antagonist opioid drug, buprenorphine. Acta Endocrinol (Copenh). 1983; 104:257–260. [PubMed: 6415992]

102. Kosten TR, Morgan C, Kreek MJ. Beta endorphin levels during heroin, methadone, buprenorphine, and naloxone challenges: preliminary findings. Biol Psychiatry. 1992; 32:523–528. [PubMed: 1445968]

103. Kakko J, von WJ, Svanborg KD, Lidstrom J, Barr CS, Heilig M. Mood and neuroendocrine response to a chemical stressor, metyrapone, in buprenorphine-maintained heroin dependence. Biol Psychiatry. 2008; 63:172–177. [PubMed: 17850768]

104. Fatseas M, Denis C+ Massida Z, Verger M, Franques-R+¬n+¬ric P, Auriacombe M. Cue-Induced Reactivity, Cortisol Response and Substance Use Outcome in Treated Heroin Dependent Individuals. Biological Psychiatry. 2011; 70:720–727. [PubMed: 21741031]

105. Blumberg H, Pachter I, Matossian Z. inventors. 14-hydroxydihydronormorphinone derivatives. 1967 3,332,950.

106. Verebey K, Volavka J, Mule SJ, Resnick RB. Naltrexone: disposition, metabolism, and effects after acute and chronic dosing. Clin Pharmacol Ther. 1976; 20:315–328. [PubMed: 954353]

107. Wall ME, Brine DR, Perez-Reyes M. Metabolism and disposition of naltrexone in man after oral and intravenous administration. Drug Metabolism and Disposition. 1981; 9:369–375. [PubMed: 6114837]

108. Pfohl DN, Allen JI, Atkinson RL, et al. Naltrexone hydrochloride (Trexan): a review of serum transaminase elevations at high dosage. NIDA Res Monogr. 1986; 67:66–72. [PubMed: 3092099]

109. Martin WR. Realistic Goals for Antagonist Therapy. Am J Drug Alcohol Abuse. 1975; 2:353–356. [PubMed: 1227296]

110. Volavka J, Resnick RB, Kestenbaum RS, Freedman AM. Short-term effects of naltrexone in 155 heroin ex-addicts. Biol Psychiatry. 1976; 11:679–685. [PubMed: 999987]

111. Dunbar JL, Turncliff RZ, Dong Q, Silverman BL, Ehrich EW, Lasseter KC. Single- and Multiple-Dose Pharmacokinetics of Long-acting Injectable Naltrexone. Alcoholism: Clinical and Experimental Research. 2006; 30:480–490.

112. Julius, D.; Renault, P., editors. National Institutes of Health. Narcotic antagonists: Naltrexone progress report. Virginia: DHEW; 1976. National Institute on Drug Abuse research Monograph Series 9.
113. O'Brien CP, Greenstein RA, Mintz J, Woody GE. Clinical Experience with Naltrexone. Am J Drug Alcohol Abuse. 1975; 2:365–377. [PubMed: 1227298]
114. Hollister LE, Schwin RL, Kasper P. Naltrexone treatment of opiate-dependent persons. Drug Alcohol Depend. 1977; 2:203–209. [PubMed: 880876]
115. Judson BA, Carney TM, Goldstein A. Naltrexone treatment of heroin addiction: efficacy and safety in a double-blind dosage comparison. Drug Alcohol Depend. 1981; 7:325–346. [PubMed: 7023894]
116. Minozzi, S.; Amato, L.; Vecchi, S.; Davoli, M.; Kirchmayer, U.; Verster, A. Minozzi Silvia, Amato Laura, Vecchi Simona, Davoli Marina, Kirchmayer Ursula, Verster Annette Oral naltrexone maintenance treatment for opioid dependence Cochrane Database of Systematic Reviews: Reviews. Ltd Chichest: John Wiley & Sons; 2011. Oral naltrexone maintenance treatment for opioid dependence. 2011.
117. Comer SD, Sullivan MA, Yu E, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. Arch Gen Psychiatry. 2006; 63:210–218. [PubMed: 16461865]
118. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet. 2011; 377:1506–1513. [PubMed: 21529928]
119. Hulse GK, Morris N, rnold-Reed D, Tait RJ. Improving Clinical Outcomes in Treating Heroin Dependence: Randomized, Controlled Trial of Oral or Implant Naltrexone. Archives of General Psychiatry. 2009; 66:1108–1115. [PubMed: 19805701]
120. Kunøe N, Lobmaier P, Vederhus JK, et al. Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial. The British Journal of Psychiatry. 2009; 194:541–546. [PubMed: 19478295]
121. Ngo HTT, Tait RJ, Hulse GK. Comparing Drug-Related Hospital Morbidity Following Heroin Dependence Treatment With Methadone Maintenance or Naltrexone Implantation. Archives of General Psychiatry. 2008; 65:457–465. [PubMed: 18391134]
122. Weerts EM, Kim YK, Wand GS, et al. Differences in delta- and mu-opioid receptor blockade measured by positron emission tomography in naltrexone-treated recently abstinent alcohol-dependent subjects. Neuropsychopharmacology. 2008; 33:653–665. [PubMed: 17487229]
123. Volpicelli JR, Clay KL, Watson NT, O'Brien CP. Naltrexone in the treatment of alcoholism: predicting response to naltrexone. J Clin Psychiatry. 1995; 56(Suppl 7):39–44. [PubMed: 7673104]
124. Krupitsky EM, Zvartau EE, Masalov DV, et al. Naltrexone with or without fluoxetine for preventing relapse to heroin addiction in St. Petersburg, Russia. J Subst Abuse Treat. 2006; 31:319–328. [PubMed: 17084785]
125. Dijkstra BAG, De Jong CAJ, Bluschke SM, Krabbe PFM, van der Staak CPF. Does naltrexone affect craving in abstinent opioid-dependent patients? Addiction Biology. 2007; 12:176–182. [PubMed: 17508990]
126. Shaham Y, Funk D, Erb S, Brown TJ, Walker CD, Stewart J. Corticotropin-releasing factor, but not corticosterone, is involved in stress-induced relapse to heroin-seeking in rats. J Neurosci. 1997; 17:2605–2614. [PubMed: 9065520]
127. Kosten TR, Kreek MJ, Ragunath J, Kleber HD. Cortisol levels during chronic naltrexone maintenance treatment in ex- opiate addicts. Biol Psychiatry. 1986; 21:217–220. [PubMed: 3947698]
128. O'Malley SS, Krishnan-Sarin S, Farren C, Sinha R, Kreek MJ. Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo-pituitary-adrenocortical axis. Psychopharmacology (Berl). 2002; 160:19–29. [PubMed: 11862370]

129. Ahmadi J, Ahmadi K, Ohaeri J. Controlled, randomized trial in maintenance treatment of intravenous buprenorphine dependence with naltrexone, methadone or buprenorphine: a novel study. European Journal of Clinical Investigation. 2003; 33:824–829. [PubMed: 12925043]
130. Schottenfeld RS, Chawarski MC, Mazlan M. Maintenance treatment with buprenorphine and naltrexone for heroin dependence in Malaysia: a randomised, double-blind, placebo-controlled trial. Lancet. 2008; 371:2192–2200. [PubMed: 18586174]
131. Bart G. Promise of extended-release naltrexone is a red herring. Lancet. 2011; 378:663–664. [PubMed: 21856474]
132. Kreek MJ, Bencsath FA, Field FH. Effects of liver disease on urinary excretion of methadone and metabolites in maintenance patients: quantitation by direct probe chemical ionization mass spectrometry. Biomed Mass Spectrom. 1980; 7:385–395. [PubMed: 7470591]
133. Pond SM, Kreek MJ, Tong TG, Raghunath J, Benowitz NL. Altered methadone pharmacokinetics in methadone-maintained pregnant women. J Pharmacol Exp Ther. 1985; 233:1–6. [PubMed: 3981450]
134. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med. 2010; 363:2320–2331. [PubMed: 21142534]
135. Piccolo P, Borg L, Lin A, Melia D, Ho A, Kreek MJ. Hepatitis C virus and human immunodeficiency virus-1 co-infection in former heroin addicts in methadone maintenance treatment. J Addict Dis. 2002; 21:55–66. [PubMed: 12296502]
136. Minozzi, S.; Amato, L.; Davoli, M. Minozzi Silvia, Amato Laura, Davoli Marina Maintenance treatments for opiate dependent adolescent Cochrane Database of Systematic Reviews: Reviews. Ltd Chichester, UK: John Wiley & Sons; 2009. Maintenance treatments for opiate dependent adolescent. 2009.
137. Rosenblum A, Joseph H, Fong C, Kipnis S, Cleland C, Portenoy RK. Prevalence and Characteristics of Chronic Pain Among Chemically Dependent Patients in Methadone Maintenance and Residential Treatment Facilities. JAMA: The Journal of the American Medical Association. 2003; 289:2370–2378. [PubMed: 12746360]
138. Gastfriend DR. Intramuscular extended-release naltrexone: current evidence. Annals of the New York Academy of Sciences. 2011; 1216:144–166. [PubMed: 21272018]
139. Kinlock TW, Gordon MS, Schwartz RP, Fitzgerald TT, O'Grady KE. A randomized clinical trial of methadone maintenance for prisoners: results at 12 months postrelease. J Subst Abuse Treat. 2009; 37:277–285. [PubMed: 19339140]
140. Magura S, Lee JD, Hershberger J, et al. Buprenorphine and methadone maintenance in jail and post-release: a randomized clinical trial. Drug Alcohol Depend. 2009; 99:222–230. [PubMed: 18930603]
141. Coviello DM, Cornish JW, Lynch KG, Alterman AI, O'Brien CP. A randomized trial of oral naltrexone for treating opioid-dependent offenders. Am J Addict. 2010; 19:422–432. [PubMed: 20716305]
142. Richard J. Judicially mandated naltrexone use by criminal offenders: A legal analysis. Journal of Substance Abuse Treatment. 2006; 31:121–127. [PubMed: 16919737]
143. Domino KB, Hornbein TF, Polissar NL, et al. Risk factors for relapse in health care professionals with substance use disorders. JAMA. 2005; 293:1453–1460. [PubMed: 15784868]
144. Skipper GE, Campbell MD, Dupont RL. Anesthesiologists with substance use disorders: a 5-year outcome study from 16 state physician health programs. Anesth Analg. 2009; 109:891–896. [PubMed: 19690263]
145. Ling W, Wesson DR. Naltrexone treatment for addicted health-care professionals: a collaborative private practice experience. J Clin Psychiatry. 1984; 45:46–48. [PubMed: 6469936]
146. Merlo LJ, Greene WM, Pomm R. Mandatory naltrexone treatment prevents relapse among opiate-dependent anesthesiologists returning to practice. J Addict Med. 2011; 5:279–283. [PubMed: 22107877]
147. What is recovery? A working definition from the Betty Ford Institute. J Subst Abuse Treat. 2007; 33:221–228. [PubMed: 17889294]

Table 1

Clinical Characteristics of methadone, buprenorphine, and naltrexone

	Methadone	Buprenorphine	Naltrexone
Controlled substance	Yes	Yes	No
Availability	OTP	OTP or DATA Waived practitioner	Any prescribing practitioner
1-year retention	60%	60%	20% (53% 6-months ER)
Direct expense	$	$$	$$–$$$$
Dosing frequency	Daily	Daily	Daily or monthly (ER)
Narcotic blockade	Yes, at steady-state	Yes, at steady-state	Yes
Can induce withdrawal	No	Yes	Yes
Overdose potential	Yes	Yes	No
Withdrawal upon cessation	Yes	Yes	No
Loss of tolerance on cessation	Yes	Yes	Yes
Complicates treatment of moderate-severe pain	No	No	Yes

OTP opiate treatment program; DATA Drug Addiction Treatment Act of 2000; ER extended release formulation

Table 2

Pharmacological Profile of Methadone, Buprenorphine, and Naltrexone

	Methadone	Buprenorphine	Naltrexone
Main effect	Mu full agonist, NMDA antagonist	Mu partial agonist	Mu antagonist
Bioavailability	70%–80%	50%	< 50% (~100% ER)
Half-life	28 hours	37 hours	9 hours (4.95 days ER)
Clinically apparent drug interactions	Rifampin, phenytoin, several ART	Select ART	Opioids NSAIDS (?)
Active metabolites	None	Nor-buprenorphine	6-beta-naltrexol

ART Antiretroviral therapy; NSAID Non-steroidal anti-inflammatory; ER extended release formulation

Table 3

Stress Response Hormones

	ACTH	Cortisol
Short-acting opiates	↓	↓
Opiate withdrawal	↑	↑
Methadone	↔	↔
Buprenorphine	↔	↔
Naltrexone (oral)	↑	↑
Naltrexone (ER)	?	?

ACTH adrenocorticotropic hormone; ER extended release