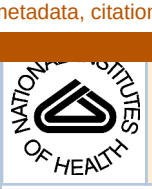

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Opioid Dependence Treatment: Options In Pharmacotherapy

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Abstract

The development of effective treatments for opioid dependence is of great importance given the devastating consequences of the disease. Pharmacotherapies for opioid addiction include opioid agonists, partial agonists, opioid antagonists, and alpha-2-adrenergic agonists, which are targeted toward either detoxification or long-term agonist maintenance. Agonist maintenance therapy is currently the recommended treatment for opioid dependence due to its superior outcomes relative to detoxification. Detoxification protocols have limited long term efficacy and patient discomfort remains a significant therapy challenge. Buprenorphine's effectiveness relative to methadone remains a controversy and may be most appropriate for patients in need of low doses of agonist treatment. Buprenorphine appears superior to alpha-2 agonists, however, and office-based treatment with buprenorphine in the US is gaining support. Studies of sustained-release formulations of naltrexone suggest improved effectiveness for retention and sustained abstinence, however, randomized clinical trials are needed.

Keywords

opioid; opiate; pharmacotherapy; heroin

1. OPIOID DEPENDENCE TREATMENT: OPTIONS IN PHARMACOTHERAPY

Annual prevalence estimates of heroin dependence in the USA remain stable at about 0.14%, although some recent indicators suggest a decrease [1]. In other countries prevalence rates are higher, e.g., 2% of the population in South East and South West Asia are heroin dependent. Prevalence of non-medical use of opioid pain relievers has increased significantly, with over 2 million people in the U.S. abusing prescription opioids [1]. While these rates are low relative to other substances of abuse, such as alcohol and marijuana, the burden of disease is substantial, with high rates of morbidity and mortality, disease transmission, increased health care, crime and law enforcement costs, and less tangible costs of family distress and lost productivity [2].

Clinically, there are two general treatment paths from which to choose, opioid maintenance treatment or detoxification. Most opioid dependent individuals engage in both, likely multiple times, during the course of their drug-using careers. Agonist and partial agonist medications

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are commonly utilized for both maintenance and detoxification purposes; alpha-2-adrenergic agonist medications are primarily used to enhance detoxification outcomes. Antagonist medications are used to accelerate the detoxification process and prescribed post-detoxification to assist in preventing relapse. Success of the various treatment approaches and combinations of treatments is assessed in a number of ways with the primary outcomes of interest being retention in treatment, and opioid and other drug use. Secondarily, HIV risk behaviors, legal/crime involvement, psychiatric symptoms, and morbidity are also used as indicators of treatment success. With regard to detoxification, there are undoubtedly differences between individuals withdrawing from illicit opioid use and those withdrawing from methadone or buprenorphine maintenance and the contexts in which these occur, however, due to limited prospective, comparative data this distinction is not highlighted for purposes of this review. The review of pharmacotherapy options for opioid dependence derives from Medline, Pubmed, and systematic reviews from the Cochrane Databases.

2. AGONIST MEDICATIONS FOR OPIOID DEPENDENCE

2.1. Methadone

Methadone is a full mu-opioid receptor agonist, typically used as a replacement therapy for heroin or other opioid dependence. Methadone's slow onset of action when taken orally and long elimination half-life (24–36 hours) allows it to be used as either a maintenance therapy or detoxification agent [3].

2.1.1. Maintenance—Methadone has been used as a substitution for heroin or other opiates and, through the mechanisms of tolerance and cross-tolerance, prevents opioid intoxication and withdrawal. Adequate dosing ranges from 80 – 150 mg, typically beginning with a daily dose of 20–30 mg with increases of 5 or 10 mg until the optimal dose is reached. Methadone maintenance treatment (MMT) is associated with retention in treatment, and reductions in IV drug use, criminal activity, and HIV risk behaviors and mortality [4–7]. It is currently the most successful treatment for chronic opioid dependence, although not without fairly substantial financial and personal costs to individuals participating in this therapy [8].

Several recent studies have found methadone to be associated with significant cardiac effects; specifically, a prolonged QT interval in the ECG of methadone patients. One study found a 16.2% rate of QT prolongation in hospitalized methadone maintained patients compared to 0% in non-methadone maintained, drug-injecting patients [9]. Another study found that methadone dose was related to a longer QT interval of .140 ms/mg in a cross-sectional study of daily methadone users in free drug treatment clinics in Copenhagen [10]. Thus, while patients in MMT may need closer medical supervision than is currently in practice, methadone has been used safely in the treatment opioid dependence for a number of years.

2.1.2. Detoxification—Methadone dose tapering or detoxification is controversial given the relative effectiveness of MMT and the low rates of detoxification success [2]. Regardless, detoxification is an important component of any comprehensive opioid treatment program [11], particularly because the demand for methadone often outstrips community resources, at least in the US. Wait-lists are long and patient financial constraints result in the premature termination of a substantial number of patients by their opiate treatment providers. Effective detoxification regimens are sorely needed.

Methadone dose reduction schedules have ranged from 2–3 weeks to as long as 180 days, with longer time periods generally associated with better outcomes [12]. Studies have indicated that the more rapid the reduction, the worse the treatment retention and heroin use outcomes are, although the optimal timeframe has yet to be clearly delineated [12, 13]. There is some evidence that higher doses of methadone are associated with more severe withdrawal symptoms during

detoxification [14]. A recent review of the evidence concludes that the use of long-acting opioids, such as methadone, and slow tapering, accompanied by medical supervision, ancillary medications, and psychosocial treatment can reduce withdrawal severity and improve outcomes [2]. Unfortunately, the vast majority of patients tend to relapse to heroin or other opiates during or post-detoxification, which is not wholly surprising given the chronic and relapsing nature of opioid dependence.

2.2. LAAM

Levomethadyl acetate or LAAM, a longer acting derivative of methadone and full mu-opioid agonist substitute, was approved by the US Food and Drug Administration for maintenance therapy in 1993. LAAM's longer acting properties allow for thrice-weekly dosing--a significant advantage over the required daily dosing of methadone. Oral LAAM typically is administered on a Monday–Wednesday–Friday schedule starting at a daily 20 mg dose with every other day increments to a maximum alternate day dosing of 130/130/180 or 100/100/140 [15]. As with methadone, stabilization doses vary widely across patients, ranging from 40 to 140 mg.

Several clinical trials comparing LAAM to methadone suggest LAAM to be at least comparable and occasionally superior on primary outcomes such as retention in treatment and frequency of opiate positive urine screens [15, 16]. Regardless, LAAM was not embraced by opioid treatment providers in the US, likely for varied and complex reasons [17]. The most cited reason, however, was concern over prolongation of the QT interval and report of several deaths in the US and in Europe [18, 19]. Although methadone has recently been associated with cardiac side effects in some patients, and despite direct comparison data indicating few differences in LAAM and methadone on cardiac measures, Roxane Laboratories has discontinued the sale and distribution of LAAM. The well-established benefits of methadone and reluctance of opiate treatment providers to shift to new treatment paradigms has reduced viable and perhaps superior treatment options to the opiate dependent population.

3. PARTIAL AGONIST MEDICATIONS FOR OPIOID DEPENDENCE

3.1. Buprenorphine

In October of 2002, sublingual buprenorphine and buprenorphine/naloxone tablets for the management of opiate dependence were approved by the FDA in the US. Prior to this time, buprenorphine has been used successfully in many European countries as well as Australia [20, 21]. Of significance in the US, buprenorphine is designated as a Schedule III drug making it legal for qualified US physicians to prescribe it for opioid dependence. Unlike methadone and LAAM which are full opioid agonists, buprenorphine is a partial agonist of mu-opioid receptors. It has a slow onset and long duration of action allowing for alternate day dosing [22–24]. Its partial agonist properties reduce the risk of unintentional overdose relative to full agonist medications. The disadvantage, however, is that the partial agonism may also limit buprenorphine's maximum efficacy [25, 26]. The recommended maximum sublingual dose is 24 or 32 mg which is equivalent to 60 to 70 mg of methadone. Many patients undergoing methadone maintenance are on higher doses, with some on much higher doses (150+ mg). Buprenorphine has also been combined with naloxone at a 4:1 ratio for the purpose of reducing abuse liability. The 4:1 ratio was chosen based on results from several clinical pharmacology studies [27–29] which suggested that this ratio results in negligible absorption of naloxone when used sublingually, i.e., no significant withdrawal symptoms, but when crushed an injected, will result in opioid receptor antagonism. Commercially available buprenorphine/naloxone is typically either a 2/.5mg or 8/2mg combination; both of which are much lower than the maximum dose and may limit the use of this product with patients at higher levels of opioid dependence. More recent studies have suggested that 8/2 and 32/8 mg buprenorphine/naloxone

are well-tolerated and more effective in reducing the reinforcing and subjective effects of heroin, relative to the 2/0.5 mg dose [30].

3.1.1. Buprenorphine Maintenance—Outcome data from several studies have established the superiority of buprenorphine maintenance over placebo [31–35]. Results from studies comparing buprenorphine and methadone, however, have been mixed, and dependent on several factors such as dose level and flexibility [36–41]. Overall, it appears that decreased illicit opiate use and increased retention are seen with both higher doses of methadone (> 60 mg) and higher doses of buprenorphine (> 8mg), although methadone appears superior to buprenorphine in retaining patients when using flexible dosing approaches [30]. There is some evidence to suggest that inducting patients too slowly onto buprenorphine may contribute to poorer retention rates [36, 42], however the lesser opioid effect and possibly mild withdrawal symptoms when transferring from heroin to buprenorphine cannot be discounted. Also for consideration, a meta-analysis by West et al. [41] indicated that buprenorphine tended to be more effective in studies with patients who reported prior methadone maintenance experience vs. studies that included subjects with no prior experience with methadone.

Given the mixed results regarding buprenorphine's effectiveness relative to methadone, controversy exists as to its role in the treatment of opioid dependence. Kakko et al. [43] suggest a stepped care approach in which buprenorphine is the first-line treatment, with patients escalated to methadone when needed. In a letter to the editor regarding Kakko and colleagues' recommendation, Byrne and Wodak [44] claim that the data do not support buprenorphine as a first-line treatment because almost two-thirds (65%) of their study patients were transferred to methadone due to illicit drug use or cravings. Neither age, gender, duration of heroin use, nor Addiction Severity Index aggregate scores predicted who stayed on buprenorphine/naloxone vs. switched to methadone. Although much more research is needed to make definitive conclusions, it has been recommended that higher dependence severity indicates placing patients on the full agonist methadone over buprenorphine. However, it is unclear as to the best way in which to measure dependence severity for this purpose. Researchers have suggested that patients who require doses of more than 30–40 mg of methadone daily would be unlikely to experience success with buprenorphine [25, 37]. A subcutaneous buprenorphine implant has also been tested, but no results have been published, and no studies are currently ongoing (Titan Pharmaceuticals, 2008). Establishing effective buprenorphine regimens is an important research goal, particularly in light of findings from a recent review which suggests a lower mortality rate with buprenorphine relative to methadone maintenance [45]. Further research is needed to delineate patient and perhaps setting characteristics which indicate the prescribing of one drug over the other.

3.1.2. Buprenorphine Detoxification—There is growing interest in using buprenorphine as a way of managing opioid withdrawal. Because of the partial agonist properties, buprenorphine is expected to produce fewer withdrawal symptoms as it is withdrawn, relative to full agonist therapies [46]. As with methadone, detoxification outcomes are likely dependent on a complex interaction of factors including dependence severity, opioid used, dose taken, duration of use, taper schedule, social/environmental circumstances, and psychological factors such as fear of withdrawal, depression, and anxiety about life without drugs [47, 48], and to date success rates have not been high. Gowing [49] reviewed 4 studies comparing the efficacy of buprenorphine and methadone detoxification protocols [42, 50–52]. Overall, the data suggest that buprenorphine and methadone have similar efficacy for detoxification purposes, although withdrawal via buprenorphine may be somewhat faster [53]. Buprenorphine has repeatedly been found superior to the alpha 2 adrenergic agonist clonidine in reducing symptoms of withdrawal, retaining patients in a withdrawal protocol, and in treatment completion [54–58].

Contrary to expectations, several studies found little difference in the severity of withdrawal when tapering from buprenorphine compared to methadone [42, 51]. However, the pattern of withdrawal symptoms may indeed be different. Petitjean and colleagues [42] reported that while patients withdrawing from methadone experienced a gradual increase in withdrawal symptoms peaking at the end of the taper, buprenorphine patients reported higher withdrawal symptoms earlier in the taper followed by a rapid decline. Similar findings were reported by Seifert [51]. Detoxification outcomes are possibly influenced by the rate of dose reduction, with several studies suggesting that gradual tapering of buprenorphine results in higher completion rates relative to rapid tapering [59, 60], and several studies indicating no reliable differences e.g., [61, 62]. Many buprenorphine detoxification studies have been conducted on an inpatient basis and were targeting withdrawal from heroin and not methadone. The extent to which results will generalize to the outpatient setting and to methadone users is not fully known. Ling et al. [63], however, conducted a multi-center randomized trial of buprenorphine-naloxone and found superior results for buprenorphine in both the inpatient and outpatient arms relative to the clonidine. Although retention rates were similar in the inpatient vs. outpatient settings, success rates were about double for inpatients. Caution must be used in interpreting these data, however, as patients were not randomly allocated to the two settings. The few studies of managed methadone withdrawal using buprenorphine have reduced the methadone dose to 30 mg or less prior to beginning buprenorphine and have delayed the first dose 24 hours after the last dose of methadone [64, 65]. The transition from methadone to buprenorphine has been found to precipitate withdrawal [66], and must be approached carefully.

To date, buprenorphine has not surpassed methadone in its effectiveness for managed withdrawal; however, there is significant potential. Additionally, there has been limited research on post-detoxification outcomes leaving it unclear as to whether one medication is superior to the other in the long-term [67]. Much research is needed to identify the optimal conditions under which buprenorphine can succeed for detoxification purposes, including optimal duration, setting, route of administration, severity of dependence, and whether patients are withdrawing from heroin vs. methadone.

3.1.3. Buprenorphine in the Primary Care Setting—In the US the ability of primary care physicians to prescribe buprenorphine for opioid dependence presents an important and far-reaching opportunity to improve access and quality of treatment as well as reduce social harm. Positive effects have been documented in many countries. European, Asian, and Australian data suggest that opioid related deaths and drug injection-related medical morbidity have decreased with the introduction of buprenorphine. In France, national surveys conducted annually in treatment facilities for drug dependent individuals suggested that widespread initiation of office-based buprenorphine treatment in 1996 was associated with a decline of heroin use among opiate users from 74% in 1995 to 25% in 1997, as well as with improvements in the social and medical status of opioid dependent patients [68–70]. Buprenorphine treatment also has reduced various infectious diseases related to intravenous drug use [71, 72].

Following four initial US studies on buprenorphine effectiveness [58, 73–75], recent studies also have supported office-based buprenorphine treatment efficacy by investigating longer retention intervals and additional settings (See Table 1) [76–78]. The 79% retention rate found by Fiellin et al. [73] in a private office setting was followed by similar evidence from Cunningham et al. [76] of 71% retention in an urban community health center setting. Buprenorphine is effective for treatment of both injection and oral opioid users, but results have been mixed over whether buprenorphine can be said to be clearly more successful for one particular route of administration over another.

Some patients may desire to transfer from methadone to primary-care based buprenorphine maintenance. At present, data regarding precipitation of withdrawal when switching from

methadone or LAAM to buprenorphine are limited, particularly for doses of methadone over 30 mg daily. Additionally, buprenorphine is quite expensive relative to methadone, making it available mainly to individuals with adequate resources.

4. ALPHA-2-ADRENERGIC AGONIST MEDICATIONS FOR OPIOID DETOXIFICATION

Several alpha-2-adrenergic agonist medications have been investigated and found to facilitate positive opioid withdrawal outcomes. One process underlying opioid withdrawal is noradrenergic hyperactivity [79]. Alpha-2-adrenergic agonists moderate the symptoms of noradrenergic hyperactivity by acting centrally. Clonidine was the first alpha-2 agonist discovered to ameliorate some signs and symptoms of withdrawal. Because it is not a drug of abuse or dependence, clonidine has gained widespread use as a non-opioid alternative for managing withdrawal [80]. Unfortunately, clonidine is associated with significant hypotension which has limited its use. This finding led to a search for alternative alpha-2 agonist medications without significant side effects. Lofexidine, guanfacine, and guanabenz acetate have been investigated to varying extents [81]. Of these, lofexidine has been the most frequently studied [82–87], and results indicate it does not appear to have the hypotension side effect that plagues clonidine. It is likely to replace clonidine as the leading opioid withdrawal treatment in this drug class.

Initial studies of clonidine reported reduction or elimination of lacrimation, rhinorrhea, muscle pain, joint pain, restlessness, and gastrointestinal symptoms [88, 89], suggesting significant potential for managing opiate withdrawal. Clonidine is typically administered orally, in three or four doses per day up to a maximum of one milligram per day. Dizziness, sedation, and lethargy attributed to orthostatic hypotension and dry mouth were the primary adverse side effects.

Lofexidine can be prescribed up to about two milligrams per day and appears to be associated with fewer adverse effects. Completion rates of managed withdrawal assisted with clonidine and other alpha-2-adrenergic agents vs. methadone have been comparable [90–92], with at least one study finding poorer outcomes for clonidine [93]. Withdrawal symptoms, while reasonably similar in intensity demonstrate a difference in time course. Symptoms occur much earlier in the withdrawal period for clonidine and lofexidine than for methadone, which perhaps has implications for length of time in treatment. In a few studies specifically reporting duration of treatment, subjects receiving reducing doses of methadone remained in treatment longer than those receiving alpha-2 agonists [92, 94].

In the United Kingdom, lofexidine has had a product license for treatment of opiate detoxification since 1992, and the extent of use has increased steadily since that time. Lofexidine treatment is typically initiated at .2 mg twice daily, increasing daily by .2–.4 mg with a recommended final dose of 2.4 mg/day. Doses required to effectively manage withdrawal symptoms, however, vary for each patient depending on the amount, frequency, and duration of opioid used. Yu et al. [87], in a phase 3 randomized, placebo-controlled trial, confirmed that lofexidine significantly decreases the signs and symptoms of opioid withdrawal. Retention was also higher in the lofexidine condition. Three studies comparing the efficacy and tolerability of lofexidine to clonidine suggested comparable efficacy in reducing withdrawal symptoms, with an advantage for lofexidine due to smaller hypotensive effect. Interestingly, Bearn et al. [90] reported that an accelerated 5-day lofexidine regimen resulted in faster attenuation of withdrawal symptoms relative to a more conventional 10-day lofexidine schedule.

As stated earlier, buprenorphine appears to be somewhat more effective in facilitating opioid withdrawal than clonidine [63, 95]. Of the two open-label trials comparing lofexidine and buprenorphine, one found the two treatments to be equivalent in effectiveness [84], while the other found buprenorphine to result in less severe withdrawal symptoms in a large portion of subjects [86]. Thus, the alpha-2-adrenergic agonists are of significance given the paucity of medications approved for opioid detoxification and relapse prevention purposes, particularly non-opioid medications; arguably, however, alpha-2 agonists may not be the best "first-line" treatment for opioid detoxification. Further research is needed to determine optimal dose, duration and perhaps combinations of medications to improve upon the typically poor detoxification outcomes.

5. ANTAGONIST MEDICATIONS FOR OPIOID DEPENDENCE

Naltrexone is an oral, long-acting, opioid antagonist with high affinity to mu-opioid receptors. A daily dose of naltrexone (50 mg) will block the pharmacologic effects of 25 mg IV heroin for as long as 24 hours, and increasing the dose extends its duration of action to 48 hours with 100 mg and 72 hours with 150 mg [96]. Neither tolerance nor dependence develops with naltrexone [97, 98]. Oral naltrexone is approved for relapse prevention of alcohol and opioid dependence in several countries, although its effectiveness for the latter remains in question [99].

In general, clinical research on naltrexone over the past few decades indicates that it is safe, associated with few side effects, and clearly blocks the reinforcing properties of heroin and other opiates. Original fears that naltrexone would cause hepatotoxicity or elevate liver function tests appear unwarranted [100–102]. It remains common practice, however, to evaluate liver function prior to administering naltrexone and refrain from prescribing if liver function tests are 3–5 times normal levels. Failure to prescribe naltrexone to patients with less elevation in LFTs is unfortunate as a significant proportion of the opiate-using population has liver disease, e.g., Hepatitis B or C [103, 104]. Naltrexone has in fact been associated with improvements in LFTs due to reductions in alcohol/opiate use [105, 106]. Further, naltrexone has few additional side effects. The most commonly reported symptoms are headache, nausea, abdominal pain, as well as dysphoria, and depression in a subgroup of patients [107, 108].

Although naltrexone has theoretically ideal properties, only weak support exists for its effectiveness in clinical settings. A recent meta-analysis [99] reviewing 10 studies (N = 696) concluded that naltrexone maintenance combined with psychosocial therapy was, in fact, more effective than placebo in reducing heroin use and re-incarceration rates during treatment. However, results of studies using naltrexone alone did not differ from placebo, and, in the majority of studies, retention, side effects and relapse rates were all similar to placebo. Most researchers would agree and there is data [109] demonstrating that the primary problem with naltrexone is low adherence to the medication and poor retention in treatment. Presumably because naltrexone has no reinforcing properties of its own, blocks reinforcement from occasional lapse to opiates, and has no associated withdrawal syndrome encouraging its continued use, acceptance of the treatment by patients is low relative to agonist-based treatments. Many studies have reported large numbers of dropouts in the first few weeks of treatment, with those lapsing to opiate use after missing naltrexone doses especially likely to dropout [110]. For example, Rothenberg [111] reported that only slightly more than half of participants completed 4 weeks of a 24 week naltrexone-behavior therapy protocol. Greenstein et al. [112] reported that 47% of opiate dependent patients dropped out of treatment in the first few weeks. Further, Tennant et al. [113] reported over a quarter of their patients dropped out after only a few days. Rothenberg [111] also reported even lower retention for patients using methadone at baseline —39% completed 1 month and no patients completed the full 6-months of treatment. These data suggest that transition from long-acting opioids to naltrexone may be

especially difficult and portend the need for improved methods for transitioning to antagonist treatment.

5.1. Sustained-Release Formulations of Naltrexone

Due to poor rates of adherence [109], sustained release formulations of naltrexone are being developed in hopes of improving outcomes, and are currently the focus of much research. Although 9 different sustained-release formulations are available, none is approved for opioid dependence in the US, Europe or Australia. Three depot injection formulations are being investigated and deliver therapeutic doses (blood levels between 1–2 ng/ml) for up to 4 weeks [114, 115]. Comer et al. [116] has conducted the only published, randomized, controlled clinical trial investigating injectable, sustained release naltrexone in 60 heroin dependent patients. Following an initial inpatient detoxification and 3 consecutive days of oral naltrexone, patients were randomized to receive placebo, 192 or 384 mg of depot naltrexone (Depotrex; BIOTEK, Inc, Woburn, MA). A second injection of the same dose was administered after week 4 of the 8 week study. Retention in treatment was superior for the two naltrexone conditions (60 and 68% remaining at end of study in the 192 and 384mg groups, respectively) relative to placebo (39% remaining). A significant dose response relationship was found on time to dropout, with the higher naltrexone group remaining in treatment the longest. Significant effects on opiate use across the study were also found, favoring the naltrexone groups over placebo. Treatment-related side effects were relatively mild (e.g., fatigue, injections site induration, and injection site pain), although 5 participants (1 in placebo and 4 in the 192 mg groups) were discharged from the study for injection site redness or induration. Injection site problems have been reported in other studies of alcohol and opioid dependent patients, and found at significantly greater frequency with naltrexone relative to placebo [117–119].

Although it is premature to conclude sufficient effectiveness, sustained release depot naltrexone formulations appear to hold significant promise in improving retention, and presumably decreasing opiate use in opioid dependent patients.

Subcutaneous naltrexone implants are also being used in the treatment of opioid dependence, particularly in Russia and China. Data on implants of 1.1, 2.2, and 3.3 g naltrexone have been reported. A recent study by Ngo et al. [120] concluded that a 3.3 g implant provided longer therapeutic coverage compared to the 1.1g implant, but was not significantly different from the 2.2 g implant. The primary difficulty in evaluating the effectiveness of sustained-release naltrexone is the lack of clinical trials, although a clinical trial has been presented showing superior treatment retention with a naltrexone implant compared to oral naltrexone and a placebo implant (College on Problems of Drug Dependence, June 2007, Quebec City, Canada). In that study 190 detoxified opiate addicts were randomized to the three treatment groups, and at the end of six months 45% of patients of the naltrexone implant group had relapsed compared to about 85% in the other two groups ($p<0.001$). Cohort studies have been reported and results are quite favorable. For example, Foster et al. [121] reported 74–79% opiate abstinence rates 12 weeks after implantation. Fifteen percent had local tissue reactions that were mild with no regional lymphadenopathy, resolving without surgical treatment.

Recent reports of serious adverse events associated with naltrexone implants have surfaced, however. A retrospective chart review of ER patients referred to Drug and Alcohol Consultation-Liaison services in 2 teaching hospitals in Sydney, Australia reported 12 patient admissions in a one-year period with implant-related presentations [122]. Six of 12 admissions were for severe dehydration and opiate withdrawal secondary to rapid opioid detoxification and naltrexone implantation in the prior 24–48 hours. Opioid overdose deaths have also been reported [123]. Conversely, longitudinal cohort data collected prospectively in Australia indicate an absence of mortality associated with naltrexone implant treatment [124], and further, naltrexone implantation has been associated with long-term reductions in opioid-related

hospital morbidity [125]. Davoli et al. [126] report that overall, overdose mortality risk while in opioid treatment is significantly lower than when out of treatment, with the first month post-treatment being a considerably risky time. Thus, although more research is needed, initial data on naltrexone implants indicate significant improvements in adherence and retention, and perhaps increased effectiveness for relapse prevention. Careful participant selection and close clinical management is clearly warranted, however, to prevent serious adverse outcomes.

5.2 Rapid and Ultra-Rapid Opiate Detoxification

While gradual dose reduction of methadone or buprenorphine is perhaps the most straightforward way in which to manage opiate detoxification, this method is time-consuming and plagued by high dropout rates. Alpha 2 adrenergic agonists, such as clonidine and lofexidine, assist in reducing some of the symptoms of opiate withdrawal, however, they do not alter the duration of withdrawal [127]. Use of the opioid antagonist naltrexone, typically combined with an alpha 2 adrenergic agonist, has been investigated as a method for rapid opiate detoxification (ROD) and has been purported to shorten the duration of withdrawal without significantly increasing patient discomfort[128]. Another benefit to ROD is the reduced time between opioid use and the commencement of naltrexone treatment. Controlled studies comparing naltrexone plus clonidine to clonidine alone or to methadone tapering have found that the former approach was well tolerated and reduced the withdrawal period while improving retention [13, 58, 129, 130]. ROD completion rates using naltrexone and clonidine range from 75%–81% compared to 40–65% for methadone or clonidine alone [58, 131]. Lofexidine has been shown to have equal efficacy with clonidine when combined with naltrexone and has fewer side effects [132], perhaps making it a more suitable detoxification medication, particularly in outpatient settings. Gowing and Ali [11], however, based on their review of 7 studies, report that it is still unclear whether withdrawal induced by opioid antagonists in combination with adrenergic agonists actually facilitates the transfer to sustained naltrexone treatment beyond 10 to 14 days, and thereby improving effectiveness, relative to adrenergic agonists alone.

Buprenorphine and methadone have also been used in combination with naltrexone. Umbricht et al. [133] stabilized patients on buprenorphine prior to detoxification with naltrexone and clonidine and found the treatment to be safe with an even shorter duration of detoxification relative to patients stabilized on methadone or using heroin (one day vs. three days of detoxification). Gerra et al. [134] conducted an observational study suggesting potential benefit from the combination of lower doses of buprenorphine (4 mg) and naltrexone as a detoxification and subsequent maintenance strategy to counteract the protracted opioid abstinence syndrome common after detoxification, i.e., dysphoria and somatic symptoms. Another uncontrolled study of 3-day ROD using one dose of 50 mg naltrexone with methadone maintenance patients reported a shortened withdrawal syndrome (managed by symptom-relief meds) [135]. Two-phases of symptoms were reported: (1) a first withdrawal phase, seen in most patients, characterized by common symptoms and likely naltrexone-induced; and (2) a second phase experienced by fewer patients (aches, insomnia and loss of appetite worsened) and likely attributed to declining methadone concentrations.

Ultra-rapid opiate detoxification (UROD) is an extension of ROD with the use of anesthetics. UROD is highly controversial due to the medical risks and mortality associated with anesthesia relative to the painful, yet non-fatal risks of untreated opiate withdrawal. At least one death during the recovery period of this intervention has been reported [136]. Further, while withdrawal severity following anesthesia-assisted withdrawal did not differ, Collins et al. [137] reported three life-threatening adverse events in the anesthesia group, but none in the buprenorphine or clonidine groups. Effectiveness relative to alternative detoxification procedures is difficult to evaluate as most studies have not included longer term follow-up data or randomization to a

comparison condition. Some studies report relatively high rates of abstinence [138, 139] while others report worse outcomes with UROD [140].

In sum, ROD with naltrexone and clonidine is safe and effective in the management of opiate withdrawal. While the duration of detoxification is shortened, effectiveness in facilitating continued use of antagonist treatments post-detoxification has yet to be established. UROD remains controversial with regard to safety and is also quite expensive, thus significantly limiting its use.

6. CONCLUSION

Given the burden of disease, the development of effective treatments for opioid dependence is of great significance. Methadone maintenance is currently the gold standard of treatments as it is associated with reductions in intravenous drug use, crime, HIV risk behaviors and mortality, and is well-established in community treatment programs around the world. New and evolving opioid treatments are held to this standard. Yet even when comparing favorably to methadone (e.g., LAAM), new pharmacotherapies may be viewed with reluctance, which can have the untoward effect of prematurely limiting use and availability. Cardiac side effects have been documented for both LAAM and methadone, though, and patients should be carefully monitored for such. In recent years, buprenorphine has emerged as a potential first-line treatment for opioid dependence and may be ideal for patients needing lower doses of agonist medications. Buprenorphine has a reduced risk of overdose relative to full agonist therapies, and in combination with naloxone, has reduced abuse liability. Office-based buprenorphine treatment has the potential to expand the reach of opioid treatment thereby improving the social and medical status of increasing numbers of opioid dependent patients. Further research is needed to identify patient and setting characteristics best suited for buprenorphine vs. methadone.

Opioid detoxification remains a critical area of focus. There is no consensus on the most effective pharmacological strategy to achieve complete abstinence from all opiates. Relapse either during or after detoxification occurs in the majority of patients, and, for those who have the resources, return to maintenance treatment is common. Despite the dismal rates of success, a minority of patients are able to detoxify successfully from methadone, heroin and other opiates. Research has yet to determine, however, who will succeed and who will fail. In a recent manuscript reporting on a 6-month LAAM detoxification study in which almost every participant returned to opioid use (methadone maintenance or illicit opioids), Grabowski et al. (under review) concluded that neither patients nor clinical researchers are adequately equipped to determine a patient's preparedness for complete withdrawal[141]. For these reasons, experts understandably have recommended agonist maintenance treatment over detoxification. However, long-term methadone maintenance treatment is not without adverse consequences. Methadone like other opioids produces sustained constipation in some individuals which if left untreated can lead to toxic megacolon. The only fatalities from methadone unrelated to overdose have been caused by this side effect. Methadone also elevates serum prolactin and lowers testosterone levels which can impair sexual functioning. Further, under many circumstances, such as lack of financial resources to initiate or continue maintenance treatment, detoxification of opioid dependent patients is essential. Thousands of patients each year (at least in the US) are terminated from opiate treatment programs for failure to pay and other "non-therapeutic" reasons [142]. Without effective detoxification protocols, individuals lacking resources will inevitably continue or return to illicit opiate use and, consequently, the myriad of associated psychosocial and health problems.

Various pharmacotherapies and dose reduction protocols have been tested to improve detoxification outcomes. Alpha 2 adrenergic agonist medications, such as clonidine and

lofexidine, have gained widespread use because they are a non-opioid alternative. Their effectiveness as single agents is inferior to managed withdrawal using buprenorphine, however, they have had more patient acceptance as adjunctive agents during buprenorphine tapering. Naltrexone, a long-acting opioid antagonist seems an ideal candidate medication for prevention of relapse to opiates, but is associated with unacceptably low adherence and retention rates. Sustained-release formulations have been developed with strong support for naltrexone implants from mostly uncontrolled studies, although questions regarding safety have yet to be answered. Further research attending to issues of both efficacy and safety is needed to rigorously test this promising treatment.

7. EXPERT OPINION

Opioid pharmacotherapy faces a significant challenge because the most rapidly growing populations needing treatment in the United States are adolescents and young adults. Prescription opioids have become the most commonly abused illicit drug during the last 5 years among these young abusers [1, 143]. In the treatment of young abusers, it is necessary to recognize that developmental processes are ongoing and hormone levels are changing and influencing growth in many organs, including the brain. This developmental perspective must inform any pharmacotherapy decision, and a decision to simply provide withdrawal treatment and no ongoing relapse prevention treatment is simply untenable in this era of infectious diseases such as HIV and hepatitis C which are frequent comorbidities of opioid abuse and dependence [144].

Chronic opioid agonist treatments are the gold standards for efficacy, but providers and parents have significant reluctance to enroll adolescents in a sustained program of maintenance on methadone, and the usual treatment for opioid-addicted youth is detoxification and counseling. Extended medication-assisted therapy may be more helpful, and a different attitude may be developing for buprenorphine, particularly as an office-based therapy. A recent study at six community programs evaluated the efficacy of continuing buprenorphine-naloxone for 12 weeks vs. detoxification for opioid-addicted youth [145]. They enrolled 152 patients aged 15 to 21 years who were randomized to 12 weeks of buprenorphine or a 14-day taper detoxification. The patients in the detoxification group had higher proportions of opioid-positive urine tests at weeks 4 and 8, and by week 12, only 21% remained in treatment compared to 70% of those maintained on buprenorphine. Thus, continuing treatment with buprenorphine improved outcome compared with short-term detoxification, which encourages further research into the efficacy and safety of longer-term treatment with buprenorphine for young individuals with opioid dependence.

The antagonist naltrexone seems an ideal treatment for these reluctant young patients, since we have developed long lasting depot formulations such as Vivitrol and naltrexone implants that can overcome these patients' poor adherence to taking daily medications [116, 117, 121]. Starting naltrexone requires initial withdrawal treatment, however, and our treatments have had limited efficacy using clonidine. Lofexidine availability in the US is expected to improve upon clonidine-assisted withdrawal treatments, as it has in many European countries. Lofexidine may have a second important role during naltrexone maintenance as stress-induced relapse may be reduced by several months of sustained treatment with lofexidine after detoxification is completed. Nevertheless, a problem for commercial depot naltrexone products such as Vivitrol is that its FDA approval is limited to alcoholism, thereby making its use for opioid dependence "off label" and potentially a medical and economic risk. The economic risk is that depot naltrexone is relatively expensive at about five times the cost of oral naltrexone. Since opioid dependence is not an approved FDA indication, insurance carriers may not reimburse its substantial cost of about $10,000 for a year's treatment. The medical risk involves these antagonists' significant hormonal effects on increasing cortisol, growth hormone,

lutenizing and follicle stimulating hormones (LH and FSH) [146]. The unintended consequences of these hormonal perturbations range from growth retardation and affective instability to increased fertility in adolescent girls leading to pregnancy when effective birth control is not used. In summary, current pharmacotherapies have great potential, but have associated risks in our growing population of young opioid abusers.

A very attractive, more cost-effective alternative has been potential therapeutic vaccination or even monoclonal immunotherapy [147]. These immunotherapies are very appealing because they have no direct effects on the brain, endocrine system or any other organs. Their mechanism of action is simply that the anti-opioid antibody binds to the abused opioid and thereby holds the opioid in the blood stream preventing its entry into any of these organs [148]. As this opioid-antibody complex passes through the liver, the opioid is extracted and converted into inactive metabolites that are then excreted in the bile and kidney. Vaccination-induced antibody levels remain high enough to block a specific opiate for about 8–12 weeks after which a booster is needed to get the antibody levels back for 2–3 months. This vaccine approach has been quite feasible for both nicotine and cocaine in human vaccines [147, 149]. A significant challenge to this approach has been the wide range of abused prescription opioids. Because antibodies are highly specific for the chemical structures of the various opioids, an antibody to morphine will not be effective for oxycodone or codeine or fentanyl or many other abused opioids. Making vaccines or monoclonal antibodies to the wide range of opioids is possible, but a logistic challenge that seems still more than 5 years in the future as we understand how to provoke stronger immune responses to haptens like these drugs and to produce monoclonals more cost-effectively. Thus, new options are evolving in pharmacotherapy of opioid dependence, and the increased safety and efficacy of these options will be particularly important as we target these abusers early in their addiction careers in order to avoid the major life-threatening complications that arise from sustained abuse of these drugs.

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Table 1

Studies of Buprenorphinein Primary Care Settings

Authors	Comparison Drugs	Assessment Time Points	Percent retained	Percent negative urine screens
	Maintenance			
Cunningham et al., 2008	None	3 months	71%	76%
Fiellin et al., 2002	None	13 weeks	79%	75%
Fiellin et al., 2008	None	5 years	38%	91%
Fiellin et al., 2006; Moore et al., 2007	None	24 weeks	43% overall; 59% of prescription only users, 30% of heroin only, 38% who used both	41% overall; 75% of prescription only users, 52% of heroinonly, 48% who used both
Fudala et al., 2003	Bup only, Bup+Naloxone, Placebo	4 weeks	82% 75% 69%	21% 18% 6%
Mintzer et al., 2007	None	6 months	100%	54%
O'Connor et al., 1996	None	6 months	71%	80%
O'Connor et al., 1998	None	12 weeks	78%, 52%	43%, 13%
	Detoxification			
O'Connor et al., 1997	Clonidine; Clonidine+Naltrexone	8 days	60% for Bup, 65% for Clonidine, 54% for Clonidine+Naltrexone	81% for Bup, 65% for Clonidine, 81% for Clonidine+Naltrexone
Wright et al., 2007	Dihydrocodeine	15 days, 3 months, 6 months	Completed 15 day detox: 32% for Bup, 13% for Dihydrocodeine	21% for Bup, 3% for Dihydrocodeine; At 3 months: 37% for Bup, 17% for Dihydrocodeine; At 6 months: 32% for Bup 16% for Dihydrocodeine