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Potential uses of naltrexone in emergency department patients with opioid use disorder

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Abstract

Introduction: Despite widespread recognition of the opioid crisis, opioid overdose remains a common reason for Emergency Department (ED) utilization. Treatment for these patients after stabilization often involves the provision of information for outpatient treatment options. Ideally, an ED visit for overdose would present an opportunity to start treatment for opioid use disorder (OUD) immediately. Although widely recognized as effective, opioid agonist therapy with methadone and buprenorphine commonly referred to as “medication-assisted therapy” but more correctly as “medication for addiction treatment” (MAT), can be difficult to access even for motivated individuals due to shortages of prescribers and treatment programs. Moreover, opioid agonist therapy may not be appropriate for all patients, as many patients who present after overdose are not opioid dependent. More treatment options are required to successfully match patients with diverse needs to an optimal treatment plan in order to avoid relapse. Naltrexone, a long-acting opioid antagonist, available orally and as a monthly extended-release intramuscular injection, may represent another treatment option.

Methods: We conducted a literature search of MEDLINE and PubMed. We aimed to capture references related to naltrexone and its use as MAT for OUD, as well as manuscripts that discussed naltrexone in comparison to other agents used for MAT, opioid detoxification, and naltrexone metabolism. Our initial search logic returned a total of 618 articles. Following individual evaluation for relevance, we selected 65 for in-depth review. Manuscripts meeting criteria were examined for citations meriting further review, leading to the addition of 30 manuscripts.

Conclusions: Here, we review the pharmacology of naltrexone as it relates to OUD, its history of use, and highlight recent studies and new approaches for use of the drug as MAT including its potential initiation after ED visit for opioid overdose.

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Disclosure statement

No potential conflict of interest was reported by the authors.

Keywords

Naltrexone; overdose; medication-assisted therapy; addiction; abstinence

Background

The Centers for Disease Control and Prevention (CDC) report that Emergency Department (ED) visits related to opioid overdose increased 27.7% between 2015 and 2016 in a study group of representative hospitals across the country [1]. Deaths from opioid overdose continue to rise with a total of 49,068 opioid overdose deaths occurring in 2017, representing a 13.9% increase from 2016 [2]. Combined with the increasing prevalence of potent synthetic opioids detected in illicitly purchased drugs, non-medical opioid use presents a serious and escalating public health threat [3,4]. Because high-risk patients with Opioid Use Disorder (OUD) frequently present to the ED following overdose, public health officials and lawmakers are turning attention to these visits as an opportunity for intervention. Massachusetts passed “An Act Relative to Substance Use, Treatment, Education, and Prevention” on March 14 2016 that requires hospitals provide a “Substance Use Disorder Evaluation,” conducted by a licensed mental health professional, within 24 h of presentation to an ED for patients who are experiencing an opioid-related overdose [1]. The goal of this legislation is to assist individuals with treatment options on a voluntary basis.

The use of the ED as a site for initiation of medications for addiction treatment (MAT, formerly used to refer medication-assisted treatment) is a concept that is gaining traction [5]. Currently, the only available option for most emergency providers is referring patients with OUD to an inpatient or outpatient opioid addiction treatment program. These programs may carry significant waitlists for initiating patients on MAT or have no availability at the time of overdose; physicians need viable alternatives for patients in crisis. A study by D’Onofrio et al. showed increased engagement in office-based opioid addiction treatment at 30 days if buprenorphine treatment was initiated during the ED visit [6]. While still in the early stages of widespread implementation, ED-initiated MAT shows promise as an important treatment strategy for patients with OUD. Moreover, Massachusetts legislation passed in July 2018 mandates an offer of MAT to patients who present after overdose, or for opioid-related complaints.

The most common regimens utilized for MAT include the opioid agonists’ buprenorphine or methadone. This review focuses on the potential role of naltrexone, an opioid antagonist, in ED-initiated MAT. Oral naltrexone gained FDA approval for use as MAT for OUD in 1984, followed by approval of a depot intramuscular (IM) injection formulation in 2010 [7]. Favorable characteristics of naltrexone include lack of abuse potential, and the possibility of reduced risk of fatality during relapse in adherent patients due to its opioid receptor blockade [8]. Naltrexone may prove useful for a subset of patients presenting for emergency care following overdose who decline agonist therapy, are not interested in inpatient opioid addiction treatment, or for whom those resources are unavailable.

Methods

We conducted a literature search of MEDLINE and PubMed. We aimed to capture references related to naltrexone and its use as MAT for OUD, as well as manuscripts that discussed naltrexone with a comparison to other agents used for MAT, opioid detoxification, and naltrexone metabolism. We chose these topics for their relevance to naltrexone use in opioid use disorders. We also sought to include articles that evaluated the ED as a location to initiate treatment for OUD. Search terms and logic are included in Supplementary Appendix 1.

Reference lists of retrieved articles were reviewed for additional studies not identified by the search method. Manuscripts were limited to the English language. Searches were not limited by date. The initial search was performed in October 2017.

Results

Our initial search logic returned a total of 618 articles. Following individual evaluation for relevance, we selected 65 for in-depth review. Manuscripts meeting criteria were examined for citations meriting further review, leading to 30 additional manuscripts. Articles irrelevant to our topics of interest were excluded. Not all manuscripts selected for in-depth review were included in the cited references. The initial reservoir of articles was created by the first author using the above method to determine relevance to the subject and provided to the remaining authors, who then used a more focused search to clarify specific data.

Pharmacodynamics and pharmacokinetics

Naltrexone is a long-acting, reversible opioid antagonist which blocks both the subjective and objective effects of intravenous and oral opioids [9,10]. A cyclopropyl derivative of oxymorphone, naltrexone shares structural similarity with naloxone (see Figure 1). Naltrexone is a competitive opioid antagonist with high affinity for μ - and κ - opioid receptors, and a weaker affinity for δ - opioid receptors based on its ability to displace radiolabeled ligands *in vitro* and *in vivo* [11,12]. Naltrexone itself does not display any significant opioid agonism; however, it can evoke miosis via an unknown mechanism [13].

Indicated for OUD and alcoholism, oral naltrexone is administered daily. Following oral administration, ~96% of naltrexone dose is rapidly absorbed through the gastrointestinal tract. Oral naltrexone undergoes significant first-pass metabolism, limiting bioavailability to 5–40%. Metabolism via hepatic cytosolic dihydrodiol enzymes produces its primary metabolite, 6 β -naltrexol [14]. Both naltrexone and 6 β -naltrexol reach peak plasma concentrations within one hour after ingestion [9]. The metabolite 6 β -naltrexol has a longer elimination half-life than naltrexone (~12 h and 4 h, respectively) [15]. Naltrexone and 6 β -naltrexol are primarily renally excreted. Less than 2% of naltrexone is excreted unchanged, and fecal elimination is minimal.

In contrast to oral dosing, naltrexone extended-release suspension (Vivitrol®, Alkermes, Waltham, MA) is administered as 380 mg gluteal injection every 4 weeks (or one month). The extended-release formulation incorporates the drug into microspheres, which are then

solubilized in a diluent prior to injection. When plasma naltrexone concentrations are measured, an initial peak occurs 2 h after injection, with a second peak, 2–3 days later. After day 14, plasma concentrations slowly decline; however, naltrexone remains measurable for more than one month. In a cohort of heroin-dependent adults, mean naltrexone plasma concentrations ranged from 1.3 to 3.2 ng/mL, after administration of injectable sustained-release naltrexone [16]. For reference, a concentration of 2 ng/mL is generally considered sufficient to prevent high-dose opioid effects [16]. After intramuscular naltrexone administration, there is less generation of 6 β -naltrexol due to the absence of first-pass metabolism [17]. The elimination half-life for both naltrexone and 6 β -naltrexol is 5–10 days, and correlates to microsphere degradation.

Use of naltrexone as medication assisted therapy for opioid use disorder

Drugs currently approved by the Food and Drug Administration for the treatment of OUD include methadone, buprenorphine and naltrexone [18]. Buprenorphine and methadone both significantly improve retention in OUD treatment programs over therapy without opioid agonists [19,20]. However, treatment of OUD with these agonists is highly regulated (42 CFR § 8) (Controlled Substances Act, 21 U.S.C Ch 13). Practitioners can prescribe buprenorphine after completion of special training and receipt of a waiver from the Drug Enforcement Administration. Methadone maintenance therapy is restricted to credentialed Opioid Treatment Programs (OTP).

Despite proven efficacy, there are barriers to entry into a MAT program utilizing opioid agonists. Waiting times for enrollment into established OTPs, or initiation of care with a buprenorphine-waivered practitioner, can be months long [21]. This is due in part to a mismatch between the number of individuals seeking treatment for OUD and the availability of buprenorphine-waivered practitioners or space in OTPs [22]. Although access to OTPs varies by region, a study reviewing data from 2012 suggested the nationwide rate of OUD was 891.8 per 100,000; however, maximum potential buprenorphine and methadone treatment capacity was 420.3 and 119.9 per 100,000, respectively [22], demonstrating a gap in treatment availability. While clinicians should actively work to minimize barriers to treatment with buprenorphine and methadone, naltrexone can potentially fill gaps in our existing treatment paradigms.

Physicians have explored the use of naltrexone as a treatment for OUD since the 1970s [23]. Attractive features include mitigation of opioid effects via competitive antagonism [24], lack of incentive for diversion, and absence of withdrawal with discontinuation of therapy [25]. Some researchers proclaim it an “ideal drug” for MAT [26] based on its safety and lack of abuse potential. *In vivo* pharmacodynamic data suggest that a single dose of oral naltrexone can effectively occupy the μ -opioid receptor for 72 h [27]. Typical oral outpatient regimens consist of either 50 mg/day or alternating doses of 100 mg and 150 mg administered three times per week [8]. Although there is no opioid receptor agonism with naltrexone, some studies suggest that it mitigates opioid cravings [28]; however, this is not a consistent finding [29], and does not translate into superior abstinence outcomes [30].

In theory, the μ -opioid receptor blockade produced by naltrexone prevents overdose in the time after initiating MAT for OUD. However, studies of patients on oral naltrexone for MAT

fail to show this benefit. One study showed that oral naltrexone was associated with an increased risk of an overdose after starting treatment and an increased risk of fatal overdose when leaving treatment [31], possibly due to a loss of tolerance. Increased mortality was also seen in two Australian studies of patients treated with naltrexone when compared to those treated with agonist therapy [32,33]. In addition, an Italian study observed that when patients receiving naltrexone left treatment, they were at increased risk of fatal overdose in the first 30 days [34]. This increased risk of overdose and overall mortality is not seen in patients treated with naltrexone implants [35] or in those treated with the depot formulation of naltrexone when compared to agonist treatment [36,37].

The central problem surrounding the widespread use of naltrexone in MAT for OUD is therapeutic adherence with the prescribed regimen. This may be why the previously mentioned studies documented an increased rate of overdose despite antagonist therapy. One of the earliest trials demonstrated that the vast majority of patients dropped out within two months, with many individuals not even starting treatment due to the need for a period of abstinence from opioids prior to naltrexone initiation [38]. Predictors of poor adherence to a naltrexone treatment regimen include patients using opioids in higher amounts, those with longer-term use, those who use longer-acting opioids, and older age at initiation of treatment [39]. Additionally, patients who are being treated with opioids for chronic pain who may have OUD are generally not interested in antagonist therapy [40]. A recent Cochrane review investigating oral naltrexone for maintenance therapy after opioid detoxification found it to be no more effective than placebo or no pharmacologic treatment [41].

Despite the evidence supporting the use of opioid agonists as MAT for the treatment of OUD and associated prevention of overdose deaths, many providers and patients believe that opioid agonist therapy substitutes one addiction for another [42]. This belief can be deeply entrenched among patients with OUD, even when they are provided with detailed information and evidence to the contrary. With this in mind, naltrexone could be a treatment option for motivated patients who wish to avoid long-term opioid agonist therapy [25]. For example, patients with careers that preclude treatment with agonist therapy, such as physicians or law enforcement officers, may be ideal candidates for naltrexone treatment [43]. Naltrexone use has been studied in anesthesiologists being treated for OUD and was associated with decreased cravings and decreased rate of relapse [44]. Greater success with oral naltrexone has also been demonstrated in Russia, where opioid agonist therapy is not available [45]. Efficacy in that setting was attributed to the lack of alternative regimens and greater family support to encourage compliance. As such, the more apt comparison may be between naltrexone and abstinence, rather than naltrexone and other forms of MAT.

Precipitated withdrawal and ultra-rapid detoxification

Opioid withdrawal is a necessary precursor to many addiction treatment regimens including naltrexone maintenance. Typical withdrawal from short-acting opioids such as heroin starts 6–12 h from last use, peaks in 48–96 h, and persists for 7–14 days [46]. A single dose of naltrexone precipitates severe withdrawal in patients with physical dependence [30], explaining the rationale behind the standard recommendation of 7–10 days of opioid

abstinence prior to initiation of naltrexone maintenance therapy, longer periods of abstinence may be required for patients using long-acting opioids, such as methadone.

Instances of naltrexone-precipitated opioid withdrawal have been well documented in dependent individuals inadvertently using naltrexone that they misidentified as an opioid [47–49], or those who were prescribed naltrexone for alcohol addiction without consideration of underlying opioid dependence [50,51]. Practitioners have leveraged this property of naltrexone and other antagonists for the purpose of medically-supervised precipitated withdrawal procedures, in which a rapid transition to withdrawal starts minutes after antagonist administration and continues for 48–72 h. The objective is to create a more severe, yet abbreviated, opioid withdrawal syndrome, shortening the time to initiation of naltrexone maintenance therapy, and potentially decreasing opioid cravings [52,53].

This method of antagonist-precipitated opioid withdrawal is referred to in the literature as Rapid Opioid Detoxification (ROD), or UltraRapid Opioid Detoxification (UROD). Published protocols for UROD typically involve intubation and general anesthesia with propofol for several hours while naltrexone or another opioid antagonist (such as naloxone or nalmefene) is administered [54,55]. The appeal of UROD is the promise of a painless and rapid detoxification process, which minimizes the patient's experience of unpleasant opioid withdrawal symptoms. However, recent literature suggests this practice subjects patients to additional risks without clear benefit in long-term outcomes over traditional approaches [56–60]. The low rates of long-term success after UROD are likely attributable to the lack of focus on psychosocial issues surrounding addiction that lead to relapse, or the adherence issues that limit the effectiveness of subsequent treatment with oral naltrexone [41,61]. Multiple cases of sudden death attributed to UROD procedures have been described, as well as severe agitation and delirium requiring intubation, exacerbations of the psychiatric disease, metabolic derangements, and pulmonary edema [54,58,62,63]. A recent Cochrane review on heavy sedation/anesthesia for precipitated opioid withdrawal concluded these practices are associated with significant, life-threatening risks and increased cost without clear benefit with regard to treatment success; thus, rapid opioid detoxification should not be pursued [64]. The 2015 American Society of Addiction Medicine National Practice Guideline for the use of medication in the treatment of addiction involving opioids specifically discourages UROD under anesthesia due to the high risk of adverse events, including death.

New approaches for use of naltrexone for medication-assisted therapy

The FDA approved naltrexone extended-release injectable suspension in 2010. This formulation addresses the issue of daily compliance through regular monthly injections. Extended-release naltrexone therapy (XRNT) demonstrates improved outcomes with respect to opioid abstinence when contrasted with oral naltrexone treatment regimens [65]. A randomized, controlled trial comparing XRNT to oral buprenorphine-naloxone noted non-inferiority with the primary outcome of opioid abstinence, and a trend toward decreased cravings in the naltrexone-treated group [36]. A meta-analysis of older studies involving extended-release naltrexone systems did note some improvements in abstinence and treatment retention over oral naltrexone or usual care, but not when compared to opioid

replacement therapy with methadone. Relapse to opioid use was similar between those treated with methadone and naltrexone implants [35].

Although the ideal candidates for XRNT are yet unknown, demonstrated benefits, including lack of opioid-agonist-related side effects and decreased cravings, make it attractive to some patients [36]. Intuitively, XRNT might mitigate opioid overdose mortality due to opioid receptor antagonism when compared to agonist treatments. In reality, there is uncertainty due to difficulty in measuring morbidity in past observations [35]. Two recent studies indicate equivalent death rates due to overdose between XRNT and buprenorphine-naloxone treated groups [36,66]. Use of higher doses of opioids can overcome the opioid receptor blockade induced by naltrexone [67,68]. In addition, the prevalence of potent synthetic opioids in the illicit drug supply [69] raises the concern of opioid-antagonist efficacy with exposure to these drugs. A recent retrospective analysis of patients who died of an opioid overdose in proximity to treatment with XRNT showed that 5 out of 52 deaths occurred within 28 days of receiving the injection, indicating that the blockade can be overcome [70].

In a cohort study of patients in Massachusetts from 2011–2015, an all-cause and opioid-related mortality benefit were observed with methadone maintenance therapy and buprenorphine treatment. There was no mortality benefit seen in patients who received naltrexone [71]. The authors noted limitations in this finding, including small numbers of patients treated with naltrexone. Moreover, the authors speculated that the lack of mortality benefit with XRNT may be related to poor treatment retention as only about 19% of patients initially treated with XRNT received a second treatment [71]. This study reinforces the critical role of opioid-agonist treatment as the first-line intervention in preventing overdose deaths. However, the comparison of agonist therapy to naltrexone may be less clinically relevant than the comparison of naltrexone to standard care in individuals who are unwilling or unable to receive opioid agonists.

Many factors influence the abandonment of naltrexone treatment. With respect to XRNT, the cost may represent a significant driver of behavior. In an analysis performed in Washington state, median out-of-pocket monthly costs for patients on Medicare Advantage plans was \$56 for buprenorphine, compared to \$285 for XRNT [72]. Indeed, a follow-up study of patients treated with XRNT indicated a higher socioeconomic status is associated with prolonged XRNT treatment adherence [73].

A substantial barrier to XRNT is the recommendation that patients be free of opioids for 7 days prior to initiation of treatment due to the risk of severe precipitated withdrawal. In a recent head-to-head trial (the X:BOT trial), buprenorphine-naloxone was favored over XRNT in the intention-to-treat analysis due to fewer patients being successfully inducted into naltrexone therapy [66], suggesting the abstinence period is a significant barrier to induction. There was, however, no significant difference in relapse in the per-protocol analysis, indicating that the treatment was effective once patients were successfully inducted.

With that in mind, safe treatment with naltrexone may not require opioid abstinence for 7 days. Evaluation of ultra-rapid detoxification studies demonstrates that users of long-acting

opioids such as methadone are at increased risk for severe precipitated withdrawal [74,75]. However, patients who are not dependent on opioids but have experienced a recent relapse were not included in these studies. Evaluation of the risk in patients who were previously abstinent, but have suffered a relapse, lacks formal study. This may represent a population that would be eligible for early treatment with naltrexone, if desired. The safety of oral or extended-release intramuscular naltrexone to this population without a mandated abstinence period is a potential area for future research.

Another promising approach to the use of naltrexone utilizes very low oral doses for opioid detoxification in the acute setting. Oral naltrexone at a reduced dose (e.g., 0.25 mg) appears to mitigate some opioid withdrawal symptoms without precipitating severe withdrawal [76,77]. Similar effects are also noted in animal models of opioid dependence and withdrawal [78]. Investigators are actively evaluating the use of very low-dose naltrexone in the acute detoxification period. Preliminary data are limited, but the approach appears to be safe, with decreased withdrawal symptoms and decreased opioid use after discharge in the short-term [76]. When used in the 21 days after acute detoxification, reduced-dose oral naltrexone in the 1–10 mg range also led to greater abstinence than treatment with clonidine [79]. An intriguing theory based on animal models is that 6 β -naltrexol, the primary product of first-pass metabolism, mitigates the effects of opioid withdrawal [80,81].

The use of buprenorphine and oral naltrexone to bridge patients to XRNT is also an area of ongoing research, and early results are promising. In one study, patients received three days of sublingual buprenorphine, while concomitantly receiving escalating doses of oral naltrexone and comfort medications for opioid withdrawal. In patients self-reporting abstinence for 24 h, this regimen did not lead to severe precipitated withdrawal, and was considered to be safe in an outpatient setting [82]. The previously mentioned study escalated naltrexone to a mean dose of 30 mg within 7 days, and these patients did not experience severe withdrawal symptoms. In another study, patients were randomized to escalating doses of oral naltrexone, maintenance buprenorphine, or both prior to treatment with XRNT [83]. All patients received 15 mg of oral naltrexone prior to treatment with XRNT; patients treated with naltrexone alone did not report higher withdrawal scores [83]. Based on these data, it seems reasonable to surmise that if a patient tolerates a therapeutic dose of oral naltrexone in the range of 15–30 mg without experiencing severe withdrawal, they could safely receive an injection of naltrexone extended-release suspension.

A potential study of this approach would involve ED administration of naltrexone and include patients with a self-reported period of abstinence of at least 10 days before relapse who are not concurrently treated with agonist MAT or chronic opioids. Such a study would require observation in a monitored setting for at least two hours after drug administration to evaluate for signs of precipitated withdrawal, but this is similar to what office-based buprenorphine prescribers perform for new patient inductions [84]. These patients would not require prolonged observation, as oral naltrexone reaches peak serum concentrations in one hour [9], but staff would have to prepare to treat precipitated withdrawal should it occur. Additional safety measures should include liver-function testing and on-site drug testing for long-acting agonists such as buprenorphine and methadone. If the patient or physician has concern for precipitated withdrawal, treatment could start with a very low dose and escalate,

0.25 mg of naltrexone was safely used in patients also on agonist therapy [85]. Escalation could be halted if the patient begins to experience withdrawal symptoms. A patient who safely tolerates a standard oral dose of 25 mg naltrexone may be appropriate for discharge with additional doses of oral naltrexone and expedited XRNT treatment.

Previous studies of the safety and efficacy of naltrexone as MAT have taken place in inpatient and outpatient addiction-treatment programs; none has taken place in the emergency department. In our experience with patients presenting to the ED after near-fatal opioid overdose, 20 out of 30 reported at least two weeks without drug use prior to the relapse leading to ED presentation. Some reported months or years without drug use prior to the relapse resulting in their presentation [69], although the accuracy of these statements was not investigated in this study. In our practice, patients with an overdose after extended periods of abstinence frequently decline opioid-agonist treatment, and may be candidates for treatment with naltrexone.

Conclusion

There is a large unmet need for in treating OUD with MAT. The ED has already been studied as a place to start MAT with agonist therapy, and represents an opportune location to trial therapy with naltrexone, especially for those who have had a near-fatal overdose after an extended period of abstinence. We propose a further study of the safety and effectiveness of oral naltrexone in the ED as a bridge to longer-term outpatient treatment. Future studies will need to determine whether naltrexone treatment for this group of patients has similar efficacy in terms of abstinence and mortality to agonist therapy with buprenorphine or methadone, but we anticipate that ED-initiated treatment will facilitate engagement with outpatient treatments such as XRNT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

- [1]. An Act relative to substance use, treatment, education and prevention, 4056 (2015–2016).
- [2]. Vivolo-Kantor AM, Seth P, Gladden RM, et al. Vital signs: trends in emergency department visits for suspected opioid overdoses—United States, July 2016–September 2017. *MMWR Morb Mortal Wkly Rep.* 2018;67:279. [PubMed: 29518069]
- [3]. National Center for Health Statistics. Drugs involved in U.S. overdose deaths, 1999 to 2017. 2018;1–13.
- [4]. Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioid analgesics from 2004 to 2011. *Pain Physician.* 2014;17:E119–E128. [PubMed: 24658483]
- [5]. Peterson AB, Gladden RM, Delcher C, et al. Increases in fentanyl-related overdose deaths - Florida and Ohio, 2013–2015. *MMWR Morb Mortal Wkly Rep.* 2016;65:844–849. [PubMed: 27560948]
- [6]. Inocencio TJ, Carroll NV, Read EJ, et al. The economic burden of opioid-related poisoning in the United States. *Pain Med.* 2013;14: 1534–1547. [PubMed: 23841538]
- [7]. D’Onofrio G, O’Connor PG, Pantalon MV, et al. Emergency department–initiated buprenorphine/naloxone treatment for opioid dependence. *JAMA.* 2015;313:1636–1639. [PubMed: 25919527]

- [8]. Kjome KL, Moeller FG. Long-acting injectable naltrexone for the management of patients with opioid dependence. *Subs Abuse Res Treatment*. 2011;5:1–9.
- [9]. Tetrault JM, Fiellin DA. Current and potential pharmacological treatment options for maintenance therapy in opioid-dependent individuals. *Drugs*. 2012;72:217–228. [PubMed: 22235870]
- [10]. Duramed Pharmaceuticals Inc. Product information: REVIA(R) oral tablets, naltrexone HCl oral tablets. Pomona (NY):Duramed Pharmaceuticals; 2013.
- [11]. Rawson RA, McCann MJ, Hasson AJ, et al. Addiction pharmacotherapy 2000: new options, new challenges. *J Psychoactive Drugs*. 2000;32:371–378. [PubMed: 11210198]
- [12]. Emmerson PJ, Liu MR, Woods JH, et al. Binding affinity and selectivity of opioids at mu, delta and kappa receptors in monkey brain membranes. *J Pharmacol Exp Ther*. 1994;271:1630–1637. [PubMed: 7996478]
- [13]. Weerts EM, Kim YK, Wand GS, et al. Differences in delta-and muopioid receptor blockade measured by positron emission tomography in naltrexone-treated recently abstinent alcohol-dependent subjects. *Neuropsychopharmacology*. 2008;33:653–665. [PubMed: 17487229]
- [14]. Yancey-Wrona J, Dallaire B, Bilsky E, et al. 6beta-naltrexol, a peripherally selective opioid antagonist that inhibits morphine-induced slowing of gastrointestinal transit: an exploratory study. *Pain Med*. 2011;12:1727–1737. [PubMed: 22123184]
- [15]. Porter SJ, Somogyi AA, White JM. Kinetics and inhibition of the formation of 6beta-naltrexol from naltrexone in human liver cytosol. *Br J Clin Pharmacol*. 2000;50:465–471. [PubMed: 11069441]
- [16]. Meyer MC, Straughn AB, Lo MW, et al. Bioequivalence, dose-proportionality, and pharmacokinetics of naltrexone after oral administration. *J Clin Psychiatry*. 1984;45:15–19. [PubMed: 6469932]
- [17]. 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]
- [18]. Alkermes, Inc. Product information: VIVITROL(R) intramuscular injection extended-release suspension, naltrexone intramuscular injection extended-release suspension. Waltham (MA): Alkermes, Inc; 2013.
- [19]. Schuckit MA. Treatment of opioid-use disorders. *N Engl J Med*. 2016;375:357–368. [PubMed: 27464203]
- [20]. Mattick RP, Breen C, Kimber J, Cochrane Drugs and Alcohol Group, editor, et al. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev*. 2009;72:59–27.
- [21]. Mattick RP, Breen C, Kimber J, Cochrane Drugs and Alcohol Group, editor, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2014;66:111–163.
- [22]. Sigmon SC, Meyer A, Hruska B, et al. Bridging waitlist delays with interim buprenorphine treatment: initial feasibility. *Addict Behav*. 2015;51:136–142. [PubMed: 26256469]
- [23]. Jones CM, Campopiano M, Baldwin G, et al. National and state treatment need and capacity for opioid agonist medication-assisted treatment. *Am J Public Health*. 2015;105:e55–e63.
- [24]. Martin WR, Jasinski DR, Mansky PA. Naltrexone, an antagonist for the treatment of heroin dependence. Effects in man. *Arch Gen Psychiatry*. 1973;28:784–791. [PubMed: 4707988]
- [25]. Preston KL, Bigelow GE. Differential naltrexone antagonism of hydromorphone and pentazocine effects in human volunteers. *J Pharmacol Exp Ther*. 1993;264:813–823. [PubMed: 7679737]
- [26]. Klein JW. Pharmacotherapy for substance use disorders. *Med Clin North Am*. 2016;100:891–910. [PubMed: 27235620]
- [27]. Kleber HD. Pharmacologic treatments for heroin and cocaine dependence. *Am J Addict*. 2003;12:S5–S18. [PubMed: 12857659]
- [28]. Lee MC, Wagner HN, Tanada S, et al. Duration of occupancy of opiate receptors by naltrexone. *J Nucl Med*. 1988;29:1207–1211. [PubMed: 2839637]
- [29]. Krupitsky EM, Zvartau EE, Masalov DV, et al. Naltrexone with or without fluoxetine for preventing relapse to heroin addiction in St. Petersburg, Russia. *J Subs Abuse Treatment*. 2006;31:319–328.

- [30]. Dijkstra BA, De Jong CA, Bluschke SM, et al. Does naltrexone affect craving in abstinent opioid-dependent patients? *Addict Biol.* 2007;12:176–182. [PubMed: 17508990]
- [31]. Bart G. Maintenance medication for opiate addiction: the foundation of recovery. *J Addict Dis.* 2012;31:207–225. [PubMed: 22873183]
- [32]. Digiusto E, Shakeshaft A, Ritter A, et al. Serious adverse events in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD). *Addiction.* 2004;99:450–460. [PubMed: 15049745]
- [33]. Degenhardt L, Larney S, Kimber J, et al. Excess mortality among opioid-using patients treated with oral naltrexone in Australia. *Drug Alcohol Rev.* 2015;34:90–96. [PubMed: 25302627]
- [34]. Gibson AE, Degenhardt LJ. Mortality related to pharmacotherapies for opioid dependence: a comparative analysis of coronial records. *Drug Alcohol Revs.* 2007;26:405–410. [PubMed: 17564876]
- [35]. Davoli M, Bargagli AM, Perucci CA, for the VEdeTTE Study Group, et al. Risk of fatal overdose during and after specialist drug treatment: the VEdeTTE study, a national multi-site prospective cohort study. *Addiction.* 2007;102:1954–1959. [PubMed: 18031430]
- [36]. Larney S, Gowing L, Mattick RP, et al. A systematic review and meta-analysis of naltrexone implants for the treatment of opioid dependence. *Drug Alcohol Rev.* 2014;33:115–128. [PubMed: 24299657]
- [37]. Tanum L, Solli KK, Latif Z-E-H, et al. The effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence. *JAMA Psychiatry.* 2017;74:1197–1205. [PubMed: 29049469]
- [38]. Kunoe N, Opheim A, Solli KK, et al. Design of a randomized controlled trial of extended-release naltrexone versus daily buprenorphine-naloxone for opioid dependence in Norway (NTX-SBX). *BMC Pharmacol Toxicol.* 2016;17:18. [PubMed: 27121539]
- [39]. Hollister LE, Schwin RL, Kasper P. Naltrexone treatment of opiate-dependent persons. *Drug Alcohol Depend.* 1977;2:203–209. [PubMed: 880876]
- [40]. Sullivan MA, Rothenberg JL, Vosburg SK, et al. Predictors of retention in naltrexone maintenance for opioid dependence: analysis of a stage I trial. *Am J Addict.* 2006;15:150–159. [PubMed: 16595353]
- [41]. Ahamad K, Milloy MJ, Nguyen P, et al. Factors associated with willingness to take extended release naltrexone among injection drug users. *Addict Sci Clin Practice.* 2015;10:12.
- [42]. Minozzi S, Amato L, Vecchi S, et al. Oral naltrexone maintenance treatment for opioid dependence Minozzi S, editor. *The Cochrane database of systematic reviews.* Chichester, UK: John Wiley & Sons, Ltd; 2011; p. CD001333.
- [43]. Volkow ND, Frieden TR, Hyde PS, et al. Medication-assisted therapies-tackling the opioid-overdose epidemic. *N Engl J Med.* 2014; 370:2063–2066. [PubMed: 24758595]
- [44]. O'Brien CP. A 50-year-old woman addicted to heroin: review of treatment of heroin addiction. *JAMA.* 2008;300:314–321. [PubMed: 18594026]
- [45]. 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]
- [46]. Krupitsky E, Zvartau E, Woody G. Use of naltrexone to treat opioid addiction in a country in which methadone and buprenorphine are not available. *Curr Psychiatry Rep.* 2010;12:448–453. [PubMed: 20640538]
- [47]. Gowing L, Ali R, White JM. Opioid antagonists with minimal sedation for opioid withdrawal. *Cochrane Database Syst Rev.* 2017;5: Cd002021.
- [48]. Yeo M, Campbell V, Bonomo Y, et al. Acute opioid withdrawal on accidental injection of naltrexone. *J Paediatr Child Health.* 2003; 39:315–317. [PubMed: 12755943]
- [49]. Hassanian-Moghaddam H, Afzali S, Pooya A. Withdrawal syndrome caused by naltrexone in opioid abusers. *Hum Exp Toxicol.* 2014;33:561–567. [PubMed: 23690227]
- [50]. Lubman D, Koutsogiannis Z, Kronborg I. Emergency management of inadvertent accelerated opiate withdrawal in dependent opiate users. *Drug Alcohol Rev.* 2003;22:433–436. [PubMed: 14660133]

- [51]. Franchitto N, Jullian B, Salles J, et al. Management of precipitated opiate withdrawal syndrome induced by nalmeferne mistakenly prescribed in opiate-dependent patients: a review for clinicians. *Expert Opin Drug Metab Toxicol*. 2017;13:669–677. [PubMed: 28343423]
- [52]. Donnerstag N, Schneider T, Luthi A, et al. Severe opioid withdrawal syndrome after a single dose of nalmeferne. *Eur J Clin Pharmacol*. 2015;71:1025–1026. [PubMed: 26050241]
- [53]. Elman I, D'Ambra MN, Krause S, et al. Ultrarapid opioid detoxification: effects on cardiopulmonary physiology, stress hormones and clinical outcomes. *Drug Alcohol Depend*. 2001;61:163–172. [PubMed: 11137281]
- [54]. Lorenzi P, Marsili M, Boncinelli S, et al. Searching for a general anaesthesia protocol for rapid detoxification from opioids. *Eur J Anaesthesiol*. 1999;16:719–727. [PubMed: 10583357]
- [55]. Gold CG, Cullen DJ, Gonzales S, et al. Rapid opioid detoxification during general anesthesia: a review of 20 patients. *Anesthesiology*. 1999;91:1639–1647. [PubMed: 10598605]
- [56]. Hensel M, Wolter S, Kox WJ. EEG controlled rapid opioid withdrawal under general anaesthesia. *Brit J Anaesth*. 2000;84:236–238. [PubMed: 10743458]
- [57]. Lawental E. Ultra rapid opiate detoxification as compared to 30day inpatient detoxification program—a retrospective follow-up study. *J Subs Abuse*. 2000;11:173–181.
- [58]. McGregor C, Ali R, White JM, et al. A comparison of antagonist-precipitated withdrawal under anesthesia to standard inpatient withdrawal as a precursor to maintenance naltrexone treatment in heroin users: outcomes at 6 and 12 months. *Drug Alcohol Depend*. 2002;68:5–14. [PubMed: 12167548]
- [59]. Collins ED, Kleber HD, Whittington RA, et al. Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial. *JAMA*. 2005;294:903–913. [PubMed: 16118380]
- [60]. Rabinowitz J, Cohen H, Atias S. Outcomes of naltrexone maintenance following ultra rapid opiate detoxification versus intensive inpatient detoxification. *Am J Addict*. 2002;11:52–56. [PubMed: 11876583]
- [61]. Favrat B, Zimmermann G, Zullino D, et al. Opioid antagonist detoxification under anaesthesia versus traditional clonidine detoxification combined with an additional week of psychosocial support: a randomised clinical trial. *Drug Alcohol Depend*. 2006;81:109–116. [PubMed: 16024184]
- [62]. Singh J, Basu D. Ultra-rapid opioid detoxification: current status and controversies. *J Postgrad Med*. 2004;50:227–232. [PubMed: 15377814]
- [63]. Armstrong J. Emergency department presentations of naltrexone-accelerated detoxification. *Acad Emerg Med*. 2003;10:860–866. [PubMed: 12896887]
- [64]. Pfab R, Pfab R, Hirtl C, et al. Opiate detoxification under anesthesia: no apparent benefit but suppression of thyroid hormones and risk of pulmonary and renal failure. *J Toxicol Clin Toxicol*. 1999;37:43–50. [PubMed: 10078159]
- [65]. Gowing L, Ali R, White J. Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal Gowing L, editor. *The Cochrane database of systematic reviews*. 2006 ed. Chichester, UK: John Wiley & Sons, Ltd; 2006;294:CD002022.
- [66]. Krupitsky E, Zvartau E, Blokhina E, et al. Randomized trial of long-acting sustained-release naltrexone implant vs oral naltrexone or placebo for preventing relapse to opioid dependence. *Arch Gen Psychiatry*. 2012;69:973–981. [PubMed: 22945623]
- [67]. Lee JD, Nunes EV J, Novo P et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *Lancet*. 2018 1;391:309–318. [PubMed: 29150198]
- [68]. Kunoe N, Lobmaier P, Vederhus JK, et al. Challenges to antagonist blockade during sustained-release naltrexone treatment. *Addiction*. 2010;105:1633–1639. [PubMed: 20707781]
- [69]. Krupitsky EM, Burakov AM, Tsoy MV, et al. Overcoming opioid blockade from depot naltrexone (Prodexon). *Addiction*. 2007; 102:1164–1165. [PubMed: 17498182]
- [70]. Griswold MK, Chai PR, Krotulski AJ, et al. Self-identification of nonpharmaceutical fentanyl exposure following heroin overdose. *Clin Toxicol*. 2018;56:37–42.

- [71]. Saucier R, Wolfe D, Dasgupta N. Review of Case Narratives from Fatal Overdoses Associated with Injectable Naltrexone for Opioid Dependence. *Drug Safety*. 2018 10;41:981–988. [PubMed: 29560596]
- [72]. Larochelle MR, Bernson D, Land T, et al. Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: a cohort study. *Ann Intern Med*. 2018;169:137–110. [PubMed: 29913516]
- [73]. Kennedy J, Dipzinski A, Roll J, et al. Medicare prescription drug plan coverage of pharmacotherapies for opioid and alcohol dependence in WA. *Drug Alcohol Depend*. 2011;114:201–206. [PubMed: 21134724]
- [74]. Saxon AJ, Akerman SC, Liu C-C, et al. Extended-release naltrexone (XR-NTX) for opioid use disorder in clinical practice: vivitrol's cost and treatment outcomes registry. *Addiction*. 2018;113:1477–1487. [PubMed: 29493836]
- [75]. Tretter F, Burkhardt D, Bussello-Spieth B, et al. Clinical experience with antagonist-induced opiate withdrawal under anaesthesia. *Addiction*. 1998;93:269–275. [PubMed: 9624727]
- [76]. Hensel M, Kox WJ. Safety, efficacy, and long-term results of a modified version of rapid opiate detoxification under general anaesthesia: a prospective study in methadone, heroin, codeine and morphine addicts. *Acta Anaesthesiol Scand*. 2000; 44:326–333. [PubMed: 10714849]
- [77]. Mannelli P, Patkar AA, Peindl K, et al. Early outcomes following low dose naltrexone enhancement of opioid detoxification. *Am J Addict*. 2009;18:109–116. [PubMed: 19283561]
- [78]. Mannelli P, Gottheil E, Buonanno A, et al. Use of very low-dose naltrexone during opiate detoxification. *J Addict Dis*. 2003;22: 63–70.
- [79]. Olmstead MC, Burns LH. Ultra-low-dose naltrexone suppresses rewarding effects of opiates and aversive effects of opiate withdrawal in rats. *Psychopharmacology*. 2005;181:576–581. [PubMed: 16010543]
- [80]. Mannelli P, Patkar AA, Peindl K, et al. Effectiveness of low-dose naltrexone in the post-detoxification treatment of opioid dependence. *J Clin Psychopharmacol*. 2007;27:468–474. [PubMed: 17873678]
- [81]. Ko MC, Divin MF, Lee H, et al. Differential in vivo potencies of naltrexone and 6beta-naltrexol in the monkey. *J Pharmacol Exp Ther*. 2006;316:772–779. [PubMed: 16258020]
- [82]. Raehal KM, Lowery JJ, Bhamidipati CM, et al. In vivo characterization of 6beta-naltrexol, an opioid ligand with less inverse agonist activity compared with naltrexone and naloxone in opioid-dependent mice. *J Pharmacol Exp Ther*. 2005;313: 1150–1162. [PubMed: 15716384]
- [83]. Mannelli P, Wu LT, Peindl KS, et al. Extended release naltrexone injection is performed in the majority of opioid dependent patients receiving outpatient induction: a very low dose naltrexone and buprenorphine open label trial. *Drug Alcohol Depend*. 2014;138:83–88. [PubMed: 24602363]
- [84]. Mannelli P, Patkar AA, Peindl K, et al. Very low dose naltrexone addition in opioid detoxification: a randomized, controlled trial. *Addict Biol*. 2009;14:204–213. [PubMed: 18715283]
- [85]. Bisaga A, Mannelli P, Yu M, et al. Outpatient transition to extended-release injectable naltrexone for patients with opioid use disorder_ A phase 3 randomized trial. *Drug Alcohol Depend*. 2018;187:171–178. [PubMed: 29674251]

Figure 1.
Naltrexone and related structures.